SHORT STRUCTURAL PAPERS

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9α-Methoxycortisol

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Abstract. $C_{22}H_{32}O_6$, orthorhombic, $P2_12_12_1$, $a=13{\cdot}100$ (1), $b=14{\cdot}075$ (1), $c=10{\cdot}658$ (1) Å, $V=1965{\cdot}1$ Å^3, $Z=4$, $M=392{\cdot}5$, $D_c=1{\cdot}33$, $D_m=1{\cdot}35$ g cm^{-3}. The methoxy carbon is in the *anti–syn–syn* position relative to C(8), C(10), and C(11).

Introduction. The crystal structure of 9α-methoxycortisol (9α-methoxy-11β,17α,21-trihydroxy-4-pregnene-3,20-dione) was determined as part of a study of the conformations of 9α-substituted cortisol derivatives. The systematic absences in the diffraction pattern indicated the space group to be $P2_12_12_1$ (D_2^4, No. 19), and the cell constants were determined by a least-squares analysis of the 2θ values of 15 reflections [at 20°C; λ(Cu $K\alpha$) = 1·54178 Å]. Integrated intensities for 2304 independent reflections with $2\theta < 150°$ were measured on an Enraf–Nonius CAD-4 diffractometer using Cu $K\alpha$ radiation. After the Lorentz and polarization corrections $[(1+\cos^2 2\theta)/2 \sin 2\theta]$ had been applied, normalized structure factor amplitudes were computed, and the structure was solved by direct methods (Germain, Main & Woolfson, 1971).

The atomic parameters of 9α-methoxycortisol were refined by full-matrix least-squares calculations. After

Table 1. *Final atomic coordinates and thermal parameters for the nonhydrogen atoms* ($\times 10^4$)

The form of the anisotropic thermal parameter is exp $[-(\beta_{11}h^2+\beta_{12}hk+\cdots)]$. Standard deviations are given in parentheses.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	7804 (3)	8143 (3)	9497 (3)	42 (2)	55 (2)	57 (3)	−30 (4)	13 (4)	−19 (4)
C(2)	7299 (3)	8361 (4)	10751 (4)	45 (2)	61 (3)	81 (3)	−9 (4)	38 (5)	−9 (5)
C(3)	8088 (3)	8439 (3)	11755 (3)	52 (2)	45 (2)	56 (2)	10 (4)	19 (4)	6 (4)
C(4)	9002 (3)	8966 (3)	11407 (3)	40 (2)	45 (2)	41 (2)	−1 (3)	3 (4)	−5 (3)
C(5)	9241 (2)	9194 (2)	10226 (3)	31 (2)	28 (1)	45 (2)	6 (2)	−2 (3)	−6 (3)
C(6)	10119 (3)	9839 (3)	9962 (3)	53 (2)	45 (2)	42 (2)	−40 (3)	6 (4)	−23 (3)
C(7)	10807 (3)	9479 (3)	8904 (3)	34 (2)	38 (2)	59 (3)	−31 (3)	7 (3)	−25 (3)
C(8)	10205 (2)	9176 (2)	7739 (3)	33 (2)	23 (1)	41 (2)	−14 (2)	9 (3)	−9 (3)
C(9)	9350 (2)	8457 (2)	8104 (3)	28 (1)	25 (1)	39 (2)	2 (2)	−1 (3)	−7 (3)
C(10)	8601 (2)	8895 (2)	9111 (3)	30 (1)	27 (1)	37 (2)	−2 (2)	7 (3)	−13 (3)
C(11)	8804 (2)	8055 (2)	6919 (3)	25 (1)	29 (1)	46 (2)	−8 (2)	−3 (3)	−11 (3)
C(12)	9535 (3)	7716 (3)	5886 (3)	35 (2)	38 (2)	41 (2)	−8 (3)	7 (3)	−24 (3)
C(13)	10379 (2)	8437 (2)	5565 (3)	31 (2)	26 (1)	38 (2)	4 (3)	6 (3)	−1 (3)
C(14)	10905 (2)	8726 (2)	6780 (3)	28 (1)	31 (1)	44 (2)	−8 (3)	−1 (3)	−4 (3)
C(15)	11850 (3)	9281 (3)	6335 (4)	33 (2)	44 (2)	73 (3)	−14 (3)	28 (4)	−16 (4)
C(16)	12143 (3)	8783 (3)	5091 (3)	33 (2)	50 (2)	65 (3)	−14 (3)	20 (4)	−13 (4)
C(17)	11313 (2)	8048 (2)	4807 (3)	31 (1)	32 (1)	45 (2)	8 (3)	9 (3)	6 (3)
C(18)	9928 (3)	9296 (3)	4844 (3)	38 (2)	41 (2)	51 (2)	14 (3)	8 (4)	11 (3)
C(19)	8028 (3)	9813 (3)	8688 (3)	52 (2)	49 (2)	56 (2)	32 (4)	4 (4)	−17 (4)
C(20)	11099 (3)	7926 (3)	3405 (3)	37 (2)	42 (2)	48 (2)	21 (3)	10 (4)	−00 (4)
C(21)	10517 (3)	7049 (3)	2985 (3)	53 (2)	62 (2)	46 (2)	−14 (4)	5 (4)	−19 (4)
C(22)	9689 (4)	6722 (3)	8641 (4)	70 (3)	24 (2)	91 (3)	−2 (3)	−14 (5)	3 (4)
O(3)	7954 (3)	8135 (2)	12825 (3)	71 (2)	66 (2)	56 (2)	−3 (3)	44 (3)	15 (3)
O(9)	9900 (2)	7707 (2)	8754 (2)	42 (1)	25 (1)	58 (2)	5 (2)	−15 (3)	8 (2)
O(11)	8141 (2)	8779 (2)	6451 (2)	31 (1)	54 (1)	50 (2)	17 (2)	−14 (2)	−16 (3)
O(17)	11604 (2)	7109 (2)	5209 (2)	40 (1)	33 (1)	52 (2)	24 (2)	−6 (3)	−8 (2)
O(20)	11351 (3)	8503 (3)	2631 (2)	72 (2)	61 (2)	58 (2)	−3 (3)	23 (4)	29 (3)
O(21)	10373 (3)	6997 (2)	1683 (2)	80 (2)	69 (2)	48 (2)	16 (4)	−23 (4)	−31 (3)

three cycles of anisotropic refinement, a Fourier difference map was computed, and the hydrogen atoms were located. The parameters of all atoms including the H atoms were then refined for three final cycles. The weights used were the quantities $(1/\sigma_F^2)$ where σ_F is as defined by Stout & Jensen (1968, equation H. 14) and the instability correction was 0·06 rather than 0·01. The 581 reflections with $|F_o| < 3\sigma_F$ were excluded from the refinement. The R index was defined as $\sum(||F_o| - |F_c||)/\sum|F_o|$, and its final value was 8·2% for all data and 4·6% for the 1723 reflections used in the refinement. The final refined positional and thermal parameters are given in Tables 1 and 2. A list of the structure factors is obtainable.*

Discussion. 9α-Methoxycortisol is a member of a series of cortisol derivatives† whose crystal structures have been analyzed in order to study the effects of 9α-substitution on molecular conformation. The bond distances and angles for 9α-methoxycortisol are given in Fig. 1, and the standard deviations of the distances and angles involving non-hydrogen atoms are in the ranges 0·004–0·006 Å and 0·2–0·3°, respectively. The geometry of the two intermolecular hydrogen bonds is also illustrated. Endocyclic torsion angles are shown in Fig. 2.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31335 (12 pp., 1 microfiche). Copies may be obtained from The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

† Cortisol: Roberts, Coppola, Isaacs & Kennard (1973); 9α-fluorocortisol: Dupont, Dideberg & Campsteyn (1972) and Weeks, Duax & Wolff (1973); 9α-bromocortisol: Weeks & Duax (1973); 9α-chlorocortisol: Weeks, Duax & Wolff (1974).

The 9α-region of cortisol is surrounded by the α-axial H atoms bonded to C(1), C(7), C(12), and C(14), and the 9α-substituent has close nonbonded contacts

Table 2. *Final atomic coordinates* ($\times 10^3$) *and thermal parameters* ($\times 10$) *for the hydrogen atoms*

	x	y	z	B_{iso}
H(1*A*)	806 (4)	743 (4)	945 (4)	56 (14)
H(1*B*)	721 (3)	810 (3)	890 (4)	24 (8)
H(2*A*)	683 (3)	785 (3)	1087 (3)	10 (6)
H(2*B*)	695 (4)	910 (4)	1079 (4)	42 (11)
H(4)	939 (4)	918 (4)	1208 (5)	53 (13)
H(6*A*)	1037 (4)	994 (4)	1073 (4)	56 (14)
H(6*B*)	979 (3)	1048 (3)	970 (3)	14 (6)
H(7*A*)	1116 (4)	899 (4)	910 (4)	36 (10)
H(7*B*)	1124 (3)	991 (3)	862 (4)	28 (9)
H(8*B*)	985 (4)	978 (4)	734 (4)	30 (10)
H(11*A*)	829 (4)	747 (4)	706 (4)	32 (10)
H(12*A*)	995 (3)	707 (3)	611 (3)	11 (6)
H(12*B*)	918 (3)	768 (3)	519 (4)	33 (9)
H(14*A*)	1109 (4)	814 (3)	712 (4)	33 (11)
H(15*A*)	1273 (5)	921 (5)	684 (6)	87 (20)
H(15*B*)	1161 (4)	999 (4)	605 (4)	39 (11)
H(16*A*)	1284 (4)	845 (4)	521 (4)	38 (10)
H(16*B*)	1232 (4)	918 (4)	443 (5)	58 (15)
H(18*A*)	939 (4)	963 (5)	548 (4)	56 (13)
H(18*B*)	1046 (4)	969 (4)	453 (4)	39 (11)
H(18*C*)	940 (4)	916 (4)	404 (4)	33 (11)
H(19*A*)	781 (3)	1019 (3)	939 (4)	33 (10)
H(19*B*)	848 (3)	1034 (3)	832 (3)	20 (7)
H(19*C*)	755 (4)	981 (4)	803 (4)	40 (11)
H(21*B*)	1086 (4)	645 (4)	331 (4)	34 (9)
H(21*C*)	988 (4)	692 (3)	337 (5)	41 (11)
H(22*A*)	993 (4)	644 (4)	950 (4)	38 (10)
H(22*B*)	891 (5)	662 (5)	836 (7)	76 (16)
H(22*C*)	998 (5)	646 (4)	790 (4)	44 (12)
H(110)	780 (4)	856 (4)	586 (4)	40 (10)
H(170)	1194 (4)	711 (4)	595 (5)	40 (12)
H(210)	1047 (4)	759 (4)	137 (5)	40 (12)

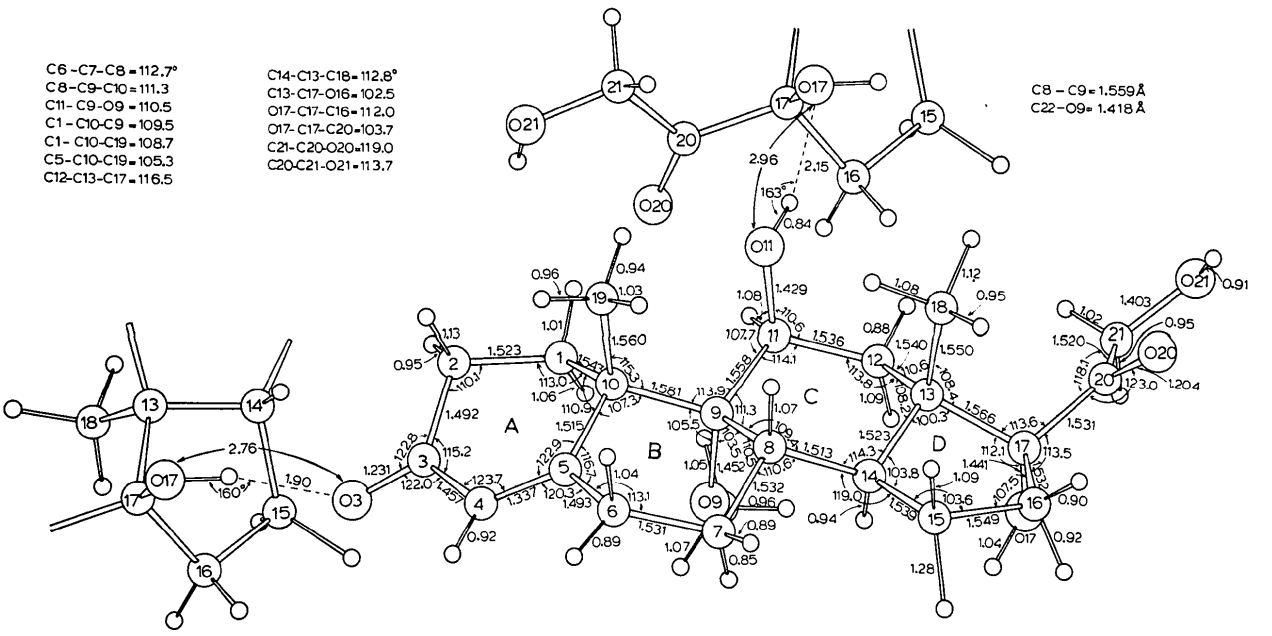

Fig. 1. Interatomic bond distances and angles in 9α-methoxycortisol. Intermolecular hydrogen bonding is also illustrated.

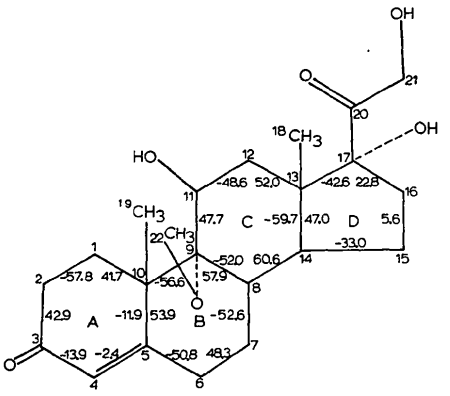

Fig. 2. Endocyclic torsion angles. A torsion angle α–β–γ–δ is positive if, when viewed down the β–γ bond, the α–β bond will eclipse the γ–δ bond when rotated less than 180° in a clockwise direction.

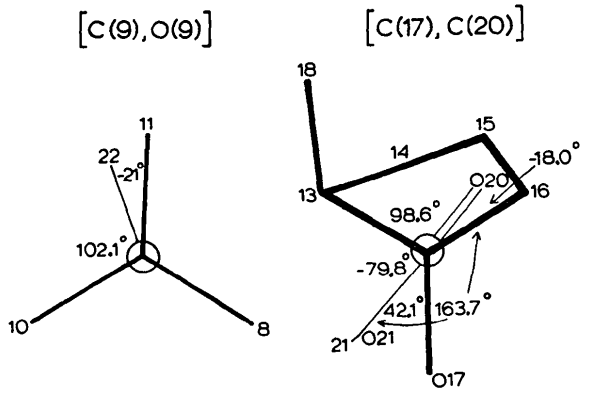

Fig. 3. Newman projections. (*a*) [C(9), O(9)], (*b*) [C(17), C(20)].

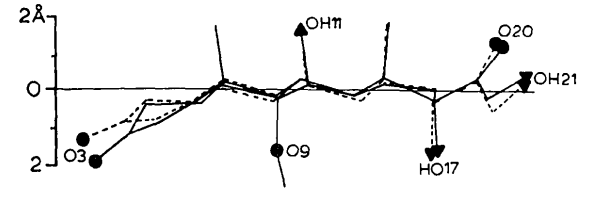

Fig. 4. The 9α-methoxycortisol (——) and cortisol (– – – –) structures are seen in a projection parallel to a plane passed through atoms C(5) to C(17) inclusive.

with these H atoms. In 9α-methoxycortisol, this nonbonded strain is alleviated by the positioning of the methoxy carbon, C(22), in the *anti–syn–syn* position relative to C(8), C(10), and C(11) as illustrated in Fig. 3(*a*). The valency angle C(9)–O(9)–C(22) has the unusually large value of 125°, and this also helps to reduce unfavorable nonbonded interactions involving C(22). The average C–O–C angle for 25 methoxy substituents in 22 steroid structures is 115·5°. There are no exceptionally small endocyclic torsion angles in the *B*- and *C*-rings such as the angles C(5)–C(6)–C(7)–C(8) = 38·4° and C(8)–C(9)–C(11)–C(12) = 39·3° observed in 9α-chlorocortisol. Endocyclic torsion angles in saturated steroid rings are normally in the range 50–55° (Duax & Norton, 1975). The *A*-ring is bent beneath the plane of the *B*-, *C*-, and *D*-rings considerably more than it is in cortisol (Fig. 4). This aspect of the 9α-methoxycortisol conformation resembles the 9α-fluorocortisol conformation.

The 17β side chain has the orientation normally observed in corticoid structures (Weeks, Duax & Wolff, 1973). Atoms O(20) and O(21) are *cis* coplanar [torsion angle O(20)–C(20)–C(21)–O(21) = 2·5°], and O(20) is situated over the *D*-ring [Fig. 3(*b*)]. This orientation is in agreement with solution spectral measurements (Wellman & Djerassi, 1965).

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