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The Crystal and Molecular Structure of 3 β -Chloro-5-androsten-17 β -ol

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The crystal structure of the methanol complex of 3 β -chloro-5-androsten-17 β -ol (C₁₉H₂₉OCl · ½CH₃OH) has been determined from three-dimensional X-ray data collected by the stationary-counter stationary-crystal technique and refined to a final reliability index of $R=9.0\%$ for 2456 observed reflections. Crystals formed in methanol are monoclinic, space group $P2_1$, with cell constants $a=22.565$, $b=12.319$, $c=6.656$ Å, and $\beta=95.5^\circ$. The asymmetric unit consists of one methanol and two steroid molecules which are all joined by hydrogen bonds to form helices in the direction of the c axis. The two steroid molecules in the asymmetric unit are related by a non-crystallographic, approximate twofold rotation axis.

Introduction

Two features of the crystal and molecular structure of 3 β -chloro-5-androsten-17 β -ol (Fig. 1) are of particular interest. First, it was desired to determine what, if any, distortion of the normal geometry of the steroid nucleus is caused by the presence of unsaturation at the C(5)–C(6) bond. Previous crystal structure determinations of molecules possessing isolated double bonds at this position (Carlisle & Crowfoot, 1945; Burki & Nowacki, 1956; O'Donnell & Ladd, 1967; Solo, Singh, Shefter & Cooper, 1968) have been re-

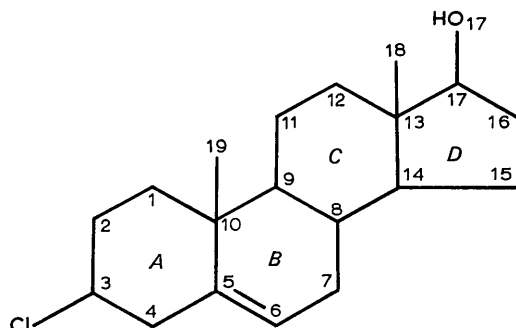


Fig. 1. Atomic numbering for 3 β -chloro-5-androsten-17 β -ol.

latively inaccurate because of the presence of very heavy atoms.

The second interesting feature of this molecule is that two steroid molecules are present in the asymmetric unit. The early crystallographic investigations of steroids by Bernal and his collaborators revealed that the presence of more than one molecule in the asymmetric unit is frequent among the sterols (Bernal, Crowfoot & Fankuchen, 1940), and later X-ray studies have shown that this phenomenon occurs in other classes of steroids as well including the estrogens (Ohrt, Haner & Norton, 1964), pregnanes (Haner & Norton, 1963), and androstanes (Norton, Lu & Campbell, 1962). Consequently, the presence of more than one molecule in the asymmetric unit of steroid crystal structures does not appear to be correlated in a simple way with any particular hydrocarbon skeleton or the nature and location of functional groups.

Experimental

Slow evaporation of a solution of 3 β -chloro-5-androsten-17 β -ol in methanol results in the formation of a crystalline 2:1 complex of the steroid with methanol. The systematic absences ($0k0$ for k odd) in the diffraction pattern of these crystals are consistent with the monoclinic space group $P2_1$. The unit-cell dimensions were determined by a least-squares analysis of 35 independent measurements of 2θ for high angle data. The crystal data are:

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were determined. This information was used to calculate an initial Fourier synthesis, and the remaining nonhydrogen atoms were located by routine application of the heavy atom method. Least-squares refinement of the positional and anisotropic thermal parameters of the nonhydrogen atoms was carried out using a block-diagonal approximation to the normal equa-

tions, and when the R index† was 10.9% for the observed reflections, two successive difference maps were

† R index: $\frac{\sum(|F_o| - |F_c|)}{\sum|F_o|}$.

Quantity minimized: $\sum w(|F_o| - |F_c|)^2$.

Weighting scheme: $\sqrt{w} = 1$ if $|F_o| < 15$, $\sqrt{w} = 15/|F_o|$ otherwise. Scattering factors: *International Tables for X-ray Crystallography* (1962).

Table 3. *Least-squares planes*

(a) Least-squares planes through the atoms of the steroid nucleus

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

		l	m	n	p
A_1	C(2), C(3), C(4)	0.8605†	0.5092†	0.0058†	21.213†
		0.7408	-0.6707	0.0346	2.394
A_2	C(1), C(2), C(4), C(5)	0.2112	0.8690	-0.4473	2.387
		-0.0331	0.8785	0.4765	3.935
B_2	C(6), C(7), C(9), C(10)	-0.2211	-0.6222	0.7509	-0.978
		-0.0859	0.6492	0.7556	3.866
B_3C_1	C(7), C(8), C(9), C(11)	0.8104	0.5362	-0.2359	16.010
		0.6067	-0.7444	-0.2786	2.693
C_2	C(8), C(11), C(12), C(14)	0.1119	0.7357	-0.6679	-0.189
		0.8959	0.7365	0.6704	6.089
C_3D_1	C(12), C(13), C(14), C(15)	0.7970	0.5367	-0.2769	14.405
		-0.5885	0.7520	0.2965	-3.488
D_2	C(13), C(15), C(16), C(17)	0.1954	0.7430	-0.6397	2.122
		0.0920	0.7447	0.6609	6.722
D_3	C(14), C(15), C(16), C(17)	0.3883	0.8374	-0.3845	6.294
		-0.0791	0.9100	0.4068	3.271
A	C(1), C(2), C(3), C(4), C(5), C(10)	0.4800	0.8183	-0.3161	9.590
		-0.2916	0.8961	0.3345	1.815
B	C(5), C(6), C(7), C(8), C(9), C(10)	-0.3943	-0.6107	0.6867	-5.203
		-0.2394	0.6826	0.6904	2.461
C	C(8), C(9), C(11), C(12), C(13), C(14)	0.3983	0.7402	-0.5416	6.094
		-0.1709	0.8173	0.5502	2.980
D	C(13), C(14), C(15), C(16), C(17)	0.3768	0.7284	-0.5721	5.524
		-0.0935	0.7952	0.5990	4.066
C(1)-C(17)		0.4065	0.7357	-0.5416	6.184
		-0.1977	0.8096	0.5526	2.571

† These values are given with those for molecule 1 above those for molecule 2.

(b) Interplanar angles

Plane 1	Plane 2	Angle
A_1	A_2	128.4†
		126.6
B_3C_1	B_2	133.6
		138.2
B_3C_1	C_2	130.0
		132.9
C_3D_1	C_2	131.9
		134.4
C_3D_1	D_2	137.0
		134.5
C_3D_1	D_3	149.9
		148.3
A	B	154.9
		155.8
B	C	168.8
		168.1
C	D	177.7
		174.6
C(1)-C(17)	(100)	113.9
		101.4
C(1)-C(17)	(010)	137.3
		144.0
C(1)-C(17)	(001)	122.7
		123.5

† Angles are given with the values for molecule 1 above those for molecule 2.

computed on which the positions of all but five hydrogen atoms could be located. The unresolved hydrogen atoms were placed at their geometrically expected positions, and two additional least-squares cycles were performed with all the hydrogen atoms included in the calculations. The parameters of the hydrogen atoms ($B_{\text{iso}}=3.0$) were not refined, and refinement was terminated when all calculated shifts were less than $\frac{1}{3}$ the corresponding standard deviations. The final reliability index was 12.7% for all 3657 independent spectra and 9.0% for the 2456 observed reflections. The structure factor amplitudes for all reflections are listed in Table 1, and the refined positional and thermal parameters are given in Table 2. The thermal motions of the atoms are consistent with molecular librations about the principal axes of inertia of the steroid molecules.

Discussion

The intramolecular geometries of the two independent molecules of 3 β -chloro-5-androsten-17 β -ol are similar but not identical. The interatomic distances and valency angles involving only nonhydrogen atoms are shown in Fig. 2(a) and (b), and the estimated standard deviations of these quantities lie in the ranges 0.010–0.017 Å and 0.5–0.9° respectively. The carbon–hydrogen distances are in the range 0.75–1.15 Å. The absolute value of the average deviations between corresponding bond distances and angles in the two molecules are 0.016 Å and 1.5° respectively. The ethylenic linkage joining C(5) and C(6) in each molecule is within two standard deviations of the accepted value of 1.34 Å. Similarly, the C(4)–C(5) and C(6)–C(7) distances, but not the distances C(5)–C(10), are within two standard deviations of the expected value of 1.505 Å for sp^3 – sp^2 bonds (Bartell & Bonham, 1960).

The equations of the planes through the major regions of the steroid nucleus are presented in Table 3(a), and the usual interplanar angles in Table 3(b).

As is usually observed in steroid structures (Norton, 1965), the dihedral angles between adjacent planar regions of the nucleus are greater than 120°. Fig. 3

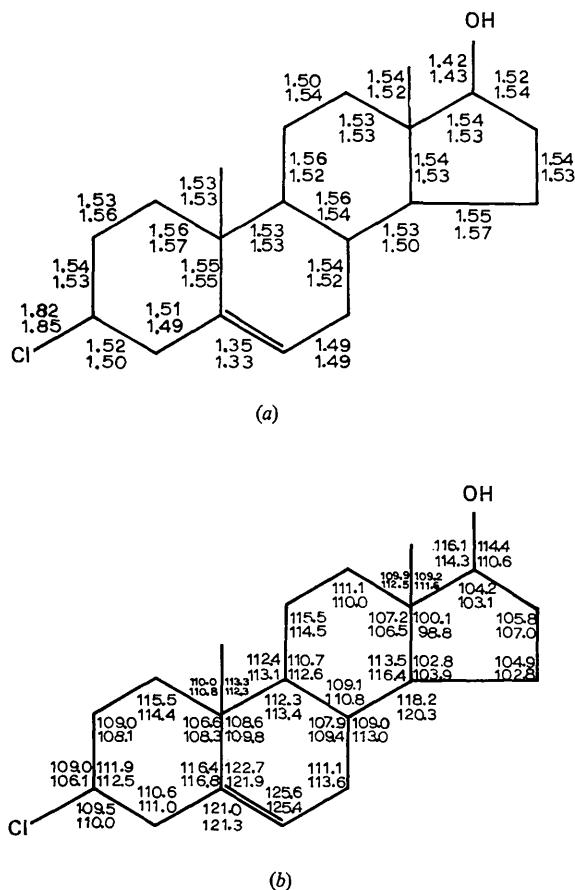


Fig. 2. Interatomic distances and valency angles for 3 β -chloro-5-androsten-17 β -ol. The values for molecule 1 are shown above these for molecule 2, and the standard deviations of these quantities lie in the ranges 0.010–0.017 Å and 0.5–0.9° respectively. (a) Interatomic distances and (b) valency angles.

Table 4. Torsional angles in the rings

$\varphi(A-B)$ 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.

A ring		B ring		C ring		D ring	
Bond	$\varphi(A-B)^*$	Bond	$\varphi(A-B)^*$	Bond	$\varphi(A-B)^*$	Bond	$\varphi(A-B)^*$
C(1)–C(2)	–56.6†	C(5)–C(6)	1.3†	C(8)–C(9)	–49.0†	C(13)–C(14)	45.5†
	–55.0		0.6		–44.6		47.4
C(2)–C(3)	56.8	C(α)–C(7)	16.1	C(9)–C(11)	48.8	C(14)–C(15)	–30.8
	58.5		12.3		48.8		–30.4
C(3)–C(4)	–55.8	C(7)–C(8)	–46.8	C(11)–C(12)	–53.6	C(15)–C(16)	3.7
	–58.0		–40.6		–56.7		1.2
C(4)–C(5)	54.2	C(8)–C(9)	66.0	C(12)–C(13)	57.4	C(16)–C(17)	24.9
	53.0		60.1		58.1		28.2
C(5)–C(10)	–50.2	C(9)–C(10)	–47.5	C(13)–C(14)	–62.8	C(13)–C(17)	–43.6
	–47.5		–46.8		–59.5		–46.0
C(1)–C(10)	51.6	C(5)–C(10)	14.4	C(8)–C(14)	59.1		
	48.5		16.6		52.6		

* The sign convention for the direction of the torsional angle is that of Klyne & Prelog (1960).

† These values are given with those for molecule 1 above those for molecule 2.

illustrates the projections of the molecules parallel to the respective least-squares planes through C(1)–C(17). The presence of unsaturation at C(5)–C(6) does not significantly affect the overall planarity of the steroid nucleus, since the root-mean-square deviations of atoms C(1) to C(17) from planarity for the two molecules are 0.274 and 0.278 Å. The torsion angles are given in Table 4. The *A* and *C* rings are in the chair conformation, the *B* rings have half-chair conformations, and the *D* rings have β -envelope conformations as shown by the torsional angles C(14)–C(15)–C(16)–C(17) which are each only slightly different from 0°,

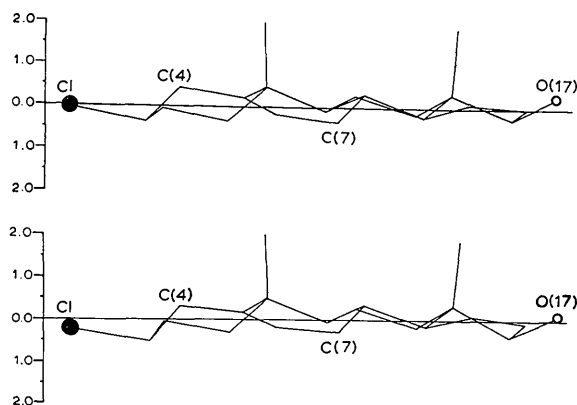


Fig. 3. Projections of single molecules parallel to the least-squares planes through the steroid nucleus, C(1)–C(17). The projection of molecule 1 is above that for molecule 2.

and the parameters Δ and φ_m (Altona, Geise & Romers, 1968) which have the values 27.3 and 46.8 for molecule 1 and 32.5 and 49.3 for molecule 2.

The packing of the molecules is shown in Fig. 4. The two steroid molecules and the methanol molecule comprising the asymmetric unit are joined by hydrogen bonds and form helices in the direction of the *c* axis. The two independent molecules are related by a pseudo twofold rotation axis approximately parallel to **b** and situated roughly at $(\frac{1}{2}, y, \frac{1}{2})$. The favorable hydrogen bonding pattern appears to be a major reason for the presence of two steroid molecules in the asymmetric unit in this particular instance. The geometry of these hydrogen bonds is summarized in Table 5. Half of the 28 intermolecular contacts between nonhydrogen atoms which are less than 4 Å (Table 6) are in the neighborhood of the hydrogen bonds. Hydrogen bonds also exist between crystallographically independent steroid molecules in the structures of estriol (Cooper, Norton & Hauptman, 1969) and 5 α -bromo-6 β ,19-oxido-3 β -hydroxypregnan-20-one (Gopalakrishna, Cooper & Norton, 1969). However, no hydrogen bonds were found between crystallographically independent molecules in crystals of 14 α ,17 α -ethano-16 α -iodopregn-5-ene-3 β -ol-20-one acetate (Solo, Singh, Shefter & Cooper, 1968). Crystals of 4-bromoestradiol (Norton, Kartha & Lu, 1964) and 2 β -hydroxytestosterone 2-acetate 17-chloroacetate (Duax, Osawa, Eger & Pokrywiecki, 1971), are examples of crystalline complexes where the steroid–methanol ratio is 1:1 and

Table 5. Geometry of the hydrogen bonds

Hydrogen donor–hydrogen distance A–H	Hydrogen acceptor–hydrogen distance B···H	Distance A···B	Angle A–H···B	Position* of hydrogen acceptor (B)
1O(17)–1H(17O)† † 1.04 Å	Me O···1H(17O)† 1.67 Å	2.71 Å	179°	1/000
2O(17)–2H(17O) 0.76	1O(17)···2H(17O) 2.00	2.71	154	1/000
Me O–H(Me O) 0.99	2O(17)···H(Me O) 1.76	2.65	148	1/00 $\bar{1}$

* The equivalent positions are: 1 = (x, y, z); 2 = (1 – x, $\frac{1}{2}$ + y, 1 – z). Me O–H(Me O) (1/00 $\bar{1}$) means that the second atom, H(Me O), is at equivalent position 1, translated one unit-cell in the –*c* direction.

† Position of 1H(17O) is theoretical.

Table 6. Intermolecular distances between nonhydrogen atoms which are less than 4 Å.

Contact	Position*	Distance	Contact	Position*	Distance
1C(2)–2Cl	1/101	3.95 Å	1O(17)–MeC	1/000	3.45 Å
1C(3)–1C(18)	2/1 $\bar{1}$ 1	3.99	1O(17)–MeO	1/000	2.71
1C(6)–1C(18)	2/1 $\bar{1}$ 0	3.93	2C(1)–2C(8)	1/00 $\bar{1}$	3.98
1C(12)–2O(17)	1/000	3.89	2C(2)–2C(16)	2/000	3.91
1C(12)–MeO	1/001	3.94	2C(2)–1Cl	1/ $\bar{1}$ 0 $\bar{1}$	3.91
1C(15)–2Cl	2/0 $\bar{1}$ $\bar{1}$	3.76	2C(4)–1Cl	1/ $\bar{1}$ 0 $\bar{1}$	3.81
1C(16)–2Cl	2/0 $\bar{1}$ $\bar{1}$	3.88	2C(6)–MeC	2/0 $\bar{1}$ 0	3.69
1C(17)–2O(17)	1/000	3.58	2C(16)–MeO	1/001	3.76
1C(17)–MeO	1/000	3.58	2C(17)–2C(19)	2/0 $\bar{1}$ 0	3.90
1C(18)–1Cl	2/101	3.96	2C(17)–MeO	1/001	3.74
1C(18)–MeO	1/000	3.39	2O(17)–MeC	1/001	3.34
1O(17)–2C(12)	1/000	3.96	2O(17)–MeO	1/001	2.65
1O(17)–2C(17)	1/000	3.23	MeC–1Cl	2/100	3.99
1O(17)–2O(17)	1/000	2.71	MeC–1Cl	2/101	3.77

* The equivalent positions are designated in the same manner as for Table 5.

there is only one steroid molecule in the asymmetric unit. In the 4-bromoestradiol structure, chains of hydrogen bonded molecules occur parallel to **a**, and the methanol molecule is hydrogen bonded to both of the hydroxyl groups which are also bonded to each other. In the latter example, the methanol molecules are bonded to the steroid molecules at O(3), but no extended network of hydrogen bonds occurs.

The X-ray analysis of 3β -chloro-5-androsten- 17β -ol has revealed no substantial deviations in the geometry of the steroid nucleus coincident with the introduction of unsaturation at C(5)–C(6). The presence of two molecules in the asymmetric unit of this steroid appears to result from hydrogen bonds, and the two crystallographically independent molecules are related by a noncrystallographic twofold rotation axis.

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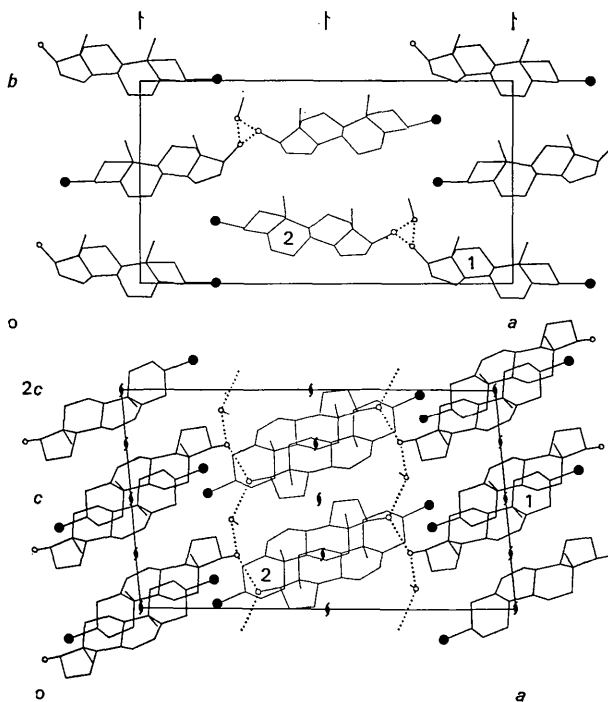


Fig. 4. The packing of the molecules as seen in projection onto the (001) plane, and the (010) plane. ● = chlorine atom; ○ = hydroxyl oxygen atom.