

Corticosteroids. I. The Structure of 4-Chlorocortisone

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The crystal structure of 4-chlorocortisone has been determined by three-dimensional X-ray analysis and refined to a final R value of 0.077 for 2076 reflections recorded by stationary-crystal stationary-counter diffractometry. Unit-cell constants are $a = 12.632$, $b = 6.579$, $c = 11.567$ Å, $\beta = 95.37^\circ$. There are two molecules per cell in the monoclinic space group $P2_1$. All hydrogen atoms were located in Fourier difference syntheses. Molecules related by unit cell-translations in the a direction are hydrogen bonded to one another *via* the 3-carbonyl oxygen atom and the 17α -hydroxyl hydrogen atom. There is no evidence of intramolecular hydrogen bonding.

Introduction

The adrenal corticoids, aldosterone and cortisol, are active hormones which are essential to life. The molecular structures of these and other adrenal corticoids are being studied in the crystalline state as part of a program investigating the structural-functional relationships of steroids. The conformations and relative positions of the functional groups on the steroid molecules are of particular interest in steroid structure studies in that they are thought to be the key to understanding the way in which steroids act upon their targets. Cortisone, an intermediate in the formation of cortisol, has a carbonyl group in a quasi-equatorial configuration at the 11 position (Fig. 1), whereas cortisol has a hydroxyl group in an axial configuration at this position. While differing slightly in structural composition, cortisone is essentially inactive and cortisol is the most active of the glucocorticoids.

Experimental

Crystal data

Modification A: Crystals of 4-chlorocortisone were grown from a mixture of acetone and hexane. The unit cell is monoclinic, space group $P2_1$ ($0k0$ absent for $k = 2n + 1$), with dimensions $a = 12.632 \pm 0.005$, $b = 6.579 \pm 0.001$, $c = 11.567 \pm 0.002$ Å [$\lambda(\text{Cu } K\alpha) = 1.5418$ Å] and $\beta = 95.37^\circ \pm 0.02^\circ$. The observed density (measured by flotation of the crystals in an aqueous solution of potassium iodide) is 1.36 g.cm^{-3} compared with a value of 1.38 g.cm^{-3} calculated for two molecules of $\text{C}_{21}\text{H}_{27}\text{ClO}_5$ per unit cell.

Modification B: Crystals were grown from a mixture of acetone and benzene. The unit cell is monoclinic, space group $P2_1$, with dimensions $a = 12.6$, $b = 9.9$, $c = 12.4$ Å, $\beta = 105.4^\circ$.

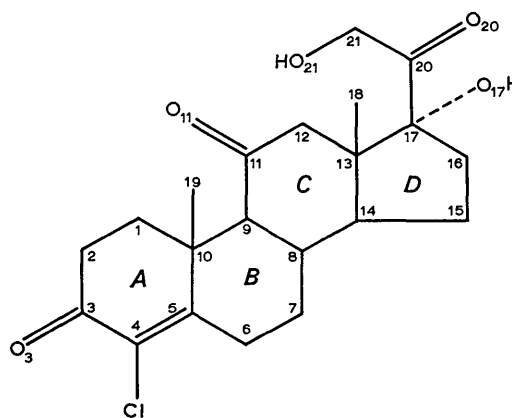


Fig. 1. 4-Chlorocortisone. Molecular skeleton and numbering of the atoms.

Crystals of modification A were chosen for the investigation of the structure, since those of modification B were unstable and appeared to be losing solvent. A crystal with dimensions $0.15 \times 0.1 \times 0.1$ mm was mounted on a General Electric single-crystal orienter, with the long axis (b) parallel to the ϕ axis of the instrument. The shape anisotropy of the crystal was found to be 6% and, with the linear absorption coefficient $\mu = 20.3 \text{ cm}^{-1}$, no absorption correction was deemed necessary.

Diffraction intensities were measured for 2076 independent spectra with 2θ less than 145° , by the stationary-crystal stationary-counter method with $\text{Cu } K\alpha$ radiation monochromatized by balanced nickel and cobalt filters and by electronic pulse height discrimination.

The chlorine atom was located from the Harker section of the Patterson synthesis and was used to solve the structure by the routine application of the heavy-atom method (Lipson & Cochran, 1953). The positional parameters of all nonhydrogen atoms were refined by the method of least squares, using a block-diagonal approximation to the normal equations.

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Table 1(a). Positional and thermal parameters of the non-hydrogen atoms, at the end of the least-squares refinement

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

	X/A	Y/B	Z/C	U11	U22	U33	U12	U13	U23
C(1)	0.04074(41)	0.3278 (11)	0.89888(50)	0.0263(23)	0.0579(38)	0.0437(27)	0.0011(27)	0.0072(20)	0.0045(30)
C(2)	-0.08072(45)	0.3188 (12)	0.89334(54)	0.0341(27)	0.0573(41)	0.0488(30)	0.0020(29)	0.0072(23)	0.0078(32)
C(3)	-0.13275(40)	0.4845 (10)	0.81991(53)	0.0262(23)	0.0415(33)	0.0551(31)	-0.0025(25)	0.0026(21)	-0.0045(29)
C(4)	-0.07162(42)	0.5683 (9)	0.72886(50)	0.0325(25)	0.0354(31)	0.0466(28)	0.0001(24)	0.0002(21)	0.0054(25)
C(5)	0.02525(38)	0.5102 (9)	0.70700(44)	0.0289(22)	0.0345(30)	0.0363(23)	-0.0035(23)	-0.0012(18)	-0.0033(23)
C(6)	0.07783(42)	0.5907 (11)	0.60522(39)	0.0319(25)	0.0539(38)	0.0408(26)	0.0065(27)	0.0053(21)	0.0185(29)
C(7)	0.19755(40)	0.6193 (11)	0.62833(51)	0.0269(24)	0.0497(36)	0.0475(28)	0.0024(25)	0.0059(21)	0.0168(29)
C(8)	0.25117(39)	0.4246 (8)	0.67742(44)	0.0288(23)	0.0395(29)	0.0318(22)	0.0021(23)	0.0040(18)	0.0074(22)
C(9)	0.20304(39)	0.3640 (9)	0.79047(42)	0.0296(24)	0.0394(28)	0.0277(21)	0.0022(22)	0.0023(17)	0.0011(21)
C(10)	0.07985(40)	0.3325 (9)	0.77445(47)	0.0296(24)	0.0381(30)	0.0403(25)	-0.0027(24)	0.0018(20)	-0.0036(26)
C(11)	0.26486(39)	0.1847 (9)	0.84893(44)	0.0301(23)	0.0458(33)	0.0304(22)	0.0043(23)	0.0105(18)	0.0041(23)
C(12)	0.38410(39)	0.2143 (10)	0.87062(47)	0.0274(22)	0.0503(39)	0.0390(25)	0.0030(25)	0.0025(19)	0.0070(27)
C(13)	0.42873(38)	0.2703 (9)	0.75638(43)	0.0296(22)	0.0359(30)	0.0340(23)	0.0033(23)	0.0048(18)	-0.0003(23)
C(14)	0.37121(38)	0.4584 (9)	0.70402(42)	0.0292(22)	0.0365(29)	0.0310(22)	0.0002(22)	0.0041(18)	0.0033(23)
C(15)	0.43680(40)	0.5214 (10)	0.60478(46)	0.0300(23)	0.0502(35)	0.0371(25)	0.0025(26)	0.0085(19)	0.0078(26)
C(16)	0.55120(45)	0.4734 (11)	0.65315(50)	0.0402(28)	0.0500(38)	0.0427(27)	0.0032(28)	0.0153(22)	0.0103(29)
C(17)	0.26434(41)	0.3523 (10)	0.76834(46)	0.0324(25)	0.0438(33)	0.0353(24)	0.0086(26)	0.0076(19)	-0.0026(26)
C(18)	0.42006(46)	0.0868 (10)	0.67269(51)	0.0422(29)	0.0395(33)	0.0458(28)	0.0025(27)	0.0058(23)	-0.0066(28)
C(19)	0.04978(46)	0.1372 (10)	0.70332(56)	0.0411(30)	0.0380(33)	0.0539(32)	-0.0102(27)	-0.0030(24)	-0.0067(28)
C(20)	0.62847(40)	0.1851 (10)	0.78829(53)	0.0277(23)	0.0427(34)	0.0506(29)	0.0028(24)	0.0061(21)	0.0024(27)
C(21)	0.65935(45)	0.1207 (12)	0.91214(55)	0.0373(29)	0.0596(44)	0.0494(31)	0.0129(30)	0.0053(24)	0.0202(33)
O(3)	-0.22292(32)	0.5423 (9)	0.83228(43)	0.0344(20)	0.0713(36)	0.0724(28)	0.0100(24)	0.0129(19)	0.0175(28)
O(11)	0.22434(31)	0.0272 (7)	0.87713(39)	0.0359(19)	0.0489(27)	0.0641(24)	0.0012(20)	0.0083(17)	0.0203(23)
O(17)	0.55577(28)	0.4881 (7)	0.86534(32)	0.0341(18)	0.0447(24)	0.0398(17)	0.0016(18)	0.0028(14)	-0.0100(19)
O(20)	0.66682(38)	0.0973 (9)	0.71070(41)	0.0627(28)	0.0737(37)	0.0561(24)	0.0373(28)	0.0108(21)	-0.0121(27)
O(21)	0.72602(39)	-0.0501 (9)	0.91856(47)	0.0598(28)	0.0665(37)	0.0764(30)	0.0299(28)	0.0110(23)	0.0251(30)
Cl	-0.14500(11)	0.7500 (-)	0.64234(16)	0.0351(6)	0.0578(9)	0.0798(10)	0.0111(7)	0.0045(6)	0.0230(9)

The scattering factors used in the refinement were taken from *International Tables for X-ray Crystallography* (1962). The real part of the anomalous dispersion correction was applied to the chlorine scattering factor. Initially, individual isotropic thermal parameters were used; these were replaced by anisotropic parameters as refinement progressed. When the *R* index (defined as $\sum |F_o - F_c| / \sum |F_o|$) had been reduced to 0.10, a three-dimensional Fourier difference synthesis was computed and the hydrogen atom positions were determined from a 19 point interpolation of 27 of the strongest 33 peaks in the difference map. The hydrogen atoms were held fixed in position and were given an isotropic thermal parameter of 2.0 Å². After a further three cycles of least-squares refinement using a weighing scheme in which

$$\begin{aligned} \sqrt{w} &= 1.0 \text{ for } |F_o| < 20.0 \\ \sqrt{w} &= 20.0/|F_o| \text{ for } |F_o| > 20.0, \end{aligned}$$

the ratio of positional and thermal parameter shifts to the standard deviations of these values was 0.3 or less, and refinement was terminated with the minimization function, $\sum w(|F_o| - |F_c|)^2 / (m - n)$ at 0.70.

While the absolute configuration of the steroid was not determined crystallographically, the material was synthesized from naturally occurring cortisone and Table 1 lists the positional and thermal parameters obtained in this structure analysis corresponding to the naturally occurring enantiomorph. Table 2 lists the comparison between the observed and calculated structure amplitudes for all measured reflections.

Discussion

Steroid geometry

In Fig. 2, all important interatomic distances and angles are given. The average standard deviations for

Table 1(b). Positional parameters of the hydrogen atoms

	X/a	Y/b	Z/c
H(1A)	0.0797	0.4474	0.9333
H(1B)	0.0829	0.2034	0.9329
H(2A)	-0.1083	0.2330	0.8502
H(2B)	-0.1069	0.3722	0.9829
H(6A)	0.0574	0.5095	0.5415
H(6B)	0.0396	0.7004	0.5776
H(7A)	0.2293	0.6766	0.5521
H(7B)	0.2103	0.7365	0.6945
H(8)	0.2449	0.3259	0.6158
H(9)	0.2017	0.4712	0.8475
H(12A)	0.4072	0.3190	0.9290
H(12B)	0.4136	0.1294	0.9227
H(14)	0.3716	0.5613	0.7639
H(15A)	0.4247	0.4363	0.5392
H(15B)	0.4216	0.6501	0.5558
H(16A)	0.5845	0.3856	0.6130
H(16B)	0.5932	0.5528	0.6477
H(18A)	0.4748	0.0241	0.7152
H(18B)	0.3474	0.0430	0.6555
H(18C)	0.4512	0.0555	0.5979
H(O17)	0.6259	0.5154	0.8763
H(19A)	0.0928	0.1517	0.6330
H(19B)	0.0566	0.0437	0.7809
H(21A)	0.6893	0.2467	0.9894
H(21B)	0.6065	0.0950	0.9515
H(O21)	0.7429	-0.1307	0.8392

these dimensions are approximately 0.007 and 0.06 Å for distances to nonhydrogen and to hydrogen atoms, respectively, and 0.5, 3 and 5° for angles of the types C-C-C, C-C-H, and H-C-H. None of these bond lengths is significantly different from those observed in other similar steroids (Cooper & Norton, 1968a; Cooper, Lu & Norton, 1968; Cooper & Norton, 1968b). The elongation of the C-C bonds in the *D* ring is consistent with the strain and intramolecular (van der Waals) interactions in this ring, and has been observed by us in many other instances. The *A*, *B*, and

Table 2. Comparison of the observed structure amplitudes (FOBS) with those calculated (FCAL) from the refined parameters

The values calculated are ten times absolute scale.

Table with multiple columns of numerical data, organized in groups of 10 columns each. Each group has a header row with labels 'H K L FO FC' and a corresponding row of numerical values.

C rings all have chair conformations. The D ring is a distorted half chair (or a very distorted β -envelope), and can be described by the parameters $\Delta=11.2$ and $\varphi_m=48.2^\circ$ (Altona, Geise & Romers, 1968). Least-squares planes through relevant portions of the steroid molecule and interplanar angles are listed in Tables 3(a) and 3(b), respectively. Fig. 3 is a projection of the entire molecule parallel to the least-squares plane through atoms C(5) to C(17) inclusive. As found in other steroids containing the Δ^4 -3-one system, atom O(3) lies considerably below this plane, in this case at a distance of 1.07 Å. Of the eight atoms that could conceivably lie within a plane due to the conjugation

of the Δ^4 -3-one system, atoms C(2), C(3), C(4), C(5), and O(3) are all within 0.015 Å of the plane

$$0.3297x + 0.6902y + 0.6442z = 7.422;^*$$

atoms C(6), C(10), and Cl are -0.14 , -0.11 , and -0.08 Å out of this plane. Influenced by bonding forces in the B ring, atoms C(6), C(10), and C(5) describe a plane which forms an angle of 8.9° with the plane whose equation is given above.

* Equations for least-squares planes are in the form $lx + my + nz = p$, where x , y , z and p are in Å and x , y and z are referred to an orthogonalized coordinate system with $x \parallel \mathbf{a}$, $y \parallel \mathbf{b}$, and $z \parallel \mathbf{a} \times \mathbf{b}$.

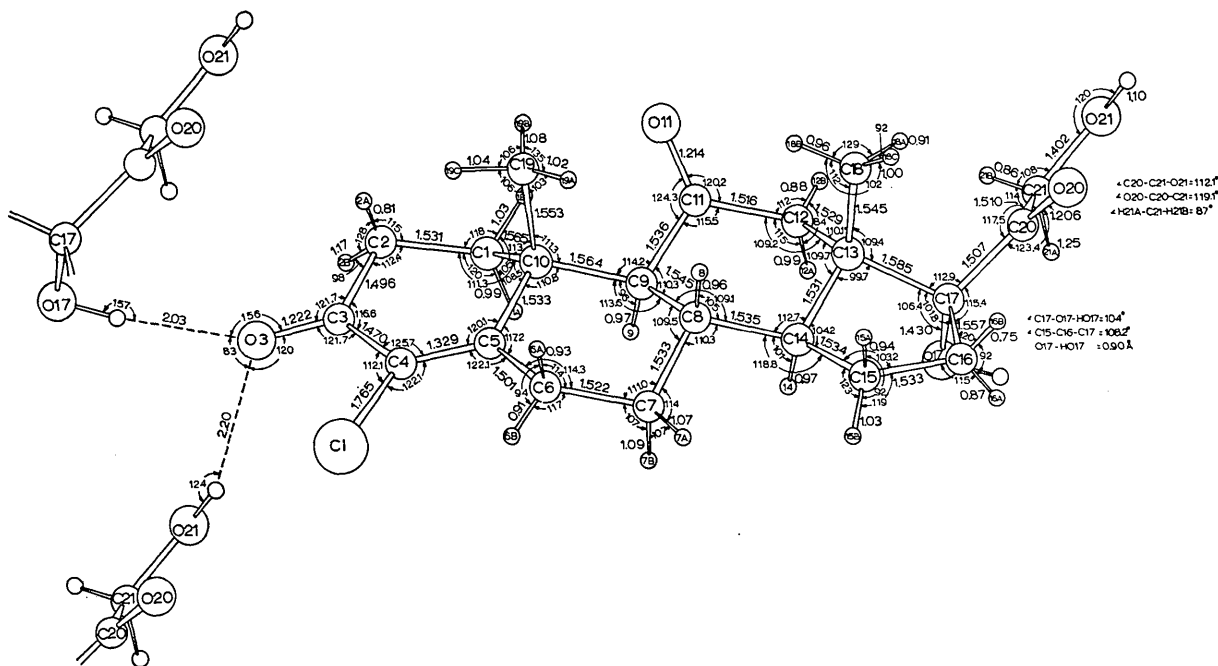


Fig. 2. Summary of interatomic bond distances and angles observed in 4-chlorocortisone. Intermolecular hydrogen bonding in the crystal is also shown.

Table 3(a). Least-squares planes through the atoms

The equations are in the form $lX + mY + nZ = p$ where X , Y , Z and p are expressed in Å units relative to the orthogonal axes parallel to \mathbf{a} , \mathbf{b} and \mathbf{c}^* .

Plane	Atom				
A1	C(2), C(3), C(4)	0.3444	0.6827	0.6445	7.378
A2	C(1), C(2), C(4), C(5)	0.1174	0.8125	0.5710	7.477
A3B1	C(1), C(5), C(6), C(10)	0.6625	0.5959	0.4538	5.560
B2	C(6), C(7), C(9), C(10)	-0.1925	0.7414	0.6428	7.310
B3C1	C(7), C(8), C(9), C(11)	0.6096	0.5954	0.5233	7.276
C2	C(8), C(11), C(12), C(14)	-0.2216	0.7558	0.6162	6.391
C3D1	C(12), C(13), C(14), C(15)	0.5648	0.5965	0.5702	8.698
D2	C(13), C(15), C(16), C(17)	-0.2100	0.7659	0.6077	5.762
D3	C(14), C(15), C(16), C(17)	0.0897	0.8778	0.4706	6.780
A	C(1), C(2), C(3), C(4), C(5), C(10)	0.3029	0.7716	0.5593	6.975
B	C(5), C(6), C(7), C(8), C(9), C(10)	0.0778	0.7432	0.6646	7.729
C	C(8), C(9), C(11), C(12), C(13), C(14)	0.0900	0.7727	0.6283	7.514
D	C(13), C(14), C(15), C(16), C(17)	-0.0094	0.7713	0.6364	7.169
C(1)-C(17)		0.1300	0.7816	0.6101	7.623

Table 3(b). *Interplanar angles*

Plane 1	Plane 2	
A1	A2	164.4°
A3B1	A2	145.2
A3B1	B2	127.3
B3C1	B2	131.3
B3C1	C2	129.6
C3D1	C2	132.6
C3D1	D2	133.2
C3D1	D3	147.4
A	B	165.6
B	C	177.2
C	D	174.3
C(1)-C(17)	100	82.5
C(1)-C(17)	010	38.6
C(1)-C(17)	001	52.4

The torsional angles for the steroid nucleus are given in Table 4. The decreased torsional angles in the *B* ring

indicate flattening of this ring, which is only partially due to the influence of the Δ^4 bond. The primary reason for this flattening is the van der Waals interaction between the chlorine atom at C-4 and hydrogen atom 6*B*. The distance between these two atoms is 2.54 Å compared with the sum of their van der Waals radii of about 2.9 Å. In the *C* ring, the main point of interest is in the conformation of the 11-ketone group. This is best described by the projections shown in Fig. 4, in which it can be seen that atoms C(9), C(11), C(12) and O(11) are almost coplanar, placing O(11) in the expected semi-equatorial configuration.

The shapes and orientations of the thermal vibration ellipsoids (Fig. 5) indicate that the thermal motion of the steroid nucleus is consistent with librational motion about the principal axes of inertia of the nucleus as previously described in detail for the structure of

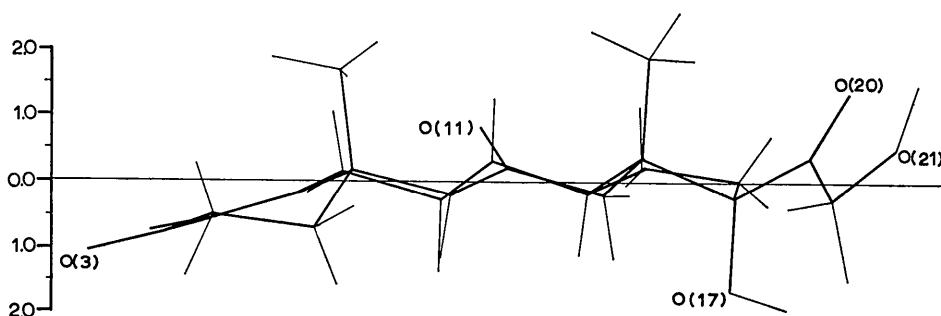


Fig. 3. Projection of the molecule parallel to the least-squares plane through atoms C(5)-C(17). The scale shows the departures (in Å) of the atoms from this plane.

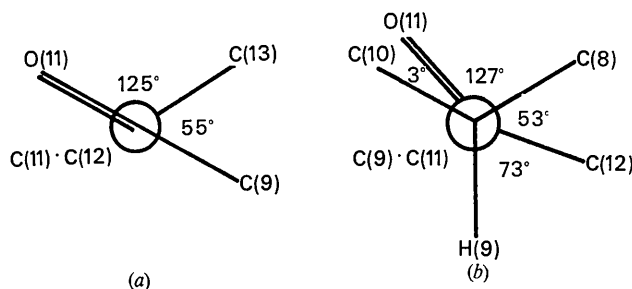


Fig. 4. Conformation of the 11-oxo group in cortisone. (a) Projection along the C(11)-C(12) bond; (b) projection along the C(9)-C(11) bond.

12 α -bromo-11 β -hydroxyprogesterone (Cooper & Norton, 1968*a*). The thermal ellipsoids of the oxygen atoms in the C(17) side chain are noticeably elongated in the direction perpendicular to the planar group C(20), C(21), O(20), O(21).

The C(17) side chain

The conformations of the C(17)-C(20) and C(20)-C(21) bonds are given in Fig. 6. The side chain atoms C(20), C(21), O(20) and O(21) are all within 0.02 Å of the plane

$$0.7867x + 0.6136y + 0.0676z - 6.946 = 0;$$

Table 4. *Torsional angles in the rings*

Ring A		Ring B		Ring C		Ring D	
Bond	$\varphi(A-B)$	Bond	$\varphi(A-B)$	Bond	$\varphi(A-B)$	Bond	$\varphi(A-B)$
C(1)-C(2)	-53.2°	C(5)-C(6)	-44.8°	C(8)-C(9)	-52.2°	C(13)-C(14)	+48.0°
C(2)-C(3)	+25.4	C(6)-C(7)	+52.3	C(9)-C(11)	+53.3	C(14)-C(15)	-36.1
C(3)-C(4)	-0.3	C(7)-C(8)	-58.0	C(11)-C(12)	-54.6	C(15)-C(16)	+9.3
C(4)-C(5)	+4.0	C(8)-C(9)	+57.3	C(12)-C(13)	+55.8	C(16)-C(17)	+19.5
C(5)-C(10)	-31.0	C(9)-C(10)	-47.8	C(13)-C(14)	-60.4	C(13)-C(17)	-40.4
C(1)-C(10)	+54.8	C(5)-C(10)	+41.4	C(8)-C(14)	+58.2		

The sign convention for torsional angles is that of Klyne & Prelog (1960).

$\varphi(A-B)$ is the torsional 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.

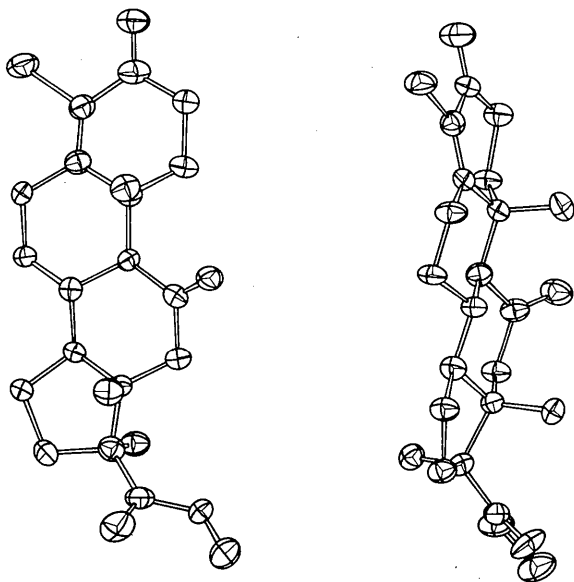


Fig. 5. Two views of the steroid molecule, including the 50% probability thermal vibration ellipsoids of the nonhydrogen atoms.

the O(21) hydroxyl hydrogen HO(21) lies 0.16 Å out of this plane, with a torsion angle C(20)–C(21)–O(21)–HO(21) of 7°. The conformation of the acetyl side chain is in agreement with conclusions drawn from optical rotary dispersion and circular dichroism measurements by Wellman & Djerassi (1965). The 17-hydroxyl group is not coplanar with the acetyl group in conflict with the prediction of planarity based upon molecular orbital calculations (Kier, 1968).

Hydrogen bonding

Intermolecular hydrogen bonding occurs in the cortisone crystals, between O(3) and the 17 α -hydroxyl group of adjacent molecules, as shown in Fig. 2. There is a possibility of very weak hydrogen bonding involving O(3) and the C(21) hydroxyl group of an adjacent molecule, but the geometry of this 'bond', as shown in Fig. 2, is at the limit of acceptable values. There is no intramolecular hydrogen bonding in 4-chlorocortisone. The closest intramolecular oxygen-oxygen approach is between O(20) and O(21), but the O(20)–H(O21)–O(21) angle of 97° is 30° smaller than the minimum required for conventional hydrogen bonding (Donohue, 1968). Even in solution the H(O21) hydrogen atom is sterically hindered from providing a true hydrogen bond between O(20) and O(21).

Fig. 7 shows the steroid stacking pattern and the intermolecular hydrogen bonding scheme viewed along the *c* axis.

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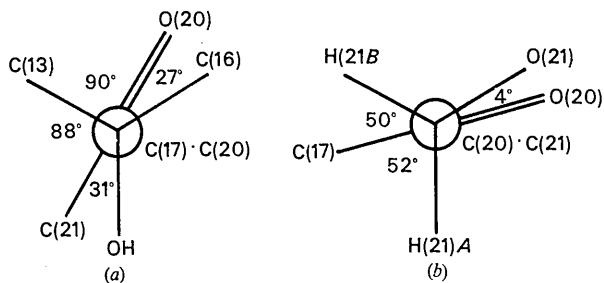


Fig. 6. Conformations in the side chain of cortisone, as determined in this structure investigation. (a) Projection along the C(17)–C(21) bond; (b) projection along the C(20)–C(21) bond.

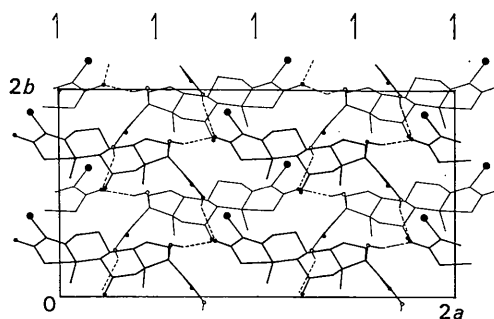


Fig. 7. Projection of four unit cells onto the *a*, *b* plane viewed along the *c* axis.

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