

Conformational Changes in Two Modifications of 2,4-Dibromoestradiol

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(Received 22 July 1970 and in revised form 11 January 1971)

Significant conformational differences in three molecules of 2,4-dibromoestradiol are seen to occur as a result of intramolecular forces involving angle strain and eclipsing strain as well as intermolecular forces of hydrogen bonding and van der Waals contacts in two crystalline modifications. Crystal *A* (orthorhombic, $P2_12_12_1$; $Z=4$, $a=11.942$, $b=13.197$, $c=10.639$ Å, $R=4.8\%$) has short bromine-bromine contacts of 3.63 Å, has a half-chair conformation of the *B* ring and has an O(3)–H(03)···O(17) hydrogen bond of 2.84 Å. Crystal *B* (monoclinic, $P2_1$; $Z=4$, $a=13.081$, $b=16.995$, $c=8.074$ Å, $\beta=111.57^\circ$, $R=5.0\%$) has no bromine contacts. Molecule *B2* has a half-chair conformation *B* ring and an O(3)–H(03)···O(17) hydrogen bond of 2.77 Å. Molecule *B1* has a sofa conformation *B*-ring and has a double hydrogen bond O(3)–H(03)···O(17) and O(17)–H(017)···O(3) of length 2.67 Å. Each of the three types of molecules form infinite chains that are packed together in parallel strands with few contacts between the chains.

Introduction

Small molecular conformational differences observed in crystal structure determinations are most often considered to be a result of packing forces. In a series of estrane structures which all have aromatic *A* rings (Cooper, Norton & Hauptman, 1969; Norton, Kartha & Lu, 1963; 1964, Busetta & Hospital, 1969; Tsukuda, Soto, Shiro & Kayama, 1968) the steroid *B* rings are observed in either a half-chair or a sofa conformation and no clear dependence of this small but significant conformational difference upon the crystalline environment has been detected. It is possible that the molecules in which the *B* rings are observed in half-chair and sofa conformations represent metastable states of estranes at room temperature. Because even small conformational differences can alter molecular reactivity (Hanack, 1965; Geise, Altona & Romers, 1967; Altona, Geise & Romers, 1968) the question of whether or not this recurring conformational difference is inherent to the molecule or just an artifact of crystal environment is a pertinent one. Another steroid in the estrane series, 2,4-dibromoestradiol (Fig. 1) recently was obtained in two crystalline modifications with no solvent of crystallization in either lattice, and structure solutions were undertaken in order to study the effect of alteration of crystal environment upon this steroid's conformation.

Crystal data

Two crystalline modifications of 2,4-dibromoestradiol were prepared. Modification *A* was recrystallized as thin plates from a benzene-methanol solution saturated with urea at 50°C and cooled slowly to 20°C. The crystal system was found to be orthorhombic and the systematic absences ($h00$, $h=2n+1$; $0k0$, $k=2n+1$; $00l$, $l=2n+1$) indicated the space group $P2_12_12_1$. Columnar crystals of modification *B* were obtained from

an ethanol solution cooled from room temperature to 5°C. These crystals were monoclinic and the systematic absences ($0k0$, $k=2n+1$) indicated the space group $P2_1$. Unit-cell dimensions were obtained from a least-squares refinement of 2θ measurements of 6 reflections per parameter having $2\theta > 45^\circ$. The cell dimensions indicated that there were two steroids in the asymmetric unit of the monoclinic crystals. Densities were measured by flotation in aqueous solutions of potassium iodide.

Crystals selected for data collection were approximately spherical (0.15 mm diameter) and were mounted with the *b* axes parallel to the φ axis of a General Electric XRD-5 diffractometer.

Table 1. Crystal data for 2,4-dibromoestradiol

Crystalline modification	<i>A</i>	<i>B</i>
	$P2_12_12_1$	$P2_1$
Space group	$P2_12_12_1$	$P2_1$
<i>a</i>	11.942 ± 0.002 Å	13.081 ± 0.003 Å
<i>b</i>	13.197 ± 0.002	16.995 ± 0.004
<i>c</i>	10.639 ± 0.001	8.074 ± 0.002
β	90.0°	$111.57 \pm 0.02^\circ$
<i>V</i>	1682 Å ³	1669 Å ³
<i>D_c</i>	1.70 g.cm ⁻³	1.70 g.cm ⁻³
<i>D_m</i>	1.37 g.cm ⁻³	1.37 g.cm ⁻³
<i>Z</i>	4	4
<i>R</i> (observed data)	4.8 (1037)	5.0 (2207)
<i>R</i> (all data*)	6.3 (1545)	6.4 (2880)
M.W.	430.19	430.19
Formula	$C_{18}H_{22}O_2Br_2$	$C_{18}H_{22}O_2Br_2$
μ (cm ⁻¹)	68.19	68.72
Total data	1769	3249

* Not including unobserved data for which $(|F_o| - |F_c|)/|F_o| < 0.7$.

The intensities of all reflections (1769 and 3249 respectively) with 2θ values less than 135° were measured by the stationary-crystal stationary-counter method with Cu *K* α radiation monochromatized by balanced nickel and cobalt filters. The shape anisotropy of the

crystals measured at $\chi=90^\circ$ indicated a less than 5% variation in intensities over the φ range of data collection. Intensities were corrected for Lorentz and polarization factors but not for absorption ($\mu R=0.5$). The crystal data are collected in Table 1.

Table 2. Variation in reliability index with application of anomalous dispersion correction

Structure	Reliability index		
	$f''=0$	$f''=1.46$	$f''=-1.46$
A	5.9%	5.86%	6.05%
B	6.0	5.76	6.12

Structure determination

Positional parameters for all bromine atoms in both structures were found from Patterson functions of the respective space groups. The complete steroids were found from repeated application of three-dimensional Fourier synthesis. Four cycles of isotropic diagonal least-squares refinement resulted in R values ($R=\sum||F_o|-|F_c||/\sum F_o$) for the orthorhombic (A) and monoclinic (B) structures of 16.4% and 10.6% respectively. Four cycles of anisotropic block diagonal least-squares refinement on observed data reduced the R values to

Table 3(a). Positional and thermal parameters of the non-hydrogen atoms at the end of the least-squares refinement

The first listing are those parameters for molecule A while molecules B1 and B2 are distinguished by the prefixes 1 and 2 respectively. Thermal parameters are listed in the form

$$\exp[-2\pi^2(U_{11}h^2a^{*2}+2U_{12}hka^*b^*+\dots)].$$

	X/A	Y/B	Z/C	U11	U22	U33	U12	U13	U23
C(1)	0.0163 (9)	0.9826 (6)	0.0191 (9)	0.0563(73)	0.0268(47)	0.0395(56)	-0.0067(50)	0.0031(55)	-0.0022(43)
C(2)	0.0417 (10)	1.0863 (6)	0.0067 (9)	0.0622(71)	0.0285(49)	0.0501(59)	-0.0028(57)	0.0032(65)	-0.0106(45)
C(3)	0.1258 (10)	1.1298 (6)	0.0765 (9)	0.0936(84)	0.0150(39)	0.0392(56)	-0.0030(53)	0.0182(61)	0.0059(43)
C(4)	0.1868 (10)	1.0654 (6)	0.1544 (9)	0.0734(80)	0.0276(46)	0.0344(54)	-0.0126(55)	0.0085(63)	-0.0067(43)
C(5)	0.1622 (9)	0.9633 (6)	0.1709 (9)	0.0597(73)	0.0218(43)	0.0402(56)	0.0017(48)	0.0039(56)	-0.0068(43)
C(6)	0.2277 (9)	0.9009 (6)	0.2643 (9)	0.0649(71)	0.0742(43)	0.0376(54)	-0.0027(45)	0.0063(59)	0.0044(43)
C(7)	0.1859 (11)	0.7928 (7)	0.2824 (9)	0.0927(92)	0.0359(51)	0.0380(59)	0.0006(62)	-0.0141(67)	-0.0059(46)
C(8)	0.1507 (9)	0.7486 (6)	0.1565 (9)	0.0697(75)	0.0218(45)	0.0422(58)	-0.0091(50)	-0.0073(60)	0.0080(45)
C(9)	0.0468 (10)	0.8091 (5)	0.1123 (8)	0.0714(72)	0.0172(39)	0.0328(49)	0.0047(48)	-0.0012(62)	0.0015(39)
C(10)	0.0754 (9)	0.9223 (6)	0.0984 (10)	0.0772(82)	0.0282(46)	0.0403(57)	0.0076(51)	0.0175(65)	0.0000(50)
C(11)	-0.0050 (10)	0.7626 (7)	-0.0102 (11)	0.0704(86)	0.0291(49)	0.0505(61)	0.0011(52)	-0.0136(63)	0.0044(47)
C(12)	-0.0287 (10)	0.6474 (6)	0.0011 (11)	0.0644(81)	0.0294(54)	0.0747(73)	-0.0169(56)	-0.0199(72)	0.0085(48)
C(13)	0.0740 (8)	0.5936 (7)	0.0431 (8)	0.0515(65)	0.0376(52)	0.0294(49)	-0.0002(50)	0.0062(49)	-0.0007(42)
C(14)	0.1179 (9)	0.6370 (6)	0.1660 (9)	0.0667(71)	0.0208(43)	0.0347(53)	0.0014(47)	-0.0012(56)	0.0097(44)
C(15)	0.2090 (11)	0.5624 (7)	0.2125 (9)	0.0904(94)	0.0319(52)	0.0472(64)	0.0093(62)	-0.0091(69)	-0.0003(44)
C(16)	0.1620 (11)	0.4588 (7)	0.1656 (11)	0.0950(98)	0.0233(47)	0.0621(75)	0.0061(59)	-0.0094(78)	0.0087(52)
C(17)	0.0601 (11)	0.4813 (6)	0.0872 (10)	0.0913(89)	0.0163(39)	0.0522(66)	0.0025(53)	0.0106(74)	-0.0096(45)
O(1)	0.1635 (11)	0.5947 (4)	-0.0618 (10)	0.0892(96)	0.0431(59)	0.0440(63)	0.0072(66)	0.0086(67)	0.0025(50)
O(3)	0.1563 (7)	1.2277 (4)	0.0712 (7)	0.0927(65)	0.0219(32)	0.0626(50)	-0.0146(39)	-0.0159(50)	0.0057(33)
O(17)	0.0507 (8)	0.4083 (5)	-0.0125 (8)	0.1114(72)	0.0306(38)	0.0810(57)	-0.0018(50)	-0.0317(64)	-0.0026(39)
BR(2)	-0.0440 (1)	1.1676 (0)	-0.1005 (1)	0.1074(10)	0.0328(5)	0.0675(7)	-0.0042(7)	-0.0238(7)	0.0077(6)
BR(4)	0.3069 (1)	1.1235 (0)	0.2463 (1)	0.0976(9)	0.0470(6)	0.0732(7)	-0.0204(7)	-0.0212(9)	0.0017(7)
IC(1)	0.2204 (8)	0.1518 (7)	0.2926 (13)	0.0358(54)	0.0456(68)	0.0336(53)	-0.0016(57)	0.0146(44)	-0.0056(55)
IC(2)	0.3230 (8)	0.1662 (7)	0.2872 (13)	0.0284(54)	0.0572(81)	0.0345(56)	0.0009(53)	0.0160(45)	0.0115(54)
IC(3)	0.3376 (8)	0.1913 (6)	0.1338 (14)	0.0328(59)	0.0376(62)	0.0422(58)	0.0011(51)	0.0200(48)	0.0075(51)
IC(4)	0.2432 (8)	0.2046 (6)	-0.0160 (12)	0.0368(55)	0.0464(66)	0.0263(47)	-0.0084(51)	0.0184(42)	0.0032(47)
IC(5)	0.1378 (8)	0.1900 (6)	-0.0197 (13)	0.0372(56)	0.0341(61)	0.0339(52)	-0.0022(50)	0.0195(45)	-0.0054(48)
IC(6)	0.0400 (9)	0.2041 (8)	-0.1854 (13)	0.0412(62)	0.0736(91)	0.0242(51)	0.0059(62)	0.0183(47)	-0.0072(57)
IC(7)	-0.0691 (8)	0.1851 (8)	-0.1733 (13)	0.0313(56)	0.0826(95)	0.0235(50)	-0.0025(59)	0.0133(44)	0.0043(56)
IC(8)	-0.0720 (8)	0.2012 (7)	0.0121 (12)	0.0387(58)	0.0456(69)	0.0276(50)	-0.0016(53)	0.0183(44)	-0.0120(49)
IC(9)	0.0118 (8)	0.1478 (6)	0.1418 (11)	0.0368(53)	0.0397(61)	0.0231(47)	-0.0016(53)	0.0168(42)	-0.0004(48)
IC(10)	0.1268 (8)	0.1639 (6)	0.1410 (12)	0.0351(55)	0.0380(66)	0.0189(45)	0.0005(49)	0.0103(41)	0.0074(44)
IC(11)	0.0094 (8)	0.1480 (8)	0.3322 (13)	0.0383(59)	0.0627(79)	0.0307(53)	0.0018(62)	0.0217(47)	-0.0080(58)
IC(12)	-0.1072 (9)	0.1346 (7)	0.3281 (14)	0.0405(62)	0.0632(85)	0.0352(58)	0.0014(59)	0.0253(51)	-0.0083(55)
IC(13)	-0.1862 (8)	0.1940 (7)	0.2054 (13)	0.0261(51)	0.0600(77)	0.0271(51)	-0.0023(53)	0.0126(41)	-0.0018(52)
IC(18)	-0.1602 (11)	0.2764 (8)	0.2792 (19)	0.0295(56)	0.0780(95)	0.0305(54)	0.0060(59)	0.0125(45)	0.0073(59)
10(1)	0.4375 (6)	0.2070 (6)	0.1221 (11)	0.0344(63)	0.1181(99)	0.0465(69)	-0.0185(78)	0.0232(56)	-0.0306(81)
IC(14)	-0.1840 (8)	0.1837 (8)	0.0176 (14)	0.0458(73)	0.1341(99)	0.0467(72)	-0.0188(92)	0.0244(61)	-0.0343(93)
IC(15)	-0.2830 (9)	0.2336 (10)	-0.0981 (16)	0.0325(59)	0.1076(99)	0.0329(58)	-0.0053(67)	0.0175(48)	-0.0120(66)
IC(16)	-0.3691 (10)	0.2239 (12)	-0.0086 (17)	0.0536(77)	0.0642(94)	0.0685(89)	0.0013(71)	0.0297(69)	0.0279(77)
IC(17)	-0.3070 (9)	0.1772 (9)	0.1628 (14)	0.0326(63)	0.1000(79)	0.0571(52)	0.0003(68)	0.0268(39)	-0.0139(53)
10(17)	-0.3464 (7)	0.1983 (7)	0.3063 (11)	0.0449(52)	0.1530(99)	0.0435(47)	-0.0120(62)	0.0312(42)	-0.0028(59)
1BR(2)	0.4501 (1)	0.1501 (1)	0.4955 (1)	0.0366(6)	0.0850(10)	0.0386(6)	-0.0105(7)	0.0115(5)	-0.0082(7)
1BR(4)	0.2638 (1)	0.2361 (1)	-0.2245 (1)	0.0528(6)	0.0979(12)	0.0396(6)	0.0032(8)	0.0281(6)	-0.0181(8)
2C(1)	0.7134 (8)	0.4185 (6)	0.5411 (13)	0.0359(54)	0.0403(66)	0.0349(53)	0.0025(51)	0.0193(44)	0.0120(50)
2C(2)	0.8160 (8)	0.4375 (7)	0.5391 (13)	0.0417(60)	0.0566(81)	0.0242(50)	-0.0062(61)	0.0079(44)	0.0033(54)
2C(3)	0.8286 (8)	0.4623 (7)	0.3800 (14)	0.0275(54)	0.0422(63)	0.0367(55)	-0.0009(50)	0.0079(45)	0.0020(49)
2C(4)	0.7326 (8)	0.4708 (6)	0.2309 (13)	0.0395(58)	0.0388(65)	0.0275(51)	-0.0053(50)	0.0127(45)	0.0007(47)
2C(5)	0.6292 (8)	0.4536 (6)	0.2287 (13)	0.0288(50)	0.0457(70)	0.0281(50)	-0.0028(47)	0.0094(41)	0.0069(47)
2C(6)	0.5290 (9)	0.4646 (8)	0.0669 (14)	0.0402(62)	0.0809(96)	0.0258(51)	0.0093(62)	0.0181(47)	-0.0049(57)
2C(7)	0.4238 (8)	0.4280 (8)	0.0717 (12)	0.0315(52)	0.0748(83)	0.0207(47)	0.0068(63)	0.0128(40)	-0.0080(57)
2C(8)	0.4123 (8)	0.4417 (7)	0.2489 (12)	0.0440(59)	0.0509(76)	0.0257(48)	-0.0065(55)	0.0211(45)	0.0049(49)
2C(9)	0.5078 (8)	0.4015 (6)	0.3958 (13)	0.0374(56)	0.0495(70)	0.0252(50)	-0.0079(52)	0.0179(44)	-0.0057(49)
2C(10)	0.4209 (7)	0.4274 (7)	0.3934 (12)	0.0278(48)	0.0498(86)	0.0229(46)	0.0033(54)	0.0140(39)	0.0074(51)
2C(11)	0.5006 (8)	0.4093 (7)	0.5806 (12)	0.0387(58)	0.0653(85)	0.0216(48)	0.0048(56)	0.0165(43)	0.0054(50)
2C(12)	0.3878 (8)	0.3804 (7)	0.5804 (13)	0.0294(56)	0.0608(81)	0.0316(55)	-0.0046(55)	0.0161(46)	-0.0006(55)
2C(13)	0.2944 (7)	0.4231 (7)	0.4366 (12)	0.0302(51)	0.0478(67)	0.0284(49)	-0.0036(54)	0.0127(41)	0.0001(52)
2C(14)	0.3058 (7)	0.4087 (6)	0.2554 (13)	0.0238(48)	0.0539(80)	0.0294(51)	0.0072(49)	0.0121(41)	0.0080(49)
2C(15)	0.1950 (9)	0.4355 (9)	0.1171 (14)	0.0438(63)	0.0853(99)	0.0308(59)	0.0068(73)	0.0100(50)	0.0053(69)
2C(16)	0.1116 (9)	0.4141 (9)	0.2055 (16)	0.0318(58)	0.1082(99)	0.0435(65)	0.0008(71)	0.0150(50)	-0.0312(75)
2C(17)	0.1805 (8)	0.3848 (7)	0.3942 (13)	0.0370(59)	0.0622(79)	0.0280(52)	-0.0017(57)	0.0160(46)	-0.0056(54)
2C(18)	0.2893 (10)	0.5093 (8)	0.4807 (16)	0.0521(71)	0.0622(88)	0.0467(67)	0.0028(66)	0.0309(58)	0.0097(63)
20(1)	0.9249 (5)	0.4811 (5)	0.3676 (10)	0.0290(39)	0.0785(68)	0.0479(45)	0.0035(42)	0.0205(35)	-0.0016(45)
20(17)	0.1255 (6)	0.4053 (6)	0.5136 (11)	0.0439(45)	0.0930(78)	0.0474(48)	-0.0116(47)	0.0290(39)	-0.0171(47)
2BR(2)	0.9423 (0)	0.4261 (0)	0.7457 (1)	0.0348(6)	0.0761(9)	0.0342(6)	-0.0006(7)	0.0008(1)	-0.0003(1)
2BR(4)	0.7503 (1)	0.4983 (1)	0.0171 (1)	0.0576(7)	0.0702(9)	0.0368(6)	0.0031(7)	0.0283(6)	-0.0114(7)

squares refinement were based upon all data, the imaginary part of the anomalous dispersion correction was included in the calculation and the weighting scheme was the following: $w^{-1} = \{1 + [(|F_o| - 43)/25]^2\}^{1/2}$. The weighting constants were evaluated to make $\langle w\Delta^2 \rangle$ invariant with changing $|F_o|$. The unobserved data were only allowed to influence the refinement if $|F_o - F_c|/F_o$ was less than 0.7. The positional parameters of the hydrogen atoms were refined with the thermal parameters held at 3.0. The refinement was terminated when all non-hydrogen parameter shifts were less than one half standard deviations. The molecular geometry indicated that the hydrogen atom positions were improved by the refinement but in some cases they were still oscillating at standard deviations when refinement was terminated, with the minimization function, $\sum w(|F_o| - |F_c|)^2/m - n$, at 2.35 and 2.39 for structures *A* and *B* respectively. The final *R* values were 6.3% and 6.4% for all data except unobserved reflections with $|F_o - F_c|/F_o < 0.7$ and 4.8% and 5.0% for observed data only. Data were considered observed if their intensities were greater than twice their estimated standard deviation.

The final fractional coordinates and anisotropic thermal parameters for the three molecules are given in Table 3(a) while the hydrogen parameters are listed in 3(b). The observed and calculated structure factor amplitudes for all observed data are listed in Table 4.

Results

Steroid geometry

The bond lengths, valency angles and torsional angles for the three molecules are listed in Table 5. The average standard deviations for interatomic distances and angles are 0.015 Å and 1.2° respectively. Although the observed bond lengths and angles may be as much as three standard deviations from theoretical values they are all within one standard deviation of values in similar steroid determinations (Cooper, Norton & Hauptman, 1969). The primary causes of bonding distortions observed in steroid structures are strains imposed by ring junctions, crowding due to the angular methyl groups and conformational transmission effects associated with bond unsaturation or side chain substitutions. The averages of corresponding bond lengths in the three molecules are presented in 5(a). All bond lengths are within two standard deviations of the averages and no significant differences are observed.

Similarly all of the valency angles are within two standard deviations of the average of the corresponding values in the three molecules [Table 5(b), column 4] and no significance can be attached to individual differences. However, inspection of the torsional angles [Table 5(c)] indicates significant differences in the *B* rings of the three molecules. The magnitudes of the differences in corresponding torsional angles, Δtor [Table 5(c)], are less than 4.0° for the torsional angles of the *A*-, *C*- and *D* rings. In contrast to this, the mag-

nitude of the differences in corresponding torsional angles in the *B* ring exceeds 4° in all cases. The *B* ring conformation of no one of the three molecules is responsible for these large deviations. Each molecule has some singularity in the *B* ring torsional angles.

Table 5(a). *Interatomic distances observed in three molecules of 2,4-dibromoestradiol in crystalline modifications A and B*

	Molecule <i>A</i>	Molecule <i>B1</i>	Molecule <i>B2</i>	Average
C(1)—C(2)	1.407 Å	1.380 Å	1.387 Å	1.391 Å
C(2)—C(3)	1.375	1.388	1.418	1.393
C(3)—C(4)	1.393	1.384	1.392	1.389
C(4)—C(5)	1.390	1.386	1.378	1.384
C(5)—C(10)	1.401	1.427	1.444	1.424
C(10)—C(1)	1.357	1.392	1.359	1.369
C(2)—Br(2)	1.871	1.900	1.877	1.882
C(4)—Br(4)	1.898	1.893	1.882	1.891
C(3)—O(3)	1.344	1.370	1.337	1.350
C(5)—C(6)	1.509	1.492	1.484	1.495
C(6)—C(7)	1.523	1.501	1.524	1.516
C(7)—C(8)	1.521	1.535	1.511	1.522
C(8)—C(9)	1.549	1.509	1.530	1.529
C(9)—C(11)	1.567	1.549	1.535	1.550
C(11)—C(12)	1.551	1.530	1.554	1.545
C(12)—C(13)	1.487	1.522	1.525	1.511
C(13)—C(14)	1.521	1.538	1.544	1.534
C(14)—C(8)	1.526	1.512	1.521	1.519
C(14)—C(15)	1.548	1.543	1.538	1.543
C(15)—C(16)	1.560	1.554	1.551	1.555
C(16)—C(17)	1.505	1.542	1.540	1.529
C(17)—C(13)	1.562	1.515	1.544	1.540
C(17)—O(17)	1.438	1.475	1.441	1.451
C(13)—C(18)	1.545	1.511	1.515	1.523

The bromine-carbon distances (average = 1.882 Å) are in good agreement with those found in tetrabromobenzene (Gafner & Herbstein, 1960) and are shorter than the C-Br distances of 1.92 Å and 1.93 Å observed in the 4-monobrominated estranes (Norton, Kartha & Lu, 1963, 1964).

The observed carbon-hydrogen distances range from 0.76 to 1.30 Å (two values exceed 1.18 Å) and

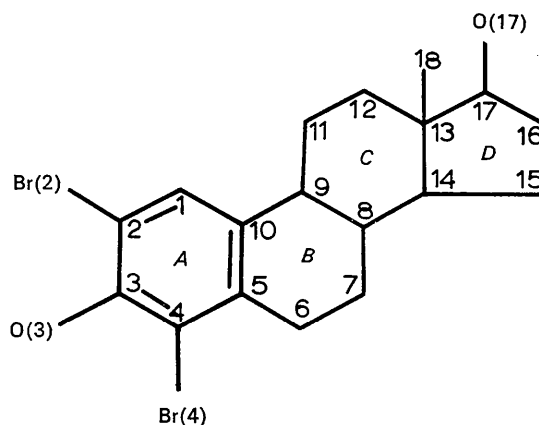


Fig. 1. Schematic representation of the steroid molecule showing the numbering of atoms and rings designations.

Table 5(b). Valency angles observed in three molecules of 2,4-dibromoestradiol

	Molecule A	Molecule B1	Molecule B2	Average
C(10)—C(1)—C(2)	121.1°	119.8°	121.1°	120.7°
C(1)—C(2)—C(3)	120.9	122.5	121.0	121.5
C(2)—C(3)—C(4)	116.6	116.6	116.5	116.6
C(3)—C(4)—C(5)	123.8	124.2	124.0	124.0
C(4)—C(5)—C(10)	117.5	117.2	117.4	117.4
C(5)—C(10)—C(1)	120.0	119.7	119.9	119.9
C(1)—C(2)—Br(2)	119.6	119.4	120.4	119.8
C(3)—C(2)—Br(2)	119.3	118.1	118.5	118.6
C(2)—C(3)—O(3)	125.3	124.7	124.4	124.8
C(4)—C(3)—O(3)	118.0	118.7	119.0	118.6
C(3)—C(4)—Br(4)	117.1	116.4	116.3	116.6
C(5)—C(4)—Br(4)	119.4	119.3	119.5	119.4
C(4)—C(5)—C(6)	120.2	121.1	122.0	121.1
C(6)—C(5)—C(10)	122.4	121.7	120.6	121.6
C(9)—C(10)—C(5)	119.1	119.1	119.6	119.3
C(1)—C(10)—C(9)	120.0	121.2	120.2	120.5
C(5)—C(6)—C(7)	115.1	115.4	116.1	115.5
C(6)—C(7)—C(8)	109.8	112.9	111.5	111.4
C(7)—C(8)—C(9)	107.0	107.3	109.2	107.8
C(8)—C(9)—C(10)	110.6	110.7	112.0	111.1
C(7)—C(8)—C(14)	112.5	111.4	112.7	112.2
C(10)—C(9)—C(11)	112.8	112.4	112.8	112.7
C(12)—C(11)—C(9)	113.0	111.2	111.7	112.0
C(11)—C(9)—C(8)	111.6	114.4	113.0	113.0
C(9)—C(8)—C(14)	108.2	109.0	107.8	108.3
C(8)—C(14)—C(13)	113.3	112.1	112.5	112.6
C(14)—C(13)—C(12)	111.3	108.2	108.4	109.3
C(13)—C(12)—C(11)	109.9	110.4	110.2	110.2
C(12)—C(13)—C(17)	117.1	115.2	114.0	115.4
C(8)—C(14)—C(15)	117.0	118.8	119.8	118.5
C(13)—C(14)—C(15)	106.1	102.6	104.3	104.3
C(14)—C(15)—C(16)	101.7	104.5	103.4	103.2
C(15)—C(16)—C(17)	107.1	103.8	106.0	105.6
C(16)—C(17)—C(13)	105.5	105.5	104.4	105.1
C(17)—C(13)—C(14)	97.8	98.7	98.3	98.3
C(12)—C(13)—C(18)	110.4	110.9	111.9	111.1
C(14)—C(13)—C(18)	112.3	114.2	113.8	113.4
C(17)—C(13)—C(18)	107.4	109.3	109.7	108.8
C(13)—C(17)—O(17)	115.0	114.3	115.4	114.9
C(16)—C(17)—O(17)	109.9	111.0	109.3	110.1

Table 5(c). Torsional angles observed in three molecules of 2,4-dibromoestradiol

		Torsional angles			
		A	B1	B2	Δ tor
A	C(1)—C(2)	-1.3°	-1.3°	-3.9°	2.6°
	C(2)—C(3)	2.9	2.6	3.7	1.1
	C(3)—C(4)	-4.5	-4.0	-2.8	1.7
	C(4)—C(5)	4.2	3.8	1.8	2.4
	C(5)—C(10)	-2.3	-2.1	-1.8	0.5
	C(10)—C(1)	0.9	1.0	2.8	1.9
B	C(5)—C(6)	-5.2	-3.0	-14.7	11.7
	C(6)—C(7)	39.5	33.7	42.9	9.2
	C(7)—C(8)	-66.6	-62.5	-62.5	4.1
	C(8)—C(9)	59.7	59.5	53.7	6.0
	C(9)—C(10)	-26.5	-31.2	-26.7	4.7
C	C(5)—C(10)	-1.2	1.8	6.9	8.1
	C(8)—C(9)	-52.5	-51.4	-54.8	3.4
	C(9)—C(11)	52.1	50.6	53.6	3.0
	C(11)—C(12)	-52.9	-53.9	-54.3	1.4
	C(12)—C(13)	56.0	59.6	57.3	3.6
D	C(13)—C(14)	-61.2	-62.8	-62.3	1.6
	C(14)—C(8)	57.7	57.8	59.6	1.9
	C(13)—C(14)	46.0	48.5	47.6	2.5
	C(14)—C(15)	-33.4	-34.2	-33.6	0.8
	C(15)—C(16)	6.1	6.3	5.7	0.6
	C(16)—C(17)	22.2	24.5	24.0	2.3
	C(17)—C(13)	-41.3	-45.1	-43.3	3.8

the average distances are 0.97, 0.97, and 1.00 Å for molecules *A*, *B1*, and *B2* respectively. The valency angles of the type C–C–H range in magnitude from 84 to 128° and the average magnitudes are 110, 108 and 109° for molecules *A*, *B1* and *B2*. Of the 16 hydrogen atoms that have the most distorted geometry (valency angles outside the range 99 → 121°) 10 have intermolecular van der Waals contacts of less than 2.7 Å (Table 6).

The conformations of the hydrogen atoms of the three molecules can be compared in Fig. 2. The major conformational differences in hydrogen positions are associated with hydrogens on carbon atoms C(12) of molecule *B1* and C(6) of molecule *B2*. Inspection of intermolecular contacts of less than 2.8 Å (Table 6) shows these hydrogens to be involved in several hydrogen–hydrogen contacts of less than 2.7 Å in length. The conformation of the hydrogen atoms on C(6) and

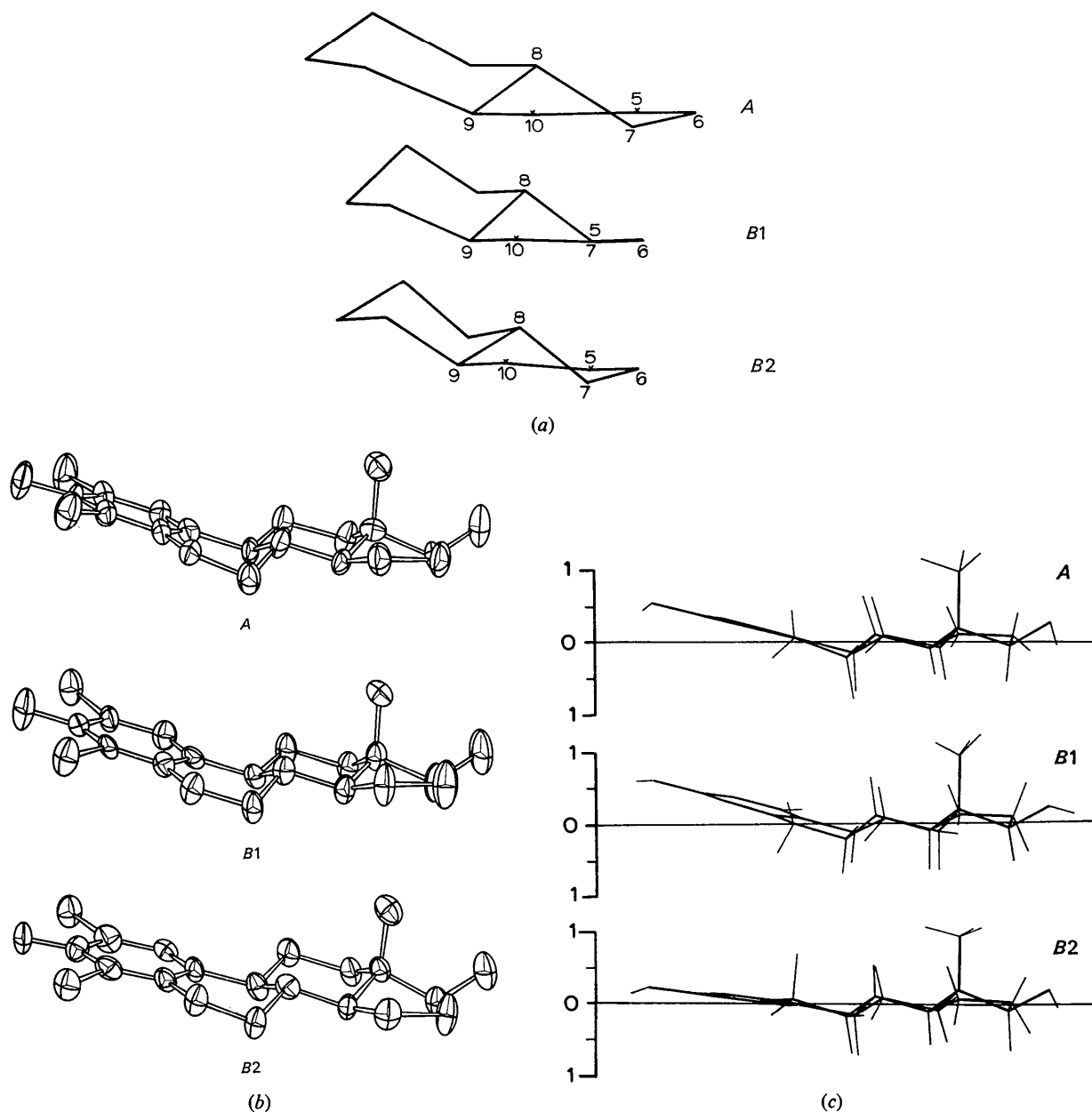


Fig. 2. (a) The *B*- and *C*-rings of the three molecules of 2,4-dibromoestradiol projected parallel to a line joining the mid points of the vectors C(9)–C(6) and C(10)–C(5). The *B*-rings of *A* and *B2* are in half-chair conformations and the *B*-ring of *B1* is in a sofa conformation. (b) Perspective views of the three molecules showing 50% probability thermal vibrational ellipsoids. (c) Projections of the three molecules perpendicular to the least squares planes through atoms C(5) to C(17). Observed hydrogen positions are included for purposes of comparison.

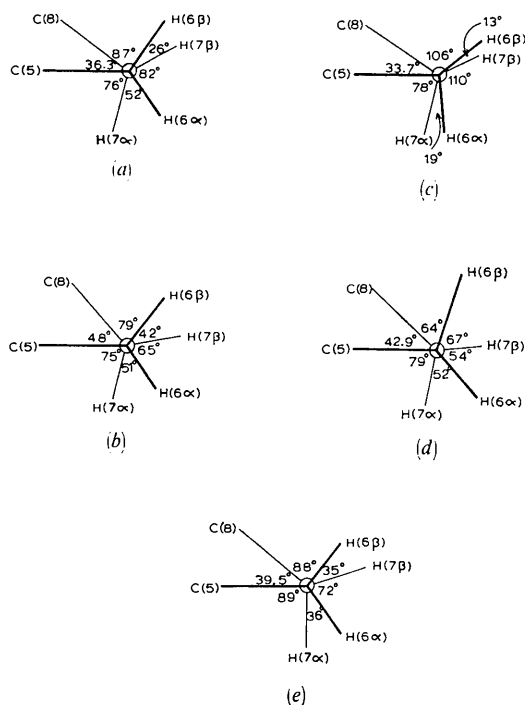


Fig. 3. Conformation of the hydrogen atoms on C(6) and C(7) in the estriol molecules 1(a) and 2(b) and in the 2,4-dibromoestradiol molecules B1(c), B2(d) and A(e). Hydrogen atoms H(6 β) and H(7 β) are most nearly eclipsed in the sofa conformation B-rings of (c).

C(7) is shown in the Newman projections of Fig. 3. Similar projections of the two estriol molecules are included for purposes of comparison. In molecules *A* and *B2* and in the estriol molecules the hydrogens are in staggered conformations. Only in molecule *B1* do they come close to an eclipsed conformation. This is one of the unfavorable conditions that may occur when the *B* ring is in the sofa conformation.

The relative thermal motion of the three molecules is shown in Fig. 2(b). The greatest motion is perpendicular to the general plane of the steroid. The larger anisotropic motion of the hydroxyl groups, the angular methyl group and the bromine atoms is to be expected. The only significant difference among the three molecules is the high degree of thermal motion in the *D* ring of molecule *B1*.

Molecular packing and hydrogen bonding

Inspection of the packing diagrams [Fig. 4(a) and (b)] reveals that in all cases infinite chains of 2,4-dibromoestradiol molecules are formed by hydrogen bonding between translationally equivalent molecules. In the monoclinic crystal molecules *B1* forms chains composed entirely of *B1* type molecules.

The only intermolecular contact between chains which is closer than the sum of the van der Waals radii of the atoms involved is the Br(2)–Br(4) contact of 3.62 Å observed in the lattice of structure *A*. This value

Table 6. Intermolecular distances less than 2.8 Å in two crystalline forms of 2,4-dibromoestradiol

Molecule <i>A</i>		Molecule <i>B1</i>		Molecule <i>B2</i>	
C(5) — H(17)	2.74 Å	H(6 α) — H(12 β)	2.52 Å	H(1) — H'(15 β)	2.71 Å
C(15) — H(18C)	2.78	H(7 α) — H(12 β)	2.64	H(6 β) — H'(16 α)	2.63
O(17) — H(03)	2.26	H(7 α) — H'(18A)	2.72	H(6 β) — H'(17)	2.73
Br(4) — H(11 β)	2.69	H(7 β) — H(12 β)	2.65	H(7 β) — H(12 β)	2.48
H(1) — H(18A)	2.73	H(8) — H'(16 α)	2.28	H(11 α) — H'(15 β)	2.73
H(6 α) — H(17)	2.76	H(12 α) — H'(18C)	2.73	H(15 β) — H'(14)	2.21
H(7 α) — H(017)	2.74	H(14) — H'(15 β)	2.21	H(16 α) — H'(8)	2.28
H(8) — H(11 α)	2.59	H(15 β) — H'(1)	2.71	H(18A) — H'(7 α)	2.72
H(9) — H(16 α)	2.49	H(15 β) — H'(11 α)	2.73	H(18C) — H'(12 α)	2.73
H(11 α) — H(15 β)	2.70	H(16 α) — H'(6 β)	2.63		
H(15 α) — H(18A)	2.62	H(17) — H'(6 β)	2.73		
H(15 α) — H(18C)	2.36				
H(16 α) — H(18A)	2.71				
H(16 α) — H(18C)	2.68				
H(16 β) — H(18C)	2.75				

Table 7. Summary of the geometry of the hydrogen bonding between the molecules

		Molecule <i>A</i>	Molecule <i>B1</i>	Molecule <i>B2</i>
Torsional angle	H(03) — O(3) — C(3) — C(2)	26°	16°	24°
Valency angles	H(03) — O(3) — C(3)	108	123	130
	H(017) — O(17) — C(17)	105	111	99
	H(03) ··· Br(2)	2.73 Å	2.77 Å	2.91 Å
Interatomic distance	H(03) — O(3)	0.67	0.86	0.76
	H(017) — O(17)	1.25	0.76	0.70
	H(03) ··· O(17)	2.25	1.89	2.04
	H(017) ··· O(3)		1.95	
	O(3) ··· O(17)	2.840 Å	2.671 Å	2.768 Å
Hydrogen bond distance	O(3) — H(03) ··· O(17)	146°	150°	160°
	O(17) — H(017) ··· O(3)		160	

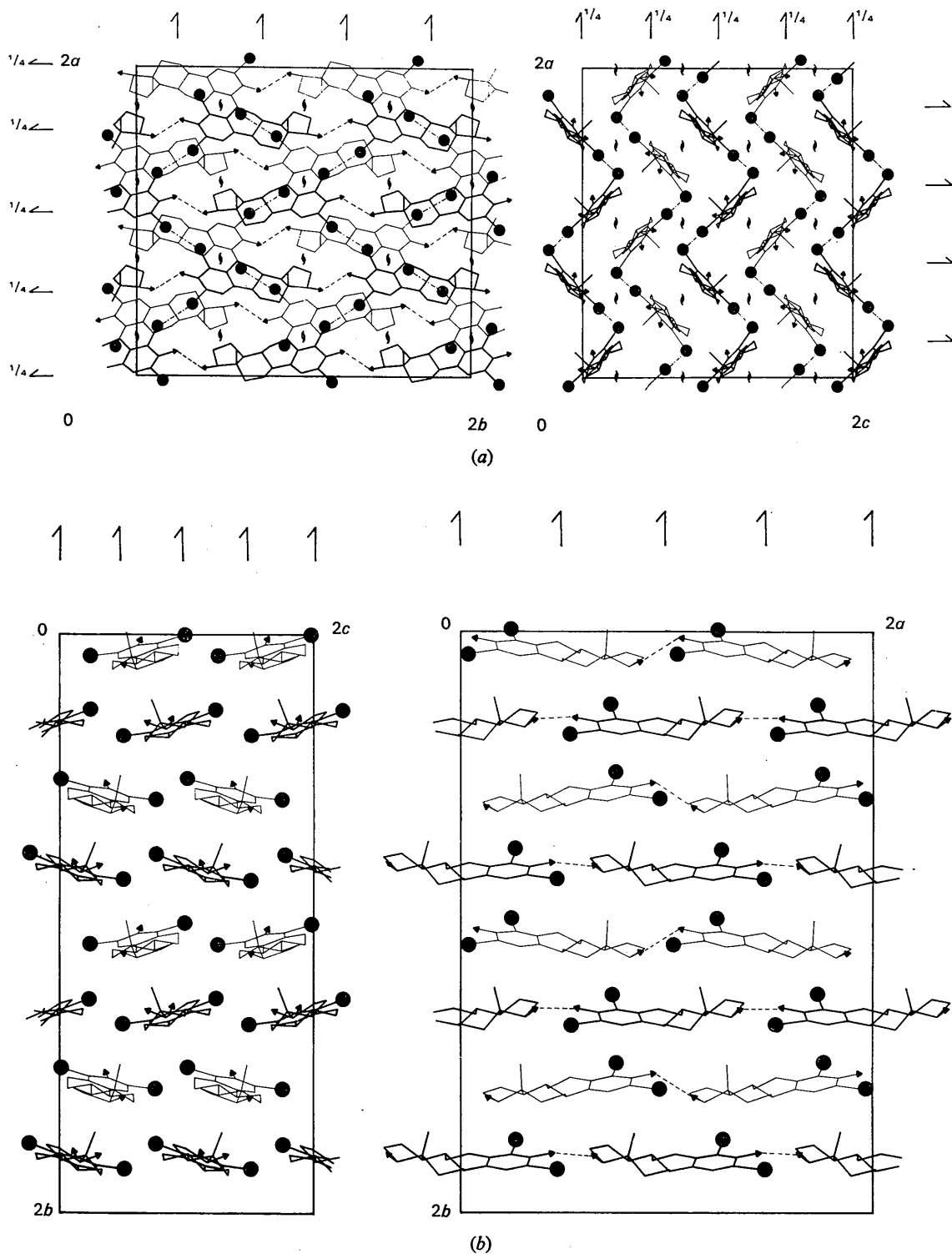


Fig. 4. (a) Projections of four unit cells of the orthorhombic structure (A) onto the (001) and the (010) planes, illustrating the infinite chain formation *via* hydrogen bonding and the nature of the bromine-bromine contacts between chains. (b) Projections of four unit cells of the monoclinic structure (B) onto the (100) and the (001) planes, illustrating the alternate layers of chain types B1 and B2.

is significantly shorter than the expected van der Waals contact of 3.90 Å using Pauling's (1960) radius of 1.95 Å for bromine. However, it is only slightly shorter than the van der Waals sum of 3.70 Å using Bondi's (1964) corrected radius of 1.85 Å for bromine.

Short Br-Br contacts have also been observed in other structures. Distances range from 3.30 Å in crystalline bromine (Vonnegut & Warren, 1936) and 3.58 Å in di-*p*-tolyselenium dibromide (McCullough & Marsh, 1950) to 3.63 Å in PaBr₅ (Brown, Petcher & Smith, 1969) and PBr₅ (Gabs & Olie, 1970). There are no intermolecular Br-Br contacts less than 4.0 Å in the lattice of structure *B*.

A summary of the geometry of the hydrogen bonding between the molecules is presented in Table 7. The hydrogen of O(3) is involved in the hydrogen bonding in all cases. The hydrogen of O(17) may be involved in the hydrogen bonding in molecule *B*1 only. The fact that the shortest hydrogen bond occurs in the *B*1 chain is consistent with the possible additional hydrogen bonding due to H(017). However the two hydrogens H(03) and H(017) of molecule *B*1 have an unfavorable close interatomic distance of 1.15 Å. The H(017) atoms of molecules *A* and *B*2 are oriented away from the hydrogen bond, in a *trans* configuration with respect to the C(16)-C(17) bond. The conformation of the hydrogen bonding region is shown in the Newman projections O(17)-C(17) of Fig. 5.

A comparison of the overall geometry and packing of the molecules of 2,4-dibromoestradiol with other estradiols shows a common preference for the formation of infinite chains of molecules connected by O(3)-O(17) hydrogen bonds. In the case of estradiol (Busetta & Hospital, 1969) there are additional hydrogen bonds to water molecules which connect adjacent steroid strands. In 4-bromoestradiol (Norton, Kartha & Lu, 1964) there is no interaction between strands even though there is additional hydrogen bonding with a methanol molecule. Although the structure of estradiol 3-*p*-bromobenzoate (Tsukuda, Sato, Shiro & Kayama, 1968) does not allow O(3)-O(17) interactions, there is hydrogen bonding between O(17) and the

benzoate carbonyl, but this is across the strands rather than along them.

Steroid molecular conformation

The major conformational differences in the three molecules of 2,4-dibromoestradiol concern the steroid's *B* ring. The *B* rings of molecules *B*2 and *A* are in a half-chair and a distorted half-chair conformation, while the *B* ring of molecule *B*1 is in a sofa conformation. The difference in these conformations is best illustrated in Fig. 2(a). The observed coplanarity of atoms C(5), C(6), C(7), C(9) and C(10) is the distinguishing feature of the sofa conformation which molecule *B*1 has in common with one of the two molecules in the asymmetric unit of estriol (Cooper, Norton & Hauptman, 1969), with 4-bromoestrone (Norton, Kartha & Lu, 1963), and with another estradiol derivative 3-methoxy-8 β -methyl-1,3,5(10)-estratriene-17 β -yl bromoacetate (Tsukuda, Soto, Shiro & Kayama, 1968). The differences in the overall conformations of the three molecules of 2,4-dibromoestradiol are shown relative to the nearly identical *C* and *D* rings in Fig. 2(b) and the molecules are projected perpendicular to the least-squares plane through atoms C(5)-C(17) in Fig. 2(c). The three diagrams show that the sofa conformation of the *B* ring results in a twisting of the *A* ring relative to the rest of the steroid, which is out of the general plane of the rest of the molecule.

Table 8. Deviations of individual atoms from the least-squares plane through atoms C(1), C(2), C(3), C(4), C(5), and C(10) of the *A* ring of the three molecules of 2,4-dibromoestradiol

Positive deviation is on the β -side of the steroid.

	<i>A</i>	<i>B</i> 1	<i>B</i> 2
C(1)	0.002 Å	0.000 Å	-0.011 Å
C(2)	0.005	0.004	0.013
C(3)	-0.016	-0.011	-0.010
C(4)	0.021	0.014	0.005
C(5)	-0.013	-0.009	-0.002
C(10)	0.002	0.002	0.005
H(1)	0.005	0.085	0.164
Br(2)	-0.038	0.011	0.012
O(3)	-0.013	0.001	0.004
Br(4)	0.061	-0.045	-0.102
C(6)	-0.068	-0.004	-0.029
C(9)	-0.011	-0.012	-0.084
H(03)	-0.278	-0.141	-0.164
C(7)	-0.231	-0.043	-0.209
C(8)	0.608	0.546	0.339

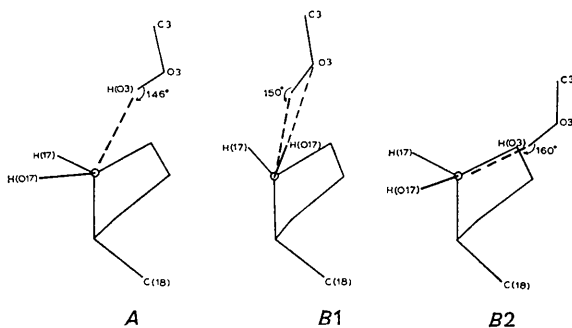


Fig. 5. Projections of the three molecules parallel to the O(17)-C(17) bond illustrating the hydrogen bonding and the orientations of the H(017) atoms.

The magnitudes of the *A* ring torsional angles [Table 5(c)] and the deviations of individual atoms from the least-squares plane through the *A* ring (Table 8) indicate that the carbon atoms of the *A* rings of all these molecules are equally planar with some puckering of the ring indicated by the alternating sign of the torsional angles. All atoms directly bonded to the *A* ring are also nearly coplanar with the carbons of the

ring. While 5 atoms of the *A* and *B* rings of molecule *A* and 6 atoms of *A* and *B* rings of molecule *B2* deviate by more than 0.05 Å from the plane, only atoms H(1), H(03) and C(8) of molecule *B2* are more than 0.05 Å from the plane. The most significant difference in the deviations from the plane of the *A* ring is in the position of C(7) which is observed to be nearly in the plane in molecule *B2*. This is a characteristic of the sofa conformation of the *B* ring.

The *C* rings of all three molecules are in normals chair conformations with some flattening of the rings due to strain at ring junctions. This flattening of the *C* ring is reflected in the decrease in the magnitudes of the torsional angles [Table 5(c)]. The most pronounced flattening is observed in molecule *A*.

The *D* rings of all three molecules are in β envelope conformations as reflected by the magnitudes of the parameters φ_{\max} and Δ (Altona, Geise & Romers, 1968).

Molecule	φ_{\max}	Δ
<i>A</i>	46.64°	19.25°
<i>B1</i>	49.36	22.11
<i>B2</i>	48.42	21.63
Ideal β -envelope	46.7	36.0

Discussion

Differences observed in the molecular geometry and conformation of the three molecules of 2,4-dibromoestradiol are caused by a combination of intramolecular bonding forces and intermolecular interactions. The occurrence of the *B* ring in the sofa and half-chair conformations in numerous estranes having a phenolic *A* ring, particularly the occurrence of the 1:1 ratio of sofa to half-chair conformation in crystals of estriol and 2,4-dibromoestradiol suggests that the potential energy of the two conformations is nearly equivalent. The distinct difference between *B* rings which are in the half-chair and the sofa conformations, a difference involving variations in angle strains and eclipsing strains is most strongly reflected in the torsional angle differences. The absence of strong parallels between the intermolecular hydrogen contacts (Table 6) of the two molecules having the *B* ring in the half-chair conformation suggests that these packing forces alone are not responsible for the adoption of a particular conformation by the *B* ring. The intermolecular forces in

the crystal, hydrogen bonding and van der Waals packing forces probably stabilize one or the other of the *B* ring conformations and may also distort the conformation to some extent as is the case in the differences between molecules *A* and *B2*.

The authors wish to thank Mrs C. DeVine for assistance in data collection, Miss M. Tugac and Mr D. Maracle for preparation of figures, Miss D. Hefner and Mrs V. Kamysz for preparation of manuscript and tables and Miss P. Strong for extensive assistance in data analysis and tabulation.

This work was supported in part by U.S. Public Health Grant No. CA 10906-02 from the National Cancer Institute and Grant No. AM 05619-01 from the National Institute of Arthritis and Metabolic Diseases.

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