

The Crystal Structure of 17 β -Hydroxyestr-5(10)-en-3-one: The Conformation of Ring A

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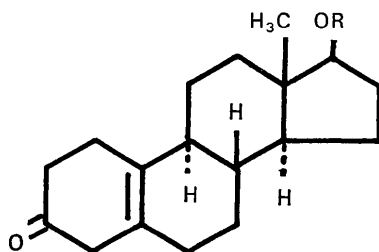
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The crystal structure of 17 β -hydroxyestr-5(10)-en-3-one, C₁₈H₂₆O₂, was determined with the aid of symbolic addition and tangent refinement techniques. The steroid crystallized in the orthorhombic space group $P2_12_12_1$ with $a=9.575$ (5), $b=8.087$ (4), $c=19.49$ (1) Å, and $Z=4$. Three-dimensional data were collected with Cu $K\alpha$ radiation on a Syntex $P\bar{T}$ diffractometer to a maximum 2θ value of 100° employing a $\theta-2\theta$ scan technique. All the coordinates and the anisotropic temperature factors of the nonhydrogen atoms were refined in a full-matrix least-squares manner. The final R index was 0.040 based on F^2 . The conformation of ring A was not the expected half chair form, but a semi-planar form similar to the one reported for the 17-iodoacetate derivative of 17 β -hydroxyestr-5(10)-en-3-one.

Introduction

Until recently it has been thought that the low energy form of the A ring in 5(10)-unsaturated steroids was the half-chair conformation (Levine, Eudy & Lefler, 1966). This proposal was recently supported by semi-empirical calculations of equilibrium geometry by Cohen (1971).

However, the recent crystal structure of the 17-iodoacetate derivative of 17 β -hydroxyestr-5(10)-en-3-one (Ib) indicated that in the solid state the conformation of ring A was semi-planar form with only C(2) appreciably out of the plane of the 5(10) double bond (Bordner, Sobti & Levine, 1971).



(Ia) R = H

(Ib) R = CCH₂I
 \parallel
 O

These crystallographic findings can now be further substantiated by the crystal structure of the parent compound (Ia).

Experimental

Crystals of (Ia) in the form of thin colorless needles were obtained by the slow evaporation of an acetone solution of the steroid. A suitable crystal (0.2 × 0.2 × 0.2 mm) was mounted on a glass fiber in a general orientation with epoxy cement. Unit-cell dimensions were obtained at room temperature on a Syntex $P\bar{T}$ diffractometer using a least-squares fit of ten high angle reflections ($2\theta > 48^\circ$) with Cu radiation (1.5418 Å). Systematic absences indicated the familiar space group

$P2_12_12_1$ ($h00: h=2n, 0k0: k=2n, 00l: l=2n$). The density was measured by the flotation technique in potassium iodide solution.

Intensity data to a resolution of 1 Å (maximum $\sin \theta/\lambda=0.5$) were collected on a Syntex $P\bar{T}$ diffractometer using copper radiation and a graphite monochromator. 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 radiation damage since the variation in its intensity was well within counting statistics. Details of the crystal survey and data collection parameters are summarized in Table 1.

The diffractometer output was processed using subroutines of the CRYM crystallographic computer system (Duchamp, 1964). The processing included corrections for background, Lorentz and polarization effects. Polarization due to the monochromator was also included in these corrections. Processing also included the calculation of F^2 and its standard deviation for each of the reflections. The standard deviations were assigned on the basis of the following equation:

Table 1. Physical data and data collection parameters

Molecular formula	C ₁₈ H ₂₆ O ₂
Molecular weight	274.4
Cell dimensions	$a=9.575 \pm 0.005$ Å $b=8.087 \pm 0.004$ $c=19.495 \pm 0.01$ $V=1509.4$ Å ³
Space group	$P2_12_12_1$
Molecules/unit cell	4
Density calculated	1.207 g.cm ⁻³
Density observed	1.18 g.cm ⁻³
Scan technique	$\theta-2\theta$
Scan width	1.2 below $K\alpha_1$, 1.2 above $K\alpha_2$
Scan speed	1° per min in 2θ
Background count time	One-half scan time on each side of peak
Number of reflections	927
Nonzero reflections*	775

* All intensities with a value less than 2 (standard deviation) were set equal to zero with zero weight.

$\sigma^2(I) = S + \alpha^2(B_1 + B_2) + (dS)^2$ 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 absolute scale by Wilson (1942) statistics. Atomic scattering factors for C and O were taken from *International Tables for X-ray Crystallography* (1962). The atomic scattering factor for H is that given by Stewart, Davidson and Simpson (1965). No corrections were made for absorption ($\mu = 6.0 \text{ cm}^{-1}$).

Phase determination

Normalized structure factors $|E|$ (Karle & Karle, 1966) were calculated using an overall temperature factor of 2.8 \AA^2 . All the observable data were used, and the symmetry effects on the average distribution of the intensity data was corrected for by the method of Wilson (1950). The observed and theoretical values for certain statistical averages and distributions are shown in Table 2.

These values indicated that the phase solution for this data set would not be routine. A recheck of the dif-

Table 2. *Distribution of normalized structure factors*

	Observed	Theoretical	
		Centric	Acentric
$\langle E \rangle$	0.811	0.798	0.886
$\langle E ^2 - 1 \rangle$	0.905	0.968	0.736
$\langle E ^2 - 1 \rangle$	0.024	0.000	0.000

fraction data confirmed that the space group was indeed $P2_12_12_1$, but the values in Table 2 indicated the 'centric nature' of the data. The reason for this was quickly determined when a list of E values was inspected. Of the 25 largest E values only 8 were from general reflections; of the remaining 17 reflections, the space group restricted the phases of 10 to 0 or π and those of 7 to $\pi/2$ or $-\pi/2$. Owing to this unusual distribution, the selection of a set of starting phases deviated from the normal procedure.

Normally, three reflections with the largest E 's and numerous relationships, would be chosen as origin defining reflections (using proper parity, of course). However, this procedure failed miserably when three two-dimension reflections were used to define the origin. The results of the symbolic addition and tangent refinement gave a set of phases having values of only, 0, $+\pi/2, \pi$. The resulting E map was, of course, unin-

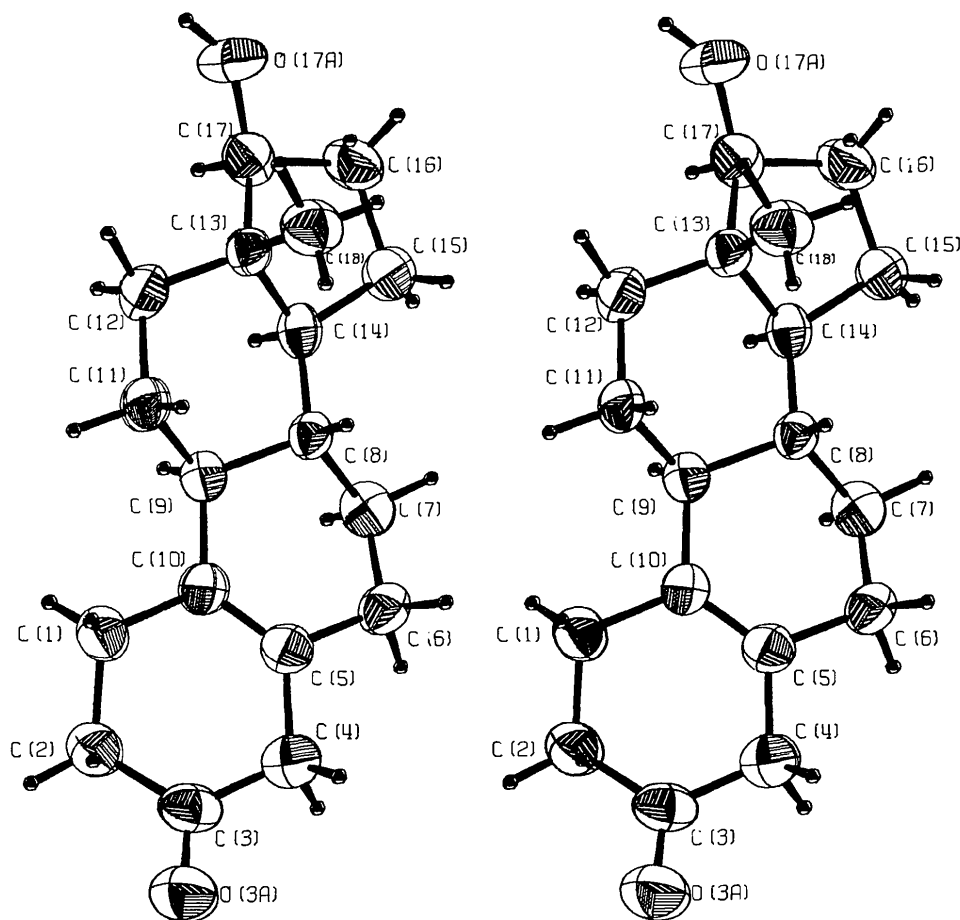


Fig. 1. A stereoscopic view of steroid (Ia).

terpretable. A new set of origin defining reflections was chosen to include a general reflection, even though this general reflection had a rather low E value and gave rise to few relationships. The reflections chosen were 3,0,14, 0,5,10, 1,6,9 and their assigned phases were 0, π/2 and π/4 respectively. The enantiomorph was fixed by assigning to the 2,0,1 reflection a phase of π/2. Since the 2,0,2 and 4,0,4 reflections were among the 4 largest E's, the phase of 4,0,4 was starting set, manual

symbolic addition using the formula φ_n ≈ ⟨φ_k + φ_{h-k}⟩_kr generated 14 additional phases. During the symbolic addition procedure a new phase was accepted if its α value was greater than 2.8 (Germain, Main & Woolfson, 1970). An α value of 2.8 corresponds to a standard deviation of about 39 degrees in a phase angle.

This set of 19 phases was used as input to a program for the iterative application of the tangent formula (Karle & Hauptman, 1956). It was possible through the cyclic application of the tangent formula to eventually

Table 3. Observed and calculated structure factors

Within each group the columns contain I, 10F_o, 10F_c, and φc(°), the phase angle. Reflections marked with an asterisk were assigned zero weight in the final least-square cycles.

Table with multiple columns containing numerical data for reflections, including indices (h, k, l), observed intensity (I), observed structure factor (10F_o), calculated structure factor (10F_c), and phase angle (φc). The table is organized into groups and includes reflections marked with an asterisk (*).

determine the phases for 139 reflections with E values greater than 1.20. During the course of tangent expansion and refinement, the phases of the original 5 reflections were not allowed to change. These 139 reflections were used to prepare an E map which revealed the entire structure.

Refinement of the structure

All calculations were carried out on an IBM 370/165 computer with subprograms operating under the

CRYM system. The full-matrix least-squares routine minimized 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 refinement was performed on the coordinates, isotropic temperature factors and a scale factor. After the R index had reached a value below 0.20, anisotropic temperature factors were introduced. After several cycles of refinement with anisotropic temperature factors, the hydrogen positions were

Table 4. *Heavy-atom parameters and their standard deviations*

The values have been multiplied by 10^5 . The temperature factor is in the form

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

	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	77450 (45)	-4291 (55)	41059 (21)	1034 (70)	1727 (106)	328 (18)	-273 (163)	6 (62)	330 (78)
C(2)	79541 (47)	-9248 (58)	48559 (22)	1237 (72)	2103 (118)	322 (17)	-382 (168)	5 (64)	468 (78)
C(3)	93874 (48)	-5083 (62)	51050 (21)	1174 (72)	2149 (124)	214 (16)	398 (175)	146 (61)	260 (77)
O(3A)	100714 (33)	-14774 (43)	54484 (17)	1546 (56)	2668 (93)	426 (13)	7 (131)	-307 (45)	814 (57)
C(4)	99086 (46)	12025 (59)	49450 (23)	1370 (73)	2153 (130)	288 (16)	-160 (188)	-142 (66)	166 (82)
C(5)	91689 (46)	20497 (56)	43578 (20)	1085 (70)	1479 (101)	220 (17)	70 (157)	58 (61)	8 (69)
C(6)	95969 (45)	38528 (58)	42640 (20)	1258 (70)	1515 (108)	253 (16)	-227 (164)	-156 (59)	-140 (68)
C(7)	85759 (47)	47872 (53)	38076 (20)	1393 (76)	1390 (99)	245 (15)	124 (166)	240 (65)	-277 (68)
C(8)	82676 (40)	38007 (51)	31646 (19)	771 (59)	1297 (94)	211 (14)	-159 (142)	72 (51)	-88 (65)
C(9)	75588 (46)	21491 (52)	33514 (19)	941 (66)	1246 (89)	237 (15)	-168 (151)	87 (67)	-37 (65)
C(10)	82368 (42)	13138 (52)	39576 (21)	835 (61)	1277 (94)	237 (15)	0 (145)	50 (55)	-84 (67)
C(11)	73904 (49)	10772 (49)	27107 (21)	1185 (68)	1033 (92)	291 (16)	-278 (156)	-140 (62)	-28 (64)
C(12)	66174 (46)	19578 (55)	21287 (21)	1038 (69)	1504 (102)	305 (16)	240 (156)	-173 (61)	-68 (70)
C(13)	72465 (43)	36297 (52)	19560 (19)	829 (64)	1278 (91)	213 (15)	-191 (152)	31 (54)	7 (66)
C(14)	74140 (47)	46448 (53)	26175 (20)	813 (62)	1338 (96)	271 (16)	-153 (155)	168 (57)	-61 (68)
C(15)	77783 (51)	63808 (57)	23604 (22)	1621 (85)	1274 (94)	341 (17)	-287 (184)	-302 (67)	198 (73)
C(16)	69950 (52)	65225 (56)	16749 (22)	1699 (89)	1456 (99)	297 (17)	122 (173)	-30 (65)	361 (72)
C(17)	63527 (46)	48195 (56)	15342 (21)	1028 (68)	1580 (106)	304 (17)	65 (164)	43 (61)	217 (73)
O(17A)	62686 (33)	45301 (40)	8213 (13)	1839 (54)	2409 (79)	200 (10)	345 (120)	-250 (43)	56 (51)
C(18)	86390 (48)	33594 (58)	15869 (20)	1240 (79)	2083 (118)	258 (16)	176 (178)	116 (60)	70 (72)

Table 5. *Coordinates and standard deviations of the hydrogen atoms*

Coordinates have been multiplied by 10^4 .

Atom bearing H	x	y	z	B	
H(21)	1	6822 (35)	-492 (43)	4021 (16)	4.56 (0.86)
H(22)	1	8280 (39)	-1250 (45)	3799 (17)	6.31 (1.02)
H(23)	2	7719 (43)	-2071 (49)	4964 (19)	6.11 (0.97)
H(24)	2	7375 (49)	-257 (51)	5162 (19)	7.99 (1.14)
H(25)	4	10871 (43)	1090 (52)	4862 (18)	6.56 (1.05)
H(26)	4	9818 (47)	1984 (59)	5446 (22)	8.19 (1.24)
H(27)	6	10603 (45)	3998 (51)	4082 (20)	7.71 (1.15)
H(28)	6	9592 (36)	4333 (45)	4777 (16)	4.68 (0.90)
H(29)	7	7698 (35)	4969 (42)	4042 (15)	4.14 (0.84)
H(30)	7	8983 (37)	5894 (42)	3667 (15)	4.27 (0.91)
H(31)	11	6945 (35)	1 (46)	2826 (17)	4.75 (0.89)
H(32)	11	8345 (35)	764 (43)	2561 (16)	3.64 (0.87)
H(33)	12	5713 (34)	2028 (42)	2236 (15)	3.02 (0.78)
H(34)	12	6643 (38)	1237 (45)	1637 (17)	5.58 (0.98)
H(35)	15	8791 (40)	6464 (46)	2301 (16)	4.68 (0.91)
H(36)	15	7544 (41)	7325 (45)	2706 (17)	5.03 (0.95)
H(37)	16	7582 (37)	6819 (39)	1283 (15)	3.64 (0.80)
H(38)	16	6204 (42)	7250 (48)	1695 (18)	6.15 (1.07)
H(39)	8	9104 (32)	3579 (36)	2940 (14)	2.24 (0.70)
H(40)	9	6562 (32)	2454 (38)	3484 (14)	2.21 (0.73)
H(41)	14	6541 (30)	4707 (36)	2809 (14)	2.18 (0.69)
H(42)	17	5414 (31)	4750 (38)	1720 (13)	2.08 (0.72)
H(43)	18	9270 (42)	2885 (50)	1853 (18)	5.88 (0.99)
H(44)	18	9083 (45)	4277 (55)	1464 (18)	6.30 (1.08)
H(45)	18	8519 (39)	2748 (48)	1101 (19)	5.86 (0.99)
H(46)	17A	6001 (80)	3946 (85)	603 (30)	16.50 (2.34)

located using difference Fourier techniques where necessary, and the methylene and methine hydrogen positions were calculated. Both the coordinates and isotropic temperature factors for the hydrogen atoms were included in the refinement. In the later stages of refinement a secondary extinction factor was also included; the expression used was $F_{\text{corrected}}^2 = (F_{\text{cal}})^2 / [1 + g\beta(F_{\text{cal}})^2]$ (Larson, 1967). During the final cycles of refinement the atomic coordinates for all atoms were contained in one matrix, and the temperature factors, scale factor and secondary extinction factor were included in a second matrix. The final value for the secondary extinction factor g was $9.38(\pm 0.6) \times 10^{-6}$. The final R index $\sum ||F_o| - |F_c|| / \sum |F_o|$, was 0.040; the 'goodness of fit', $\sum w(F_o^2 - F_c^2)^2 / (m - s)$ (where m is the number of observations and s is the number of parameters refined) was 2.62. The observed and calculated structure factors, F_o and F_c , and the phase angles, ϕ , are listed in Table 3.

The final coordinates and anisotropic temperature factors for the nonhydrogen 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 4. The positional parameters and isotropic temperature factors with their standard deviations for the hydrogen atoms are given in Table 5. The shifts calculated for the parameters in the final cycle of the least-squares refinement were all less than one-tenth of the corresponding standard deviations.

Discussion of the crystallographic results

A stereoscopic view of the molecule is shown in Fig. 1, (Johnson, 1965). The conformation of the A ring in 17 β -hydroxyestr-5(10)-en-3-one (*1a*) is compared with the conformation of ring A in the 17 β -iodoacetate derivative of 17 β -hydroxyestr-5(10)-en-3-one (*1b*) in Table 6. It can be seen that both compounds are practically identical and contain a semi-planar conformation of ring A . The bond distances and angles for (*1a*) are given in Tables 7 and 8. Bond distances and angles involving hydrogen atoms were as expected.

The standard deviations in atomic coordinates for compound (*1a*) (Tables 4 and 5) correspond to positional uncertainties of approximately 0.005 Å for the carbon atoms, 0.004 Å for the oxygen atoms, and 0.05 Å for the hydrogen atoms. The standard deviations are expected to be about 0.007 Å for the C-C distances, 0.006 Å for the C-O distances, 0.04 Å for the C-H distances, and 0.08 Å for the O-H distance. The standard deviations in the bond angles between nonhydrogen atoms are about 0.5 degrees and about 4.0 degrees for angles involving hydrogen atoms.

Discussion of chemical results

The results of this analysis are far more satisfying, crystallographically, than the results previously published for the iodoacetate derivative (*1b*). However,

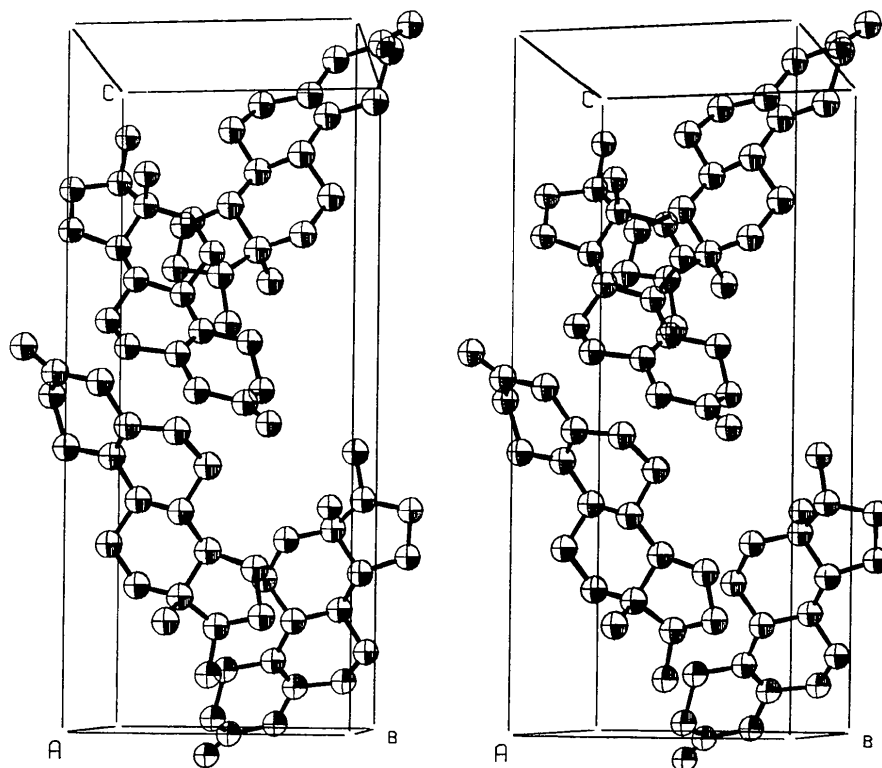


Fig. 2. A stereoscopic view down the x axis showing the packing of the molecules in the unit cell.

Table 6. Conformation of ring *A* in compounds (Ia) and (Ib)

The least-squares plane is defined by carbon atoms 1, 4, 5, 6, 9, 10. The positive direction is defined as the direction towards O(17).

Atom	Deviation (Å)	
	Ia	Ib
C(1)	-0.05	-0.04
C(2)	-0.67	-0.61
C(3)	-0.07	-0.06
C(4)	0.05	0.03
C(5)	0.00	0.00
C(6)	-0.05	-0.03
C(9)	0.04	0.03
C(10)	0.02	0.02

Table 7. Atomic distances

C(1)–C(2)	1.53 Å	C(9)–C(10)	1.51 Å
C(1)–C(10)	1.52	C(9)–C(11)	1.53
C(2)–C(3)	1.49	C(11)–C(12)	1.53
C(3)–C(4)	1.50	C(12)–C(13)	1.52
C(3)–O(3A)	1.22	C(13)–C(14)	1.54
C(4)–C(5)	1.51	C(13)–C(17)	1.53
C(5)–C(6)	1.53	C(13)–C(18)	1.53
C(5)–C(10)	1.33	C(14)–C(15)	1.53
C(6)–C(7)	1.52	C(15)–C(16)	1.54
C(7)–C(8)	1.51	C(16)–C(17)	1.53
C(8)–C(9)	1.54	C(17)–O(17A)	1.41
C(8)–C(14)	1.51		

Table 8. Bond angles

C(10)–C(1)–C(2)	113°
C(3)–C(2)–C(1)	112
C(4)–C(3)–C(2)	116
O(3A)–C(3)–C(2)	122
O(3A)–C(3)–C(4)	122
C(5)–C(4)–C(3)	115
C(6)–C(5)–C(4)	113
C(10)–C(5)–C(4)	124
C(10)–C(5)–C(6)	123
C(7)–C(6)–C(5)	112
C(8)–C(7)–C(6)	110
C(9)–C(8)–C(7)	110
C(14)–C(8)–C(7)	117
C(14)–C(8)–C(9)	109
C(10)–C(9)–C(8)	112
C(11)–C(9)–C(8)	110
C(11)–C(9)–C(10)	116
C(5)–C(10)–C(1)	121
C(9)–C(10)–C(1)	116
C(9)–C(10)–C(5)	123
C(12)–C(11)–C(9)	113
C(13)–C(12)–C(11)	113
C(14)–C(13)–C(12)	109
C(17)–C(13)–C(12)	117
C(18)–C(13)–C(12)	109
C(17)–C(13)–C(14)	100
C(18)–C(13)–C(14)	112
C(18)–C(13)–C(17)	109
C(13)–C(14)–C(8)	114
C(15)–C(14)–C(8)	122
C(15)–C(14)–C(13)	104
C(16)–C(15)–C(14)	104
C(17)–C(16)–C(15)	107
C(16)–C(17)–C(13)	104
O(17A)–C(17)–C(13)	117
O(17A)–C(17)–C(16)	110

both results seem to indicate some very interesting new chemistry – the conformation of the *A* ring in this type of steroid is not the generally accepted half-chair conformation, but the unexpected semiplanar conformation. Of course we are now left with the classic question of whether or not the conformation of ring *A* in the crystalline state is a true reflection of the conformation in the solution state. The packing diagram of (Ia) may be of interest (Fig. 2). The only close-contact distance between molecules is 2.88 Å between the alcoholic oxygen [O(17A)] in the base molecule and the carbonyl oxygen [O(3A)] of the molecule in the equivalent position $\bar{x}+1.5$, \bar{y} , $z-0.50$. The distance between the carbonyl oxygen and the alcoholic hydrogen is 2.18 Å. The angle between O(3A)–H(46)–O(17A) is 140°. This would indicate a possible hydrogen bond, but it seems unlikely that this interaction would significantly affect the conformation of ring *A* since the crystal structure of the iodoacetate derivative shows no close contacts. Since the two compounds crystallized in two different space groups (Ia: $P2_12_12_1$ and Ib: $P2_1$) and since both displayed the semi-planar configuration of ring *A*, it can be assumed that crystal packing forces are not causing this unusual conformation of ring *A*.

The above assumption, of course, is far from fully substantiated. Further experiments are in progress to verify or disprove the existence of the semi-planar configuration in ring *A* of these two steroids in solution. Hopefully, the coordinates obtained in this analysis will enable a careful inspection of n.m.r. coupling constants which will confirm or disprove the existence of the semi-planar configuration in solution.

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