hexopyranosyl rings. The 4′-OH [C5′*A*—C4′*A*—O4′*A*—H6*A* = −8 (1) and C5′*B*—C4′*B*—O4′*B*—H6*B* = 30 (2)°] and 3″-OH (C4″*A*—C3″*A*—O3″*A*—H13*A* = 93·1 (8) and C4″*B*—C3″*B*—O3″*B*—H13*B* = 74·9 (7)°] torsion angles are moderately different. The largest difference in torsion angles occurs with the 4″-hydroxyls [C5″*A*—C4″*A*—O4″*A*—H15*A* = 128·4 (7) and C5″*B*—C4″*B*—O4″*B*—H15*B* = 64·6 (8)°].

Intermolecular hydrogen bonding (Table 3) occurs between O3″*A* and O3″*B* [O3″*B*···O3″*A* = 2·80 (1) Å and 150°] of the two independent molecules. In addition, hydrogen bonding occurs between the ketonic O atom O4*A* and the phenolic O atom O4′*B* [O4′*B*···O4*A* = 2·67 (1) Å and 179°] and between the ketonic O atom O4*B* and the hydroxyl O atom O4″*A* [O4″*A*···O4*B* = 2·81 (1) Å and 150°]. There is also a network of hydrogen-bonding interactions between the aciculatin molecules and the water molecules which stabilizes the crystal lattice.

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Structure of Cortivazol, 11β,17α,21-Trihydroxy-6,16α-dimethyl-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazol-20-one 21-Acetate

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Abstract. $C_{32}H_{38}N_2O_5$, $M_r = 530{\cdot}7$, monoclinic, *C*2, $a = 30{\cdot}625$ (5), $b = 6{\cdot}229$ (2), $c = 15{\cdot}289$ (2) Å, $\beta = 93{\cdot}86$ (2)°, $V = 2909{\cdot}8$ Å^3, $Z = 4$, $D_x = 1{\cdot}211$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 6{\cdot}2$ cm^{-1}, $F(000) = 1136$, $T = 292$ K, final $R = 0{\cdot}047$ for 2415 reflections with $I > 2{\cdot}5\sigma(I)$. All bond lengths and angles are within normal limits. Ring *A* with two double bonds is not planar, but is in the 1α,10β half-chair conformation. Ring *B* is in a 9α,10β half-chair conformation distorted towards a 9α sofa. Ring *C* is in the expected chair conformation, whereas ring *D* is in the 13β envelope conformation. The C20, C26, C27 and N29 substituents are equatorial, O11, C18 and C19 are β axial, and O17 and C25 are α axial. Rings *C* and *D*

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and their substituents (except for the C19 on cortivazol) of dexamethasone, dexamethasone acetate and cortivazol are superimposable on each other with an r.m.s. difference of 0·031 Å. The torsion angles of the *A*/*B* ring junction of cortivazol are −33·3/34·6°, whereas the angles of the same junction in dexamethasone and dexamethasone acetate are −5·1/55·4 and −3·5/54·5°, respectively. There are no significant differences in the *B*/*C* and *C*/*D* ring junctions. This means that the steroid skeleton of cortivazol is slightly bent towards the α face at a lesser angle than that found in dexamethasone and dexamethasone acetate. It is suggested that instead of the 3-keto group, it is the accessibility of the α and β faces of rings *B*, *C* and *D*, as well as the bending and twisting of the molecule which may be the predominant factors that determine the activity and binding specificity of the glucocorticoid to the appropriate receptor.

Introduction. Studies have shown that for a compound to possess glucocorticoid activity, the 3-keto and Δ^4 double bond of the pregn-4-ene-11β-ol-3,20-dione moieties must be present (Goldstein, Aronow & Kalman, 1974; Liddle, 1974). Duax, Griffin, Weeks & Wawrzak (1988) reported that the glucocorticoid receptor prefers a 4-en-3-one *A* ring that is bowed toward the α face of the steroid skeleton. This is seen in structures such as dexamethasone (9α-fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione) which have a 9α-fluoro substituent or an additional unsaturation at C1—C2 (Duax *et al.*, 1988). Cortivasol 11β,17α,21-trihydroxy-6,16α-dimethyl-2′-phenyl-2′*H*-pregna-2,4,6-trieno-[3,2-*c*]pyrazol-20-one 21-acetate and its derivative, deacylcortivasol, are glucocorticoid compounds whose structural formulae would indicate that these molecules, which have a phenylpyrazole ring fused to the *A* ring in lieu of the usual 3-keto group, would not be active, nor would they bind to the glucocorticoid receptor. However, it has been shown that cortivazol and deacylcortivazol are more effective than dexamethasone in terms of cytotoxicity, glutamine synthetase induction and binding to the steriod receptor (Dausse, Duval, Meyer, Gaignault, Marchandeau & Raynaud, 1977; Harmon, Schmidt & Thompson, 1981; Simons, Thompson & Johnson, 1979; Steelman, Morgan & Glitzer, 1971). Spence, Coghlan, Denton, Mills, Whitworth & Scoggins (1986) confirmed that the 3-keto group is not essential for glucocorticoid activity if the remainder of the typical 4-pregnene-3,20-dione nucleus is present. In addition, Thompson, Srivastava & Johnson (1989) showed that cortivazol binds to glucocorticoid receptors. Since the cortivazol structural formulae and its activities are in direct contrast to the current concept of glucocorticoid structure/function, it was decided to determine the crystal structure of cortivazol in order to establish a three-dimensional structural basis for its activity. In conjunction with the three-dimensional structures of dexamethasone (Rohrer & Duax, 1977) and dexamethasone acetate (Terzis & Theophanides, 1975), the additional three-dimensional structural data of cortivazol may also provide some insight into the nature of the binding region of the glucocorticoid receptor.

Experimental. Colorless needle-shaped crystals (from ethanol), 0·08 × 0·15 × 0·90 mm; Enraf–Nonius CAD-4 diffractometer, cell parameters from 2θ values for 25 reflections from least-squares refinement with $8 < 2\theta < 24°$; ω–2θ scan, width (0·80 + 0·15tanθ)°; $[(\sin\theta)/\lambda]_{max} = 0{\cdot}6097$ Å^{-1}; $-37 \le h \le 37$, $-7 \le k \le 0$, $-18 \le l \le 8$; intensities of three standard reflections monitored every 3600 s showed neither radiation decay nor significant variation; 6053 total, 3003 unique reflections measured, 2415 reflections with $I > 2{\cdot}5\sigma(I)$, $R_{int} = 0{\cdot}043$; Lp corrections; structure solved by direct-methods program *SHELXS*86 (Sheldrick, 1985) modified for the IBM PC/AT microcomputer; full-matrix least squares minimizing $\sum w(F_o - F_c)^2$, $w = 4F_o^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2) = [\sigma_o^2(F_o^2) + (pF_o^2)^2]$, $p = 0{\cdot}04$; min. and max. absorption correction of 0·764 and 1·704, respectively, using program *DIFABS* (Walker & Stuart, 1983); final $R = 0{\cdot}047$, $wR = 0{\cdot}053$; all H atoms from ΔF map and refined isotropically; 504 total variables; secondary-extinction correction, $g = 1{\cdot}2\,(3) \times 10^{-6}$ (Stout & Jensen, 1968); $S = 1{\cdot}317$, max. $\Delta/\sigma = 0{\cdot}04$ for non-H atoms, 0·08 for H atoms; no significant features in final ΔF synthesis with max. and min. $\Delta\rho = 0{\cdot}15\,(4)$ and $-0{\cdot}24\,(4)$ e Å^{-3}, respectively; atomic scattering factors, f' and f'', from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.3.1); all refinement calculations with a DEC PDP 11/44 computer using the Enraf–Nonius *SDP-Plus* package (Frenz, 1985). Molecular modelling studies performed on the IBM PC/AT using the *ALCHEMY*II program (Tripos Associates, 1988).

Discussion. Table 1* lists the fractional atomic coordinates of the non-H atoms and isotropic thermal parameters. Table 2 shows the bond lengths, bond angles and torsion angles of the non-H atoms, which are within the range of expected values (Duax & Norton, 1975; Griffin, Duax & Weeks, 1984). Two orthogonal perspective views showing the structure

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, bond lengths and angles involving H atoms, torsion angles and least-squares-planes calculations have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54295 (20 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional and equivalent isotropic thermal parameters*

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}(Å^2)
C1	0·20944 (8)	0·3842 (5)	0·2242 (2)	4·77 (5)
C2	0·16972 (8)	0·3981 (6)	0·2770 (2)	5·25 (6)
C3	0·17012 (8)	0·5370 (5)	0·3467 (2)	5·04 (6)
C4	0·20648 (9)	0·6743 (6)	0·3710 (2)	5·01 (6)
C5	0·23821 (8)	0·7020 (5)	0·3144 (2)	4·44 (5)
C6	0·27475 (9)	0·8496 (6)	0·3340 (2)	5·35 (6)
C7	0·30572 (9)	0·8807 (5)	0·2773 (2)	5·24 (6)
C8	0·30827 (8)	0·7648 (5)	0·1924 (2)	4·22 (5)
C9	0·28038 (7)	0·5606 (4)	0·1924 (2)	3·84 (5)
C10	0·23370 (7)	0·600	0·2229 (2)	3·99 (5)
C11	0·28336 (7)	0·4266 (5)	0·1084 (2)	4·38 (5)
O11	0·25793 (5)	0·5281 (4)	0·0360 (1)	5·69 (5)
C12	0·33069 (7)	0·3869 (5)	0·0857 (2)	4·43 (5)
C13	0·35865 (7)	0·5909 (5)	0·0865 (2)	4·16 (5)
C14	0·35522 (8)	0·6982 (5)	0·1767 (2)	4·26 (5)
C15	0·39167 (8)	0·8656 (6)	0·1815 (2)	5·74 (7)
C16	0·42811 (8)	0·7716 (5)	0·1296 (2)	4·95 (6)
C17	0·40967 (7)	0·5587 (5)	0·0896 (2)	4·27 (5)
O17	0·41932 (5)	0·3750 (3)	0·1430 (1)	4·80 (4)
C18	0·34466 (9)	0·7416 (6)	0·0096 (2)	5·59 (6)
C19	0·20632 (8)	0·7596 (5)	0·1649 (2)	4·55 (5)
C20	0·42459 (8)	0·5121 (5)	−0·0031 (2)	4·78 (6)
O20	0·43663 (7)	0·6533 (4)	−0·0509 (1)	6·55 (5)
C21	0·42256 (8)	0·2828 (6)	−0·0349 (2)	5·70 (7)
O22	0·42085 (5)	0·2766 (5)	−0·1285 (1)	6·31 (5)
C23	0·45896 (8)	0·2757 (6)	−0·1646 (2)	5·51 (6)
O23	0·49340 (6)	0·2647 (4)	−0·1224 (1)	6·01 (5)
C24	0·4539 (1)	0·290 (1)	−0·2619 (2)	8·2 (1)
C25	0·47141 (9)	0·7466 (6)	0·1839 (2)	6·32 (7)
C26	0·2763 (1)	0·9769 (8)	0·4181 (2)	8·29 (9)
C27	0·1300 (1)	0·2901 (8)	0·2763 (2)	7·10 (8)
N28	0·10636 (8)	0·3554 (6)	0·3420 (2)	7·18 (7)
N29	0·13125 (8)	0·5071 (5)	0·3845 (2)	5·86 (6)
C30	0·11446 (9)	0·6123 (7)	0·4589 (2)	6·46 (8)
C31	0·1267 (1)	0·8166 (8)	0·4813 (2)	7·50 (9)
C32	0·1123 (1)	0·909 (1)	0·5584 (3)	10·4 (1)
C33	0·0857 (2)	0·793 (1)	0·6086 (3)	11·0 (1)
C34	0·0718 (1)	0·599 (1)	0·5832 (3)	10·7 (1)
C35	0·0867 (1)	0·4950 (9)	0·5090 (2)	8·4 (1)

of the molecule are given in Fig. 1. The packing of the molecules is shown in Fig. 2. Most intermolecular distances correspond to normal van der Waals interactions. There is a single intermolecular hydrogen bond of 2·798 (3) Å between the hydroxy O17 and the carbonyl O23 of the molecule at $1-x$, y, $-z$. There is a weak interaction, 3·328 (1) Å, between the hydroxy O11 atom and the O11 of molecules at $\frac{1}{2}-x$, $y-\frac{1}{2}$, $-z$ and at $\frac{1}{2}-x$, $\frac{1}{2}+y$, $-z$. The only intramolecular interaction occurs between the carbonyl O atoms O20 and O23 [3·215 (4) Å]. There are no other significant inter- or intramolecular contacts.

Steroid ring *A* (C1, C2, C3, C4, C5, C10) contains two double bonds and is fused to the planar pyrazole ring. The ring is not planar as C1 is below (α) (−0·273 Å) and C10 is above (β) (0·330 Å) the plane defined by C2, C3, C4 and C5. The asymmetry parameters defined by Duax & Norton (1975) for ring *A* are $\Delta C_2^{1,10} = 2{\cdot}7$, $\Delta C_s^1 = 22{\cdot}5$, and $\Delta C_s^2 = 41{\cdot}1°$. $\langle\tau\rangle$ is 21·2°. The predominance of the rotational symmetry parameter indicates that the conformation of ring *A* is 1α,10β-half-chair. Ring *B* (C5, C6, C7, C8, C9, C10) adopts a distorted half-chair conformation, largely because of the unsaturated

Table 2. *Bond distances* (Å), *angles* (°) *and torsion angles* (°)

C1	C2	1·508 (4)		C13	C18	1·542 (4)	
C1	C10	1·536 (4)		C14	C15	1·526 (4)	
C2	C3	1·371 (5)		C15	C16	1·529 (5)	
C2	C27	1·389 (5)		C16	C17	1·551 (5)	
C3	C4	1·433 (5)		C16	C25	1·524 (5)	
C3	N29	1·371 (4)		C17	O17	1·425 (3)	
C4	C5	1·355 (4)		C17	C20	1·546 (4)	
C5	C6	1·464 (4)		C20	O20	1·216 (4)	
C5	C10	1·536 (4)		C20	C21	1·508 (6)	
C6	C7	1·341 (4)		C21	O22	1·428 (4)	
C6	C26	1·509 (5)		O22	C23	1·324 (3)	
C7	C8	1·493 (4)		C23	O23	1·200 (3)	
C8	C9	1·532 (4)		C23	C24	1·489 (6)	
C8	C14	1·530 (4)		C27	N28	1·341 (5)	
C9	C10	1·552 (3)		N28	N29	1·353 (5)	
C9	C11	1·539 (4)		N29	C30	1·438 (5)	
C10	C19	1·542 (4)		C30	C31	1·363 (7)	
C11	O11	1·455 (4)		C30	C35	1·390 (7)	
C11	C12	1·534 (4)		C31	C32	1·408 (7)	
C12	C13	1·532 (4)		C32	C33	1·36 (1)	
C13	C14	1·543 (4)		C33	C34	1·33 (1)	
C13	C17	1·573 (4)		C34	C35	1·41 (1)	

C2	C1	C10	111·4 (3)	C17	C13	C18	109·1 (2)
C1	C2	C3	119·2 (3)	C8	C14	C13	112·2 (2)
C1	C2	C27	134·9 (3)	C8	C14	C15	120·0 (3)
C3	C2	C27	105·9 (3)	C13	C14	C15	104·2 (2)
C2	C3	C4	123·0 (2)	C14	C15	C16	105·8 (3)
C2	C3	N29	106·2 (3)	C15	C16	C17	105·8 (2)
C4	C3	N29	130·8 (3)	C15	C16	C25	113·3 (3)
C3	C4	C5	119·3 (3)	C17	C16	C25	114·1 (3)
C4	C5	C6	121·4 (3)	C13	C17	C16	103·8 (2)
C4	C5	C10	120·4 (3)	C13	C17	O17	106·8 (2)
C6	C5	C10	117·8 (2)	C13	C17	C20	110·5 (2)
C5	C6	C7	121·6 (3)	C16	C17	O17	113·9 (2)
C5	C6	C26	118·9 (3)	C16	C17	C20	113·6 (2)
C7	C6	C26	119·5 (3)	O17	C17	C20	108·1 (2)
C6	C7	C8	125·0 (3)	C17	C20	O20	122·3 (3)
C7	C8	C9	109·8 (2)	C17	C20	C21	117·7 (3)
C7	C8	C14	111·8 (2)	O20	C20	C21	119·9 (3)
C9	C8	C14	107·8 (2)	C20	C21	O22	110·3 (3)
C8	C9	C10	113·2 (2)	C21	O22	C23	116·3 (2)
C8	C9	C11	112·6 (2)	O22	C23	O23	122·9 (3)
C10	C9	C11	116·3 (2)	O22	C23	C24	112·4 (3)
C1	C10	C5	111·4 (2)	O23	C23	C24	124·8 (3)
C1	C10	C9	108·8 (2)	C2	C27	N28	111·3 (4)
C1	C10	C19	109·1 (3)	C27	N28	N29	104·9 (3)
C5	C10	C9	108·1 (2)	C3	N29	N28	111·7 (3)
C5	C10	C19	105·6 (2)	C3	N29	C30	129·7 (4)
C9	C10	C19	113·9 (2)	N28	N29	C30	118·6 (3)
C9	C11	O11	110·0 (2)	N29	C30	C31	121·1 (4)
C9	C11	C12	112·8 (2)	N29	C30	C35	117·5 (5)
O11	C11	C12	111·3 (2)	C31	C30	C35	121·4 (5)
C11	C12	C13	113·6 (2)	C30	C31	C32	119·6 (6)
C12	C13	C14	107·1 (2)	C31	C32	C33	119·3 (8)
C12	C13	C17	116·6 (2)	C32	C33	C34	120·4 (6)
C12	C13	C18	111·9 (3)	C33	C34	C35	122·7 (7)
C14	C13	C17	98·9 (2)	C30	C35	C34	116·4 (7)
C14	C13	C18	112·7 (3)				

C10	C1	C2	C3	−30·8 (4)	C11	C12	C13	C17	163·7 (2)
C10	C1	C2	C27	153·4 (4)	C11	C12	C13	C18	−69·9 (3)
C2	C1	C10	C5	44·4 (3)	C12	C13	C14	C8	−62·0 (3)
C2	C1	C10	C9	163·4 (2)	C12	C13	C14	C15	166·8 (2)
C2	C1	C10	C19	−71·8 (2)	C17	C13	C14	C8	176·5 (2)
C1	C2	C3	C4	1·3 (4)	C17	C13	C14	C15	45·2 (3)
C1	C2	C3	N29	−176·9 (3)	C18	C13	C14	C8	61·5 (3)
C27	C2	C3	C4	178·2 (3)	C18	C13	C14	C15	−69·8 (3)
C27	C2	C3	N29	0·1 (4)	C12	C13	C17	C16	−156·2 (2)
C1	C2	C27	N28	176·0 (3)	C12	C13	C17	O17	−35·6 (3)
C3	C2	C27	N28	−0·3 (4)	C12	C13	C17	C20	81·7 (3)
C2	C3	C4	C5	13·5 (5)	C14	C13	C17	C16	−41·9 (2)
N29	C3	C4	C5	−168·9 (3)	C14	C13	C17	O17	78·8 (2)
C2	C3	N29	N28	0·1 (4)	C14	C13	C17	C20	−163·9 (2)
C2	C3	N29	C30	−179·3 (3)	C18	C13	C17	C16	76·0 (3)
C4	C3	N29	N28	−177·8 (3)	C18	C13	C17	O17	−163·4 (2)
C4	C3	N29	C30	2·8 (6)	C18	C13	C17	C20	−46·1 (3)
C3	C4	C5	C6	176·6 (3)	C8	C14	C15	C16	−158·5 (2)
C3	C4	C5	C10	4·2 (4)	C13	C14	C15	C16	−31·9 (3)
C4	C5	C6	C7	−178·6 (3)	C14	C15	C16	C17	4·6 (3)
C4	C5	C6	C26	−1·5 (5)	C14	C15	C16	C25	−121·1 (3)
C10	C5	C6	C7	−6·0 (4)	C15	C16	C17	C13	23·6 (3)
C10	C5	C6	C26	171·1 (3)	C15	C16	C17	O17	−92·0 (2)
C4	C5	C10	C1	−33·3 (3)	C15	C16	C17	C20	143·6 (2)
C4	C5	C10	C9	−152·8 (3)	C25	C16	C17	C13	148·8 (2)

Table 2 (*cont.*)

C4	C5	C10	C19	85·0 (3)	C25	C16	C17	O17	33·2 (3)
C6	C5	C10	C1	154·1 (2)	C25	C16	C17	C20	−91·2 (3)
C6	C5	C10	C9	34·6 (3)	C13	C17	C20	O20	93·1 (3)
C6	C5	C10	C19	−87·6 (3)	C13	C17	C20	C21	−85·1 (3)
C5	C6	C7	C8	−3·4 (5)	C16	C17	C20	O20	−23·0 (3)
C26	C6	C7	C8	179·5 (3)	C16	C17	C20	C21	158·8 (2)
C6	C7	C8	C9	−18·0 (4)	O17	C17	C20	O20	−150·5 (2)
C6	C7	C8	C14	−137·6 (3)	O17	C17	C20	C21	31·4 (3)
C7	C8	C9	C10	48·4 (3)	C17	C20	C21	O22	157·8 (2)
C7	C8	C9	C11	−177·1 (2)	O20	C20	C21	O22	−20·4 (3)
C14	C8	C9	C10	170·4 (2)	C20	C21	O22	C23	87·7 (3)
C14	C8	C9	C11	−55·0 (2)	C21	O22	C23	O23	5·4 (5)
C7	C8	C14	C13	−176·4 (2)	C21	O22	C23	C24	−174·6 (4)
C7	C8	C14	C15	−53·6 (3)	C2	C27	N28	N29	0·3 (4)
C9	C8	C14	C13	62·8 (3)	C27	N28	N29	C3	−0·3 (4)
C9	C8	C14	C15	−174·4 (2)	C27	N28	N29	C30	179·2 (3)
C8	C9	C10	C1	−177·6 (2)	C3	N29	C30	C31	27·7 (5)
C8	C9	C10	C5	−56·5 (2)	C3	N29	C30	C35	−149·9 (3)
C8	C9	C10	C19	60·5 (2)	N28	N29	C30	C31	−151·7 (3)
C11	C9	C10	C1	49·6 (3)	N28	N29	C30	C35	30·8 (4)
C11	C9	C10	C5	170·7 (2)	N29	C30	C31	C32	−175·1 (3)
C11	C9	C10	C19	−72·4 (3)	C35	C30	C31	C32	2·4 (5)
C8	C9	C11	O11	−75·1 (2)	N29	C30	C35	C34	178·0 (3)
C8	C9	C11	C12	49·6 (3)	C31	C30	C35	C34	0·5 (5)
C10	C9	C11	O11	57·9 (3)	C30	C31	C32	C33	−1·2 (6)
C10	C9	C11	C12	−177·3 (2)	C31	C32	C33	C34	−2·9 (7)
C9	C11	C12	C13	49·6 (3)	C32	C33	C34	C35	6·1 (8)
O11	C11	C12	C13	74·4 (3)	C33	C34	C35	C30	−4·8 (7)
C11	C12	C13	C14	54·1 (3)					

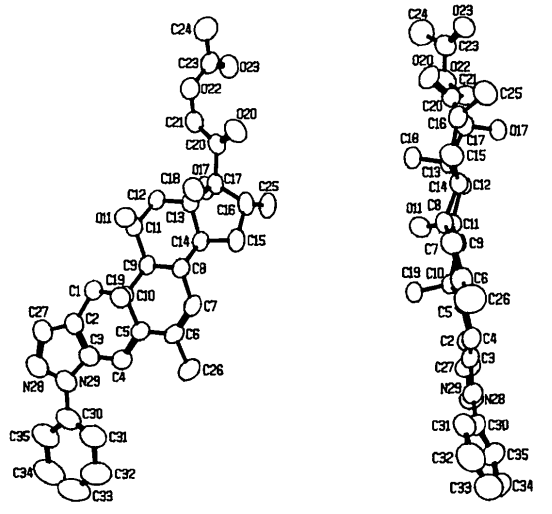


Fig. 1. Two orthogonal views of the molecular structure of cortivazol in the asymmetric unit showing the numbering scheme and the thermal vibration ellipsoids of the non-H atoms. The thick lines denote the double bonds.

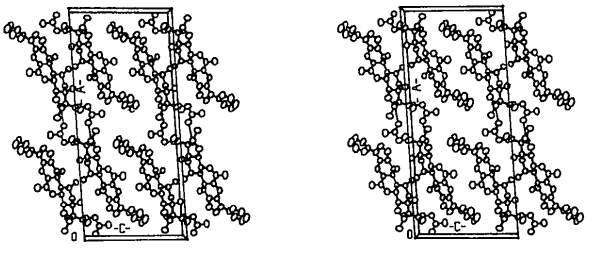


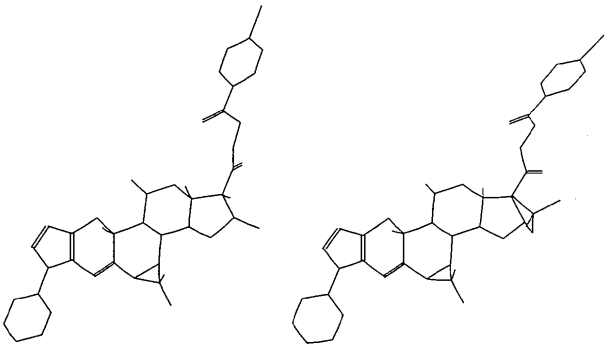
Fig. 2. Stereoview along the *b* axis showing the molecular packing. Thin lines depict the hydrogen bond between O17 and O23 of molecule at $1-x, y, -z$.

C4—C5 and C6—C7 bonds. C9 is below the C5—C6—C7—C8 plane (−0·504 Å) and C10 is above by 0·201 Å. The asymmetry parameters are $\Delta C_2^{6,7}$ = 12·9, ΔC_s^{6} = 12·0, and ΔC_s^{5} = 42·2°, with $\langle\tau\rangle$ = 27·8°. These data indicate that ring *B* is distorted from the C9α,C10β half-chair conformation ($\Delta C_2 = 0°$) towards a C9α sofa. Ring *C* (C8, C9, C11, C12, C13, C14) does not have any unusual substituents and assumes the commonly found chair conformation ($\Delta C_2^{9,11}$ = 5·9, ΔC_s^{11} = 1·2°, $\langle\tau\rangle$ = 55·5°). The *D*-ring (C13, C14, C15, C16, C17) pseudo-rotation parameter (Altona, Geise & Romers, 1968), Δ = 29·3°, is near that of a 13β envelope conformation (Δ = 35·0°). This is consistent with the finding by Duax, Weeks & Rohrer (1976) that the other steroid *D* rings which have all sp^3 hybrid C atoms have conformations between 13β,14α half-chair (Δ = 0·0°) and 13β envelope.

The conformation of the C17β acetylacetate side chain is unusual only in the C20—C21—O22—C23 torsion angle (Table 2). The positive torsion angle points the carbonyl O23 in the direction of the hydroxyl O17 of the symmetry-related molecule to form the intermolecular hydrogen bond in an end-to-end fashion in the crystal (Fig. 2). Of the ten pregnanes containing a 21-acetate moiety tabulated in the *Atlas of Steroid Structure* (Duax & Norton, 1975; Griffin *et al.*, 1984), nine have a C20—C21—O22—C23 torsion angle in the range −70·8 to −106·2° (average −84·2 ± 13·7°). Only 4α,6,7α-trichloro-3,11,20-trioxo-5-pregnene-17,21-diol 21-acetate has a positive C20—C21—O22—C23 torsion angle (95·0°) (Kierstead, Blount, Fahrenholtz, Faraone, LeMahieu & Rosen, 1970; Griffin *et al.*, 1984). The biological significance of this observation is probably not important as deacylcortivazol is as active biologically as cortivazol (Steelman *et al.*, 1971; Dausse *et al.*, 1977; Simons *et al.*, 1979; Harmon *et al.*, 1981).

The overall conformation of cortivazol is similar to the conformations of the only two phenylpyrazole-substituted pregnadiene steroids whose crystal structures are known, 6α,7α-difluoromethylene-11β,17α,21-trihydroxy-16α-methyl-2′-phenyl-2′*H*-pregna-2,4-dieno[3,2-*c*]pyrazol-20-one 21-(*p*-bromobenzoate) (Christensen, 1970) (I), and 6α,7α-difluoromethylene-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-16α-methyl-2′-phenyl-2′*H*-pregna-2,4-dieno[3,2-*c*]pyrazol-20-one 21-(*p*-bromobenzoate) (Thom & Christensen, 1971) (II). The 6α,7α-difluoromethylene groups on these two compounds constrain ring *B* in a manner analogous to the Δ^6 bond in cortivazol. The planarity of cortivazol is also evident in the twist about a line joining C10 and C13, described by the 'torsion angle' C19—C10—C13—C18. This 'torsion angle' of cortivazol is −2·7 (3)°, which is nearly the same as that in (II) (−2·8°), but significantly different from the twist in compound (I)

(−7·8°). This is somewhat unexpected since (I) has the same substituents on ring *D* as cortivazol, and (II) has the additional constraint on ring *D* with the presence of the 16α,17α-isopropylidenedioxy group, which presumably conforms ring *D* to a distorted 14α envelope. The ring-junction configurations of these three compounds are the same, *A*/*B* quasi-*trans*, *B*/*C* and *C*/*D trans* and the magnitudes of these torsion angles are within five degrees of each other (Table 2) (Duax & Norton, 1975).



(I) (II)

The plane of the benzene ring makes a dihedral angle of 28·9 (3)° with the plane of the pyrazole ring. The benzene ring in (I) and (II) makes dihedral angles of 53·6 and 48·6°, respectively. These differences are probably a manifestation of the crystal-packing forces as these three compounds crystallize in different space groups and there are no energetic barriers in this region of rotation about the N–benzene bond.

However, cortivazol is less bowed toward the α face than either of these two molecules with less than half the angle found in dexamethasone and its acetate derivative. The bowing of the *A* ring in relation to the least-squares plane of atoms C5 through C17 is −15·0° in the case of cortivazol, −18·4° for (I), −22·7° for (II) and *ca* 39° for dexamethasone and its acetate derivative. The pyrazole ring is planar within experimental error. The trigonal N29 of the pyrazole ring bonded to C3 is analogous to the O3 keto usually found in glucocorticoids. The pyrazole ring makes an angle of 6·4 (8)° with the C5—C17 least-squares plane. This is in sharp contrast to the 16·0 and 16·7° angles found in (I) and (II). The differences between the torsion angles C1—C2—C3—C4 and C27—C2—C3—N29 of cortivazol and (I) and (II) are 1·3, 0·1; 8·2, 1·0; and 5·2, −1·6°, respectively. The angles made by ring *A* with the least-squares plane of atoms C5 through C17 of cortivazol, (I), (II), dexamethasone and its acetate derivative, result in the corresponding O3 or N29 being −0·770, −0·87, −1·45, −2·19 and −2·47 Å, respectively, below the C5 through C17 least-squares plane. The decrease in the bowing angle of cortivazol compared to the dexamethasones, which are less active than cortivazol, contradicts the proposal made by Weeks, Duax & Wolff (1973) that increasing the angle made by ring *A* with the least-squares plane of C5 through C17 increases the anti-inflammatory activity. Furthermore, the benzene ring is bonded to N29 which would sterically interfere with any binding. Thus, it is not likely that the C2—C3—C4 edge of the *A*-ring portion of the glucocorticoids is important for binding or activity. The β face of rings *B*, *C* and *D* of the glucocorticoids is, for the most part, the same and may be an important factor in binding of the molecule to the glucocorticoid receptor. The remaining portion of the glucocorticoids which may be responsible for differences in glucocorticoid activity is the α-face side of the *B*, *C* and *D* rings. Cortivazol is structurally nearly identical to the phenylpyrazole compounds (I) and (II) and yet functionally similar to dexamethasone. Even though there are some significant differences between the cortivazol and dexamethasone structures, most notably the presence of the F9 atom in the dexamethasones and the phenylpyrazole in cortivazol, the conformations of rings *C* and *D* are nearly identical. Fitting the nine C atoms of rings *C* and *D* of cortivazol to the corresponding atoms of dexamethasone acetate and compounds (I) and (II) results in r.m.s. values of 0·031, 0·046 and 0·104 Å, respectively. The positional differences of C13 and the C18β methyl group are less than the corresponding r.m.s. values when fitted to cortivazol. However, C10 and the C19β methyl group differ by *ca* 0·2 and 0·3 Å, respectively. Thus, the twists of the glucocorticoids as measured by the C19—C10—C13—C18 'torsion angle' of cortivazol, dexamethasone acetate and compounds (I) and (II) are −1·3, 1·4, −7·8 and −2·8°, respectively. The result is that the C19β methyl and the O11β hydroxyl groups have different spatial relationships of each glucocorticoid to the receptor. It is plausible that it is the common elements and their spatial relationships of these glucocorticoid structures which impart the recognition signal to the glucocorticoid receptor for binding. Since rings *C* and *D* of cortivazol and (I) are conformationally nearly the same, then (I) may also have similar biological functions. The C16 methyl and O17 hydroxyl groups are replaced by a 16α,17α-isopropylidenedioxy moiety in (II), which should sterically block the α face, thus potentially preventing binding to the receptor. However, the potent glucocorticoid, triamcinoloneacetonide (9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadien-3,20-dione), has the same moieties at C16 and C17 in the same orientation (Surcouf, 1979). This leaves the α and β faces of rings *B* and *C* and the molecular edge composed of atoms C6—C7—

C8—C14—C15 to supply the recognition signal to the glucocorticoid receptor for binding. The testing of compounds (I) and (II) in binding to the glucocorticoid receptor in conjunction with the three-dimensional structure of triamcinolone acetate should resolve this question of the importance of the free access of portions of the α and β faces for glucocorticoid activity.

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X-ray Studies on Crystalline Complexes Involving Amino Acids and Peptides. XXI. Structure of a (1:1) Complex Between L-Phenylalanine and D-Valine

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Abstract. $C_5H_{11}NO_2.C_9H_{11}NO_2$, $M_r = 282{\cdot}3$, $P1$, $a = 5{\cdot}245\ (1)$, $b = 5{\cdot}424\ (1)$, $c = 14{\cdot}414\ (2)$ Å, $\alpha = 97{\cdot}86\ (1)$, $\beta = 93{\cdot}69\ (2)$, $\gamma = 70{\cdot}48\ (2)°$, $V = 356$ Å^3, $Z = 1$, $D_m = 1{\cdot}32\ (2)$, $D_x = 1{\cdot}32$ g cm^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}7107$ Å, $\mu = 5{\cdot}9$ cm^{-1}, $F(000) = 158$, $T = 298$ K, $R = 0{\cdot}035$ for 1518 observed reflections with $I > 2\sigma(I)$. The molecules aggregate in double layers, one layer made up of L-phenylalanine molecules and the other of D-valine molecules. Each double layer is stabilized by interactions involving main-chain atoms of both types of molecules. The interactions include hydrogen bonds which give rise to two head-to-tail sequences. The arrangement of molecules in the complex is almost the same as that in the structure of

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