Acta Cryst. (1974). B30, 1581

The Crystal Structure of a Potent Anti-Androgen: Cyproterone Acetate (6-Chloro-17-hydroxy-1α,2α-methylenepregna-4,6-diene-3,20-dione Acetate)

BY R. J. CHANDROSS

Laboratories for Reproductive Biology, University of North Carolina, Chapel Hill, North Carolina, 27514, *U.S.A.*

AND J. BORDNER

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27607, *U.S.A.*

(*Received* 28 *August* 1973; *accepted* 18 *February* 1974)

The crystal structure of the anti-androgen cyproterone acetate (CPA, 6-chloro-17-hydroxy-1α,2α-methylenepregna-4,6-diene-3,20-dione acetate, $C_{24}H_{29}O_4Cl$) was determined with the aid of symbolic addition. The steroid crystallized in the orthorhombic space group $P2_12_12_1$ with $a=10{\cdot}757$ (2), $b=12{\cdot}266$ (3), $c=16{\cdot}623$ (3) Å, and $Z=4$. A three-dimensional data set was collected with Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å) on a Syntex $P\bar{1}$ diffractometer to a maximum 2θ value of 100° employing a θ–2θ scan technique. The coordinates of the non-hydrogen atoms and their anisotropic temperature factors were refined in a full matrix least-squares manner to a final R index of 0·054 based on F^2. Bond distances around the cyclopropane ring were shortened, implying an interaction with the carbonyl group in ring A.

Introduction

It is convenient to place the steroid gonadotrophic hormones into well defined physiological classes such as androgens, estrogens, or progestins. Occasionally compounds are found that have their primary physiological activity in one class, but at the same time, show properties normally found in another class. For example, progestins sometimes have androgen or estrogenic effects (Goodman & Gilman, 1970*a*). Cyproterone acetate has the interesting property of being a progestogen with antiandrogenic properties (Wiechert & Neumann, 1965; Wiechert, Steinbeck, Elger & Neumann, 1967). It specifically blocks the uptake of testosterone (Sar & Stumpf, 1973). As such, it has found some clinical applications as a chemical castration agent in cases of prostatic carcinoma (Scott & Schirmer, 1966). The chemical structure is shown in Fig. 1.

Within the last few years the crystal structures of a large number of biologically active steroids have been determined as an aid towards gaining an understanding of the relationship between steroid structure and activity. Because of the unusual nature of cyproterone acetate, both in the biological and chemical sense, we felt that a determination of its crystal structure might provide some insight into the geometric nature of the androgen receptor.

Experimental

Cyproterone acetate was obtained from Berlin Laboratories through the courtesy of Professor W. E. Stumpf of the University of North Carolina. Small, colorless, well formed prisms of the steroid were obtained from the slow evaporation of an acetone solution. Observations with the polarizing microscope showed them to be biaxial and of excellent quality, with the principal axes along the growth directions of the crystal. A suitable crystal ($0{\cdot}1\times0{\cdot}1\times0{\cdot}2$ mm) was mounted on a glass fiber with epoxy cement, the long direction of the crystal being parallel to the glass fiber. Unit-cell dimensions were obtained at room temperature on a Syntex $P\bar{1}$ diffractometer using a least-squares fit of 15 reflections with Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å). Systematic absences indicated the space group $P2_12_12_1$ ($h00$: $h=2n+1$, $0k0$: $k=2n+1$, $00l$: $l=2n+1$). The density was measured by the flotation technique in KI.$HgCl_2$ solution.

Intensity data were collected at room temperature to a resolution of 1 Å (maximum $\sin\theta/\lambda=0{\cdot}5$) on the diffractometer equipped with a graphite monochromator using Cu $K\alpha$ radiation. The incident beam monochromator was mounted in the perpendicular mode. Polarization effects due to the monochromator were corrected for by a method suggested by Azaroff (1955). A single check reflection was monitored every 30 reflections and revealed no appreciable systematic fall off in intensity due to radiation damage or other causes.

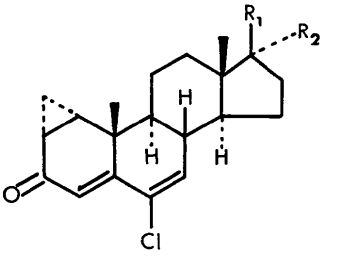

Fig. 1. The chemical structure of cyproterone acetate (where $R_1=-\overset{O}{\overset{\|}{C}}-CH_3$ and $R_2=-O-\overset{O}{\overset{\|}{C}}-CH_3$).

Details of the crystal survey and data-collection parameters are summarized in Table 1.

Table 1. *Physical data and data-collection parameters*

Molecular formula	$C_{24}H_{29}O_4Cl$
M.W.	416·95
Cell dimensions	$a=10{\cdot}757$ (2) Å
	$b=12{\cdot}266$ (3)
	$c=16{\cdot}623$ (3) $V=2193{\cdot}3$ (8) Å^3
Space group	$P2_12_12_1$
Molecules/unit cell	4
Density calculated	1·262 g cm^{-3}
Density observed	1·265
Scan technique	θ–2θ
Scan width	1·0° below $K\alpha_1$, 1·0° above $K\alpha_2$
Scan speed	2° per min in 2θ
Background count time	One-half scan time on each side of peak
Number of reflections	1325
Nonzero reflections*	1168

* All intensities with a value less than 2σ were set equal to zero with zero weight.

The diffractometer output was processed using subroutines of the CRYM crystallographic computer system (Duchamp, 1964). The processing was routine and included the usual corrections. Standard deviations of the F^2's were assigned on the basis of the following equation: $\sigma^2(I)=S+\alpha^2(B_1+B_2)+(dS)^2$, where S is the number of counts collected during the scan, B_1 and B_2 are the background counts, d is an empirical constant set at 0·02, and α is the scan time to total background time ratio.

Finally, the data were placed on an approximately absolute scale by Wilson (1942) statistics. Atomic scattering factors for C and O were taken from *International Tables for X-ray Crystallography* (1962). The scattering factor for Cl is that given by Cromer & Mann (1967). The scattering factor for H is that given by Stewart, Davidson & Simpson (1965). Both anomalous dispersion components were applied to Cl (*International Tables for X-ray Crystallography*, 1962). No corrections were made for absorption ($\mu=17{\cdot}5$ cm^{-1}).

Phase determination and structure refinement

Normalized structure factors, $|E|$, (Karle & Karle, 1966) were calculated using an overall temperature factor of 3·37 Å^2. All of the observable data were used, and the symmetry effects on the average distribution of the intensity data were corrected for by the method of Wilson (1950).

The selection of the starting reflections and the initial phasing were done with the subprograms *MULTAN* (Germain, Main & Woolson, 1971), using the 278 reflections with $|E|>1{\cdot}2$. The set of phases selected by the program as being the most consistent set was in fact the correct solution. The Fourier synthesis based on this set showed all of the non-hydrogen atoms, so the remainder of the data were introduced and full matrix least-squares refinement started, minimizing the quantity $\sum w(F_o^2-F_c^2)^2$. The weights, w, used throughout the refinement of the structure, were set equal to $1/\sigma^2(F_o^2)$ which were derived from counting statistics.

The initial R index was 30·2% and several cycles of coordinate only refinement brought R down to 18·6%. Isotropic and then, at a later stage, anisotropic temperature factors were introduced. During these final stages of refinement all the non-hydrogen atom coordinates were in one matrix, with the scale factor, secondary extinction coefficient, and the anisotropic temperature factors in a second matrix. The methylene and methine hydrogen positions were calculated; methyl hydrogens were located by difference Fourier maps. The hydrogen parameters were not refined. The expression used to correct for secondary extinction is that given by Larson (1967): $F^2\text{corrected}=(F\text{cal})^2/[1+g\beta(F\text{cal})^2]$. In this expression g is the secondary extinction coefficient and β is the angular variation of the secondary coefficient.

The final value of g was $2{\cdot}29\ (3)\times10^{-6}$. Refinement proceeded normally to a final R index $\sum||F_o|-|F_c||/\sum|F_o|$ of 0·054; the goodness of fit; $[\sum w(F_o^2-F_c^2)^2/(m-s)]^{1/2}$, (where m is the number of observations and s is the number of parameters refined) was 1·64. Both data-fit criteria were based on non-zero reflections.*

The absolute configuration of the steroid was determined by the method of Ibers & Hamilton (1964). The absolute configuration is shown in the stereo plot (Fig. 2) and is the normal steroid configuration. This configuration refined to an R index of 0·054; the mirror image to an R index of 0·057. The differences in discrepancy indices (Hamilton's R') established the correct enantiomer at the 0·5% level of significance (Hamilton, 1965).

The final coordinates and anisotropic temperature factors for the non-hydrogen atoms with their standard deviations (calculated from the least-squares residuals and the inverse matrix of the final least-squares cycle) are given in Table 2. The positional parameters of the hydrogen atoms are shown in Table 3. The shifts calculated for the parameters in the final cycle of the least-squares refinement were all less than one-sixth of the corresponding standard deviations. A final difference Fourier revealed no missing or misplaced electron density.

Discussion of the crystallographic results

A stereoscopic view of the molecule is shown in Fig. 2 (Johnson, 1965). The molecule shows a reasonably

* The observed and calculated structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30386 (8 pp.). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

strong curvature toward the α-face as can be seen from Table 4 which presents the deviations of the atoms of the steroid nucleus from the least-squares plane defined by atoms C(3), C(4), C(5), C(6), C(7), and Cl(27). The *A* ring conformation can best be described as a shallow boat; the *B* ring conformation is that of half-chair, and

Table 2. *Heavy-atom parameters and their standard deviations*

The values have been multiplied by 10^4. The temperature factor is in the form:

$$T=\exp\left[-(b_{11}h^2+b_{22}k^2+b_{33}l^2+b_{12}hk+b_{13}hl+b_{23}kl)\right].$$

	x/a	y/b	z/c	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	3999 (6)	3464 (5)	4273 (3)	82 (8)	79 (6)	33 (3)	3 (14)	9 (10)	21 (7)
C(2)	3628 (6)	4345 (5)	3721 (4)	146 (11)	81 (6)	36 (3)	−46 (15)	11 (11)	40 (9)
C(3)	2864 (6)	5253 (6)	4021 (3)	119 (11)	102 (8)	33 (3)	−58 (16)	−25 (10)	28 (9)
C(4)	2287 (6)	5103 (5)	4822 (4)	91 (8)	73 (6)	37 (3)	−15 (13)	4 (9)	2 (8)
C(5)	2621 (6)	4316 (4)	5343 (3)	89 (8)	47 (5)	34 (3)	−35 (12)	−8 (9)	9 (7)
C(6)	2016 (6)	4170 (5)	6118 (3)	105 (9)	44 (5)	37 (3)	−2 (12)	5 (10)	−14 (7)
C(7)	2206 (6)	3335 (5)	6609 (3)	119 (9)	51 (5)	31 (3)	9 (14)	34 (9)	−1 (8)
C(8)	3040 (5)	2421 (4)	6400 (3)	87 (8)	49 (5)	26 (3)	−29 (12)	−16 (9)	−2 (7)
C(9)	3330 (5)	2397 (5)	5503 (3)	72 (7)	56 (6)	26 (3)	5 (12)	−5 (8)	−1 (7)
C(10)	3705 (5)	3549 (5)	5180 (3)	73 (8)	59 (5)	28 (3)	−16 (12)	3 (8)	8 (7)
C(11)	4253 (6)	1484 (5)	5297 (3)	92 (8)	81 (6)	32 (3)	16 (14)	20 (9)	16 (7)
C(12)	3791 (6)	358 (5)	5589 (3)	95 (8)	63 (6)	38 (3)	48 (14)	39 (9)	10 (7)
C(13)	3481 (5)	386 (4)	6503 (3)	64 (7)	52 (5)	31 (3)	16 (11)	8 (8)	25 (7)
C(14)	2552 (5)	1309 (4)	6661 (3)	81 (8)	59 (5)	20 (2)	5 (11)	6 (8)	−4 (6)
C(15)	2114 (6)	1110 (4)	7525 (3)	123 (9)	48 (5)	30 (3)	−21 (13)	9 (10)	9 (7)
C(16)	2067 (5)	−148 (5)	7586 (3)	87 (8)	64 (6)	29 (3)	6 (13)	12 (9)	1 (7)
C(17)	2725 (5)	−618 (4)	6835 (3)	85 (8)	38 (5)	34 (3)	−11 (12)	−28 (9)	14 (7)
C(18)	4679 (6)	510 (5)	6991 (4)	79 (8)	76 (6)	55 (4)	−12 (13)	0 (9)	17 (8)
C(19)	4860 (6)	3989 (5)	5612 (4)	95 (8)	70 (6)	53 (4)	−46 (13)	−46 (10)	30 (8)
C(20)	3563 (6)	−1605 (5)	7001 (4)	107 (9)	69 (6)	37 (3)	−12 (14)	14 (10)	14 (8)
C(21)	3902 (7)	−2349 (5)	6324 (4)	160 (12)	105 (7)	44 (3)	81 (17)	7 (13)	8 (10)
C(22)	3030 (6)	3254 (5)	3686 (3)	119 (10)	112 (7)	27 (3)	−39 (15)	23 (10)	−23 (9)
O(23)	3954 (4)	−1770 (3)	7668 (2)	138 (6)	87 (4)	41 (2)	18 (10)	−34 (7)	24 (6)
O(24)	1835 (3)	−887 (3)	6204 (2)	99 (5)	53 (3)	33 (2)	−13 (8)	−12 (6)	5 (4)
C(25)	1065 (6)	−1762 (4)	6331 (4)	113 (9)	48 (5)	51 (4)	1 (14)	−52 (12)	7 (9)
C(26)	364 (7)	−2017 (5)	5602 (4)	137 (11)	69 (6)	62 (4)	−17 (14)	−71 (12)	−3 (8)
O(27)	1037 (5)	−2252 (3)	6954 (2)	167 (7)	73 (4)	46 (2)	−58 (10)	−51 (8)	34 (5)
O(28)	2686 (5)	6114 (3)	3652 (3)	215 (8)	106 (5)	51 (2)	−22 (12)	−15 (9)	84 (7)
Cl(29)	983 (2)	5206 (1)	6413 (1)	208 (3)	75 (1)	52 (1)	77 (4)	63 (3)	7 (2)

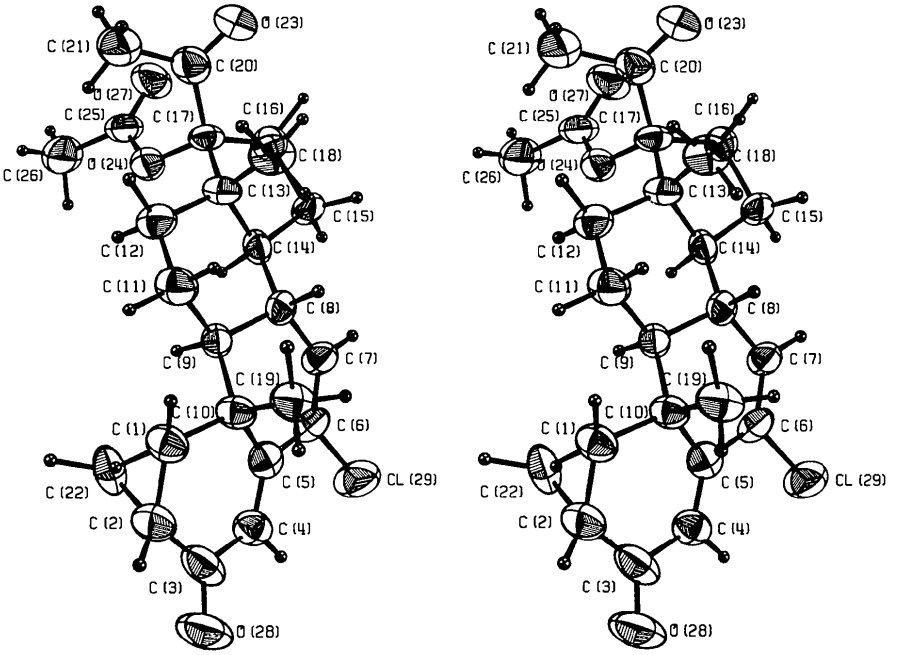

Fig. 2. A stereoscopic view of cyproterone acetate.

Table 3. *Hydrogen-atom parameters*

The values for the coordinates have been multiplied by 10^3. The values for the isotropic temperature factors are 3·2.

	Atom bearing H	X	Y	Z		Atom bearing H	X	Y	Z
H(30)	1	487	306	442	H(45)	22	207	315	388
H(31)	2	412	486	330	H(46)	22	321	271	318
H(32)	4	156	565	500	H(47)	19	557	333	572
H(33)	7	172	332	718	H(48)	19	464	428	618
H(34)	8	387	258	674	H(49)	19	523	467	530
H(35)	9	249	218	518	H(50)	18	536	2	675
H(36)	11	513	166	557	H(51)	18	446	21	758
H(37)	11	437	145	465	H(52)	18	492	132	702
H(38)	12	451	−23	548	H(53)	21	493	−235	628
H(39)	12	296	13	525	H(54)	21	361	−206	579
H(40)	14	172	130	629	H(55)	21	360	−308	639
H(41)	15	120	146	762	H(56)	26	96	−227	513
H(42)	15	276	144	795	H(57)	26	−16	−134	541
H(43)	16	111	−42	760	H(58)	26	−21	−261	573
H(44)	16	253	−41	812					

the *C* ring is a normal chair. A more quantitative treatment of the ring conformations, torsion angles, are summarized in Table 5. The bond distances and angles are shown in Tables 6 and 7 respectively. The standard deviations of C–C bond lengths are about 0·01 Å, C–O bond lengths about 0·009 Å, the C–Cl bond is known to about 0·007 Å, and the angles are known to about 0·7°.

Table 4. *Deviations of steroid nucleus from the plane defined by atoms* C(3), C(4), C(5), C(6), C(7) *and* Cl(29)

C(1)	−0·04 Å	C(11)	−0·41 Å
C(2)	−0·16	C(12)	−1·30
C(3)	0·01	C(13)	−0·93
C(4)	−0·04	C(14)	−1·00
C(5)	+0·08	C(15)	−0·93
C(6)	+0·01	C(16)	−1·70
C(7)	−0·04	C(17)	−1·96
C(8)	−0·07	C(22)	−1·36
C(9)	−0·45	O(28)	+0·14
C(10)	+0·37	Cl(29)	+0·01

Table 5. *Torsion angles in the rings*

φA–B is the torsion angle about the A–B bond in which the two atoms required to define the angle are those attached to either end of the bond and are in the same ring in question.

Ring *A*	φA–B	Ring *B*	φA–B
C(1)—C(2)	−6·2	C(5)—C(6)	−11·5
C(2)—C(3)	−12·7	C(6)—C(7)	−2·3
C(3)—C(4)	14·1	C(7)—C(8)	−16·3
C(4)—C(5)	4·9	C(8)—C(9)	47·3
C(5)—C(10)	−22·8	C(9)—C(10)	−59·2
C(1)—C(10)	23·0	C(5)—C(10)	40·5
Ring *C*	**φA–B**	**Ring *D***	**φA–B**
C(8)—C(9)	−56·3	C(13)–C(14)	46·6
C(9)—C(11)	55·2	C(14)–C(15)	−36·4
C(11)–C(12)	−54·3	C(15)–C(16)	11·4
C(12)–C(13)	54·7	C(16)–C(17)	16·7
C(13)–C(14)	−58·4	C(13)–C(17)	−38·1
C(14)–C(8)	59·3		

Table 6. *Atomic distances* (Å)

C(1)–C(2)	1·474	C(10)–C(19)	1·533
C(1)–C(10)	1·544	C(11)–C(12)	1·547
C(1)–C(22)	1·451	C(12)–C(13)	1·555
C(2)–C(3)	1·471	C(13)–C(14)	1·532
C(2)–C(22)	1·486	C(13)–C(17)	1·578
C(3)–C(4)	1·481	C(13)–C(18)	1·530
C(3)–O(28)	1·236	C(14)–C(15)	1·530
C(4)–C(5)	1·346	C(15)–C(16)	1·548
C(5)–C(6)	1·453	C(16)–C(17)	1·546
C(5)–C(10)	1·523	C(17)–C(20)	1·534
C(6)–C(7)	1·327	C(17)–O(24)	1·458
C(6)–Cl(29)	1·758	C(20)–C(21)	1·494
C(7)–C(8)	1·476	C(20)–O(23)	1·203
C(8)–C(9)	1·525	O(24)–C(25)	1·372
C(8)–C(14)	1·525	C(25)–C(26)	1·462
C(9)–C(10)	1·564	C(25)–O(27)	1·200
C(9)–C(11)	1·535		

Table 7. *Bond angles* (°)

C(10)—C(1)—C(2)	120·2	C(19)–C(10)–C(9)	111·4
C(22)—C(1)—C(2)	61·0	C(12)–C(11)–C(9)	111·9
C(22)—C(1)—C(10)	121·4	C(13)–C(12)–C(11)	110·8
C(3)—C(2)—C(1)	119·6	C(14)–C(13)–C(12)	108·9
C(22)—C(2)—C(1)	58·6	C(17)–C(13)–C(12)	115·7
C(22)—C(2)—C(3)	116·9	C(18)–C(13)–C(12)	109·8
C(4)—C(3)—C(2)	116·4	C(17)–C(13)–C(14)	100·3
O(28)—C(3)—C(2)	124·4	C(18)–C(13)–C(14)	112·6
O(28)—C(3)—C(4)	119·1	C(18)–C(13)–C(17)	109·0
C(5)—C(4)—C(3)	123·8	C(13)–C(14)–C(8)	112·7
C(6)—C(5)—C(4)	122·6	C(15)–C(14)–C(8)	121·0
C(10)—C(5)—C(4)	122·2	C(15)–C(14)–C(13)	104·1
C(10)—C(5)—C(6)	115·0	C(16)–C(15)–C(14)	103·3
C(7)—C(6)—C(5)	124·9	C(17)–C(16)–C(15)	107·7
Cl(29)–C(6)—C(5)	116·1	C(16) C(17)–C(13)	103·1
Cl(29)–C(6)—C(7)	118·9	C(20)–C(17)–C(13)	112·1
C(8)—C(7)—C(6)	122·3	O(24)–C(17)–C(13)	105·2
C(9)—C(8)—C(7)	111·6	C(20)–C(17)–C(16)	114·7
C(14)—C(8)—C(7)	113·7	O(24)–C(17)–C(16)	111·3
C(14)—C(8)—C(9)	109·3	O(24)–C(17)–C(20)	109·6
C(10)—C(9)—C(8)	111·7	C(21)–C(20)–C(17)	119·3
C(11)—C(9)—C(8)	111·3	O(23)–C(20)–C(17)	120·2
C(11)—C(9)—C(10)	114·6	O(23)–C(20)–C(21)	120·3
C(5)—C(10)–C(1)	111·8	C(2)—C(22)–C(1)	60·2
C(9)—C(10)–C(1)	109·0	C(25)–O(24)–C(17)	117·4
C(19)–C(10)–C(1)	108·3	C(26)–C(25)–O(24)	110·5
C(9)—C(10)–C(5)	107·4	O(27)–C(25)–O(24)	122·7
C(19)–C(10)–C(5)	108·6	O(27)–C(25)–C(26)	126·6

The bond distances in the three-membered ring are clearly shortened, even beyond the accepted value of 1·52 Å for cyclopropane itself (Lord, Gunthard & McCubbin, 1956). However, these distances compare favorably with an α-ketocyclopropane (Bordner, Jones & Johnson, 1972). The observed shortening may result from a further increase in the *s* character of the ring carbon due to the added overlap of the carbonyl *p* orbitals.

The only close intermolecular approaches in the crystal occur between the carbonyl oxygens in the side chains and the bridge methylene [O(19)–C–(25)= 3·28 Å; O(23)–C(25)=3·28 Å].

Biological implications

It is difficult, of course, from a single structure determination, to deduce very much about either the mode

of action of the drug or the geometry of the acceptor sites that are responsive to the drug. In the case of CPA, there are several interesting speculations that can be made.

We should like to correlate the structure of this compound with its two most important physiological activities, namely its high degree of progestenic activity and its anti-androgenic behavior. Chemically CPA can be considered a derivative of the potent progestin, chlormadinone acetate (Goodman & Gilman, 1970*b*). Chlormadinone acetate is identical with CPA with the bridge methylene removed. In order to study the relationship between the two structures, we also solved the crystal structure of chlormadinone acetate (Bordner & Chandross, 1974, unpublished). The two compounds are similar enough to be considered isomorphous. The fact that the addition of the $1\alpha,2\alpha$ methylene group does not appear to affect the progestenic activity of the steroid may indicate simply that the progesterone acceptor does not have a high degree of molecular specificity for this region of the molecule.

The geometry of the regions of the testosterone and progesterone acceptors that bind the nucleus portion of the steroids are probably similar. This is implied by the observation that weak androgens often display pronounced progestational activity (Bush, 1962) and progestins often are somewhat androgenic in nature (Goodman & Gilman, 1970*a*). Furthermore, many of the compounds normally considered to be androgenic differ from those classified as progestins only in the nature of the 17β side chain. Hence, the nature of the side chain is almost certainly a key factor in determining whether a compound is an active androgen or progestin. The side chain of CPA is typical of that of many of the progestins and probably accounts for its progestenic behavior.

Unlike other progestins, CPA is bound strongly enough to the testosterone acceptor, as shown by competitive binding experiments (Sar & Stumpf, 1973), to inhibit it.

Chlormadinone acetate does not bind tightly to the acceptor, or it too would be an anti-androgen. Hence, the unique binding properties of CPA must lie in the $1\alpha,2\alpha$ methylene group. Normally, substituents in either the 1α or 2α positions of an androgen result in reduced androgenic behavior (Vida, 1969), implying that the binding may be sensitive to increased bulk within this region of the complex. However, there is evidence (Wolff, Ho & Kwok, 1964) that a high electron density in C(2) and/or C(3) is needed for androgenic behavior. Presumably this gives this region of the *A* ring sp^2 character, resulting in a π bond to the *A* face. There is no direct evidence that a hydrogen bond between the acceptor and O(3) is needed for androgenic activity, but analogously with the work of Weeks, Duax & Wolff (1973), we would presume that this may be a factor. We would suggest, then, that the cyclopropane-induced sp^2 character in the C(1), C(2) region of the *A* ring, perhaps coupled with the binding to O(3) is resulting in an energetically favorable binding of the steroid to its acceptor protein. Perhaps in part because of the bulk of the methylene carbon, and certainly because of the unfavorable nature of the side chain, the steroid–acceptor complex geometry is unsuitable for activation and is effectively inhibited from further interaction with cellular components.

References

AZAROFF, L. V. (1955). *Acta Cryst.* **8**, 701–704.

BORDNER, J., JONES, L. H. & JOHNSON, R. L. (1972). *Cryst. Struct. Commun.* **1**, 389–391.

BUSH, I. E. (1962). *Pharmacol. Rev.* **14**, 317–445.

CROMER, D. T. & MANN, J. B. (1967). Report LA-3816, Los Alamos Scientific Laboratory, Los Alamos, New Mexico.

DUCHAMP, D. J. (1964). Amer. Cryst. Assoc. Meeting, Bozeman, Montana. Paper B-14, p. 29.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

GOODMAN, L. S. & GILMAN, A. (1970). *The Pharmacological Basis of Therapeutics*, 4th ed., (*a*) p. 1550, (*b*) p. 1552. New York: Macmillan.

HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502–510.

IBERS, J. & HAMILTON, W. C. (1964). *Acta Cryst.* **17**, 781–782.

International Tables for X-ray Crystallography (1962). Vol. III, pp. 202, 214. Birmingham: Kynoch Press.

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

KARLE, J. & KARLE, I. L. (1966). *Acta Cryst.* **21**, 849–860.

LARSON, A. C. (1967). *Acta Cryst.* **23**, 664–665.

LORD, R. C., GUNTHARD, H. H. & MCCUBBIN, T. K. (1956). *J. Chem. Phys.* **25**, 768–774.

SAR, M. & STUMPF, W. E. (1973). *Proc. Soc. Exp. Biol. Med.* **144**, 26–29.

SCOTT, W. & SCHIRMER, H. (1966). *Trans. Amer. Assoc. Genito-Urin. Surg.* **58**, 54–60.

STEWART, R. F., DAVIDSON, R. E. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

VIDA, J. A. (1969). *Androgens and Anabolic Agents: Chemistry and Pharmacology*, pp. 42–50. New York: Academic Press.

WEEKS, C. M., DUAX, W. L. & WOLFF, M. E. (1973). *J. Amer. Chem. Soc.* **95**, 2865–2868.

WIECHERT, R. & NEUMANN, F. (1965). *Arzneim. Forsch.* **15**, 244–246.

WIECHERT, R., STEINBECK, H., ELGER, W. & NEUMANN, F. (1967). *Arzneim. Forsch.* **17**, 1103–1116.

WILSON, A. J. C. (1942). *Nature, Lond.* pp. 150–152.

WILSON, A. J. C. (1950). *Acta Cryst.* **3**, 258–261.

WOLFF, M. E., HO, W. & KWOK, R. (1964). *J. Med. Chem.* **7**, 577–584.