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The Crystal and Molecular Structures of 4-Bromoestrone†

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The structure of estrone, in the form of its monobromoderivative, 4-bromoestrone, has been determined by a combination of two- and three-dimensional X-ray crystallographic methods. The resulting structure is consistent with the chemical formula $C_{18}H_{21}BrO_2$, and has four molecules per unit cell. The space groups of estrone and 4-bromoestrone are the same, namely $P2_12_12_1$. Their lattice constants ($\pm 0{\cdot}004$ Å) are respectively 10·049, 18·530, 7·798 and 13·191, 15·815, 7·333 Å units.

The bond lengths and angles in 4-bromoestrone are consistent with the currently accepted values for carbon–carbon systems. If the entire molecule is referred to a single mean plane, the root mean square distance of atoms from the plane is $\pm 0{\cdot}26$ Å. Much shorter root mean square distances are obtained if the molecule is subdivided so that the A ring is planar, B and C are chairs, and D exhibits the envelope effect. The long axes of the 4-bromoestrone molecules are more or less parallel to the x-direction. Hydrogen bridges account for the formation of molecular chains parallel to x. Van der Waals forces hold the molecules together in the y- and z-directions.

Introduction

Estrone is an estrogenic sex hormone which is significant in the study and treatment of cancer. Its configuration was established by chemical means chiefly through the work of Marrian (1929) and Butenandt (1931).

Recently the bromo-derivatives of estrone have become important in Slaunwhite's (1962) new method of analyzing for microquantities of steroids in urine. Since in this method, estrone, which has been labelled with radioactive bromine, is used as the mobility standard for paper chromatography, it becomes essential to know to which carbon atom the bromine is attached. By chemical means Slaunwhite (1962) has been able to deduce that the bromine is attached to carbon four (Fig. 1). The purposes of the structural investigation undertaken here were to verify this chemical conclusion, and to obtain detailed structural information about the 4-bromoestrone molecule.

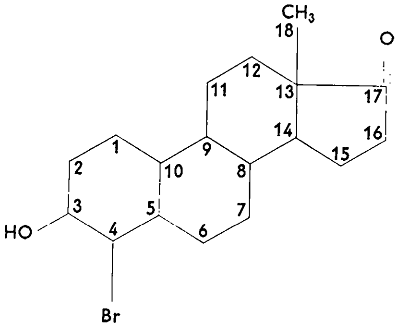

Fig. 1. 4-Bromoestrone.

Crystal data

Three crystalline modifications of estrone were reported by Bernal & Crowfoot in 1936: 'orthorhombic (stable) only grown from the vapor, orthorhombic (metastable) from solution, monoclinic (metastable) also from solution.' Our determinations of the lattice constants, space groups, and densities of estrone and 4-bromoestrone are given in Table 1. It can be seen that our values for estrone differ only slightly from the earlier measurements which Bernal & Crowfoot obtained for their type two metastable orthorhombic estrone grown from solution.

Table 1. *Crystal data for estrone and 4-bromoestrone**

	Space group	*a*	*b* (in Å ± 0·004)	*c*	*V* (Å³)	ϱ(meas.) (g.cm.⁻³)	ϱ(calc.) (g.cm.⁻³)	*Z*
Estrone (this work)	$P2_12_12_1$	10·049	18·530	7·798	1452	1·238	1·236	4
Estrone (type 2, Bernal & Crowfoot)	$P2_12_12_1$	9·9	18·2	7·7	1387	—	1·24	4
4-Bromoestrone	$P2_12_12_1$	13·191	15·815	7·333	1530	1·509	1·516	4

* The crystals of estrone and 4-bromoestrone used in this study were both grown from solution.

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Experimental measurements

Attempts were made to grind spheres of 4-bromoestrone for the collection of intensity data, but these attempts were not very successful, and eventually a small octahedral crystal of about 0·2 mm diameter was used. Preliminary studies of the extent of absorption effects on the basal reflections (040) and (080) as a function of the orientation angle φ showed that these effects were less than 10%, and, hence, no detailed absorption corrections were made.

All X-ray data were collected with the crystal mounted on a goniostat using Cu $K\alpha$ radiation produced by a General Electric XRD-5 unit. Intensities by stationary crystal and balanced filter techniques were obtained for all reflections within the copper reflecting sphere. Appropriate Lorentz and polarization corrections, calculated on an IBM 650 computer, for each reflection were obtained, and the observed structure amplitudes were placed on an absolute scale by Wilson's method (1942). This scale was adjusted later by comparison with calculated structure factors.

Structure analysis

(a) *Two dimensional work*

The x and y parameters of the bromine atom were readily obtained from a z-zone $\sin\theta$ weighted reciprocal lattice diagram, For this the values corresponding to the intensities of the $hk0$ zone of reflections were plotted on the reciprocal lattice net perpendicular to the c-axis, i.e., on the a^*–b^* net. Two such weighted reciprocal lattice maps were prepared, one corresponding to the set of reflections with $h+k$ even and another for $h+k$ odd. Now, the contribution to the structure factors due to scattering from the bromines has the form $f_{\mathrm{Br}}.\cos hx_{\mathrm{Br}}.\cos ky_{\mathrm{Br}}$ and $f_{\mathrm{Br}}.\sin hx_{\mathrm{Br}}.\sin ky_{\mathrm{Br}}$ respectively for the two sets of reflections where x_{Br} and y_{Br} are the coordinates of the bromine atom with respect to a 2-fold screw axis parallel to c. Hence, the regions of weak reflections in the $h+k$ even plot will correspond to those values h and k for which the function $\cos hx_{\mathrm{Br}}.\cos ky_{\mathrm{Br}}$ is small. Visual inspection of these maps clearly indicated the nodes and antinodes of the fringe system corresponding to the Fourier transform of the heavy atom positions giving atomic parameters for bromine which were accurate to within a tenth of an Ångström. These parameters were refined by a Fourier projection of the electron density along the c-axis. This projection also gave the approximate orientation of the molecule in the unit cell, namely, the length of the molecule parallel to the a-axis.

(b) *Three dimensional work*

The bromine x, y, and z parameters were obtained from $0kl$ and $h0l$ weighted reciprocal lattice diagrams, and the z-value refined by sharpened Patterson line syntheses and electron density projections.* Assuming that the phases of all reflections were determined mainly by the bromine, calculation of the phases and amplitudes of the bromine contribution to all reflections were made. For approximately 200 of the 2050 reflections measured, the bromine contribution is very small, and these reflections were omitted from the

Table 2. *Progress made in final stages of least-squares refinement*

	Cycle five			Cycle six			Cycle (7) final		
	Δx	Δy	Δz	Δx	Δy	Δz	Δx	Δy	Δz
Br	0·0004 Å	0·0016 Å	0·0018 Å	0·0000 Å	0·0006 Å	0·0021 Å	0·0000 Å	$0{\cdot}\overline{0002}$ Å	0·0015 Å
C_1	0·0083	$0{\cdot}\overline{0055}$	0·0053	0·0055	$0{\cdot}\overline{0028}$	0·0100	0·0051	0·0014	0·0110
C_2	0·0034	$0{\cdot}\overline{0275}$	0·0102	0·0000	$0{\cdot}\overline{0183}$	0·0038	$0{\cdot}\overline{0001}$	$0{\cdot}\overline{0087}$	$0{\cdot}\overline{0015}$
C_3	$0{\cdot}\overline{0198}$	$0{\cdot}\overline{0150}$	0·0129	$0{\cdot}\overline{0042}$	$0{\cdot}\overline{0070}$	0·0175	$0{\cdot}\overline{0029}$	0·0005	0·0169
C_4	$0{\cdot}\overline{0044}$	0·0003	0·0133	$0{\cdot}\overline{0040}$	$0{\cdot}\overline{0044}$	0·0118	$0{\cdot}\overline{0024}$	$0{\cdot}\overline{0038}$	0·0084
C_5	$0{\cdot}\overline{0028}$	0·0082	0·0003	$0{\cdot}\overline{0038}$	0·0071	0·0043	$0{\cdot}\overline{0034}$	0·0030	0·0031
C_6	$0{\cdot}\overline{0137}$	$0{\cdot}\overline{0006}$	0·0170	$0{\cdot}\overline{0088}$	0·0071	0·0140	$0{\cdot}\overline{0062}$	0·0065	0·0078
C_7	$0{\cdot}\overline{0067}$	0·0076	$0{\cdot}\overline{0090}$	$0{\cdot}\overline{0028}$	0·0046	$0{\cdot}\overline{0050}$	$0{\cdot}\overline{0029}$	0·0017	0·0006
C_8	$0{\cdot}\overline{0079}$	0·0085	0·0004	$0{\cdot}\overline{0051}$	0·0059	0·0053	$0{\cdot}\overline{0045}$	0·0013	0·0032
C_9	$0{\cdot}\overline{0026}$	0·0144	0·0125	$0{\cdot}\overline{0009}$	0·0161	0·0085	0·0007	0·0093	0·0048
C_{10}	0·0067	0·0030	0·0129	0·0058	0·0025	0·0111	0·0028	0·0016	0·0070
C_{11}	$0{\cdot}\overline{0029}$	$0{\cdot}\overline{0245}$	0·0078	$0{\cdot}\overline{0031}$	$0{\cdot}\overline{0209}$	0·0065	$0{\cdot}\overline{0029}$	$0{\cdot}\overline{0109}$	0·0029
C_{12}	0·0004	0·0090	$0{\cdot}\overline{0121}$	0·0013	0·0142	$0{\cdot}\overline{0074}$	0·0001	0·0099	$0{\cdot}\overline{0021}$
C_{13}	$0{\cdot}\overline{0028}$	0·0187	0·0073	$0{\cdot}\overline{0009}$	0·0183	$0{\cdot}\overline{0004}$	$0{\cdot}\overline{0003}$	0·0087	$0{\cdot}\overline{0009}$
C_{14}	0·0024	0·0022	0·0311	0·0003	0·0019	0·0177	0·0012	0·0005	0·0067
C_{15}	0·0100	$0{\cdot}\overline{0005}$	$0{\cdot}\overline{0128}$	$0{\cdot}\overline{0021}$	0·0006	$0{\cdot}\overline{0070}$	$0{\cdot}\overline{0004}$	0·0041	$0{\cdot}\overline{0034}$
C_{16}	$0{\cdot}\overline{0289}$	0·0106	$0{\cdot}\overline{0216}$	$0{\cdot}\overline{0095}$	0·0049	$0{\cdot}\overline{0114}$	$0{\cdot}\overline{0033}$	$0{\cdot}\overline{0025}$	$0{\cdot}\overline{0060}$
C_{17}	$0{\cdot}\overline{0191}$	$0{\cdot}\overline{0002}$	0·0100	0·0011	$0{\cdot}\overline{0052}$	0·0025	0·0017	$0{\cdot}\overline{0033}$	0·0001
C_{18}	$0{\cdot}\overline{0112}$	$0{\cdot}\overline{0095}$	0·0038	$0{\cdot}\overline{0038}$	$0{\cdot}\overline{0098}$	0·0050	$0{\cdot}\overline{0021}$	$0{\cdot}\overline{0062}$	0·0059
O_1	0·0073	$0{\cdot}\overline{0047}$	$0{\cdot}\overline{0165}$	$0{\cdot}\overline{0011}$	$0{\cdot}\overline{0011}$	$0{\cdot}\overline{0185}$	$0{\cdot}\overline{0008}$	0·0044	$0{\cdot}\overline{0177}$
O_2	$0{\cdot}\overline{0168}$	$0{\cdot}\overline{0082}$	$0{\cdot}\overline{0011}$	$0{\cdot}\overline{0034}$	$0{\cdot}\overline{0049}$	$0{\cdot}\overline{0039}$	$0{\cdot}\overline{0017}$	$0{\cdot}\overline{0017}$	0·0015
Mean ($\Delta x, y, z$)	0·0085 Å	0·0086 Å	0·0105 Å	0·0032 Å	0·0075 Å	0·0083 Å	0·0022 Å	0·0043 Å	0·0054 Å

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* All coordinates from here on are referred to the origin for the S.G. $P2_12_12_1$ given in the *International Tables for X-ray Crystallography*.

Table 3. *Final fractional atomic co-ordinates, standard deviations, and temperature factors*

	B	X	Y	Z	Standard deviations (Å) $\sigma(ax)$	$\sigma(by)$	$\sigma(cz)$
Br	3·494	$0{\cdot}427_2$	$0{\cdot}141_3$	$0{\cdot}213_0$	0·0019	0·0020	0·0018
C_1	3·840	$0{\cdot}204_8$	$0{\cdot}089_7$	$0{\cdot}695_8$	0·018	0·019	0·017
C_2	3·590	$0{\cdot}307_1$	$0{\cdot}069_8$	$0{\cdot}711_0$	0·018	0·018	0·016
C_3	4·497	$0{\cdot}372_0$	$0{\cdot}087_9$	$0{\cdot}575_9$	0·021	0·021	0·019
C_4	2·189	$0{\cdot}334_2$	$0{\cdot}121_4$	$0{\cdot}409_2$	0·013	0·014	0·013
C_5	2·608	$0{\cdot}230_6$	$0{\cdot}145_4$	$0{\cdot}388_3$	0·014	0·015	0·014
C_6	3·679	$0{\cdot}193_5$	$0{\cdot}176_5$	$0{\cdot}213_2$	0·018	0·018	0·016
C_7	3·829	$0{\cdot}081_3$	$0{\cdot}207_5$	$0{\cdot}204_1$	0·019	0·019	0·017
C_8	2·555	$0{\cdot}017_3$	$0{\cdot}146_6$	$0{\cdot}319_3$	0·014	0·015	0·014
C_9	2·617	$0{\cdot}053_5$	$0{\cdot}154_5$	$0{\cdot}521_3$	0·015	0·015	0·014
C_{10}	2·598	$0{\cdot}166_3$	$0{\cdot}127_0$	$0{\cdot}534_6$	0·015	0·015	0·014
C_{11}	2·586	$0{\cdot}988_4$	$0{\cdot}097_0$	$0{\cdot}652_6$	0·015	0·017	0·014
C_{12}	3·115	$0{\cdot}871_3$	$0{\cdot}124_3$	$0{\cdot}632_4$	0·016	0·017	0·015
C_{13}	3·727	$0{\cdot}844_5$	$0{\cdot}109_9$	$0{\cdot}429_6$	0·018	0·018	0·017
C_{14}	2·719	$0{\cdot}906_7$	$0{\cdot}169_5$	$0{\cdot}318_4$	0·015	0·016	0·014
C_{15}	3·487	$0{\cdot}850_4$	$0{\cdot}174_9$	$0{\cdot}129_7$	0·017	0·018	0·016
C_{16}	3·331	$0{\cdot}736_7$	$0{\cdot}178_2$	$0{\cdot}189_0$	0·018	0·018	0·016
C_{17}	3·931	$0{\cdot}735_7$	$0{\cdot}134_1$	$0{\cdot}380_6$	0·019	0·019	0·017
C_{18}	3·087	$0{\cdot}846_6$	$0{\cdot}013_8$	$0{\cdot}371_3$	0·016	0·016	0·015
O_1	4·645	$0{\cdot}473_3$	$0{\cdot}069_1$	$0{\cdot}588_5$	0·015	0·015	0·013
O_2	4·737	$0{\cdot}660_7$	$0{\cdot}123_8$	$0{\cdot}491_6$	0·015	0·015	0·013

initial three dimensional electron density Fourier made on an IBM 704 computer. Electron density peaks corresponding to all twenty atoms in addition to bromine showed up in this Fourier, and these peak positions could easily be fitted on a possible model of the molecule. Two cycles (cycles 1 and 2) of IBM 704 least squares refinement (Vand & Pepinsky, 1959) using low angle reflections alone (approximately 1000 reflections below $2\theta \simeq 80°$) gave an R factor of 0·12. Two more cycles (cycles 3 and 4) of least squares refinement using the co-ordinates obtained above and all reflections raised R to 0·16. For the last stage of structure refinement, all reflections for which the measured intensity was less than 100 c.p.s. were removed. The 900 surviving reflections were subjected to three cycles (cycles 5, 6 and 7) of least squares refinement. Table 2 shows the progress made in the refinement during these last three cycles. Cycle 7 gave the final co-ordinates with a R-value of 0·117

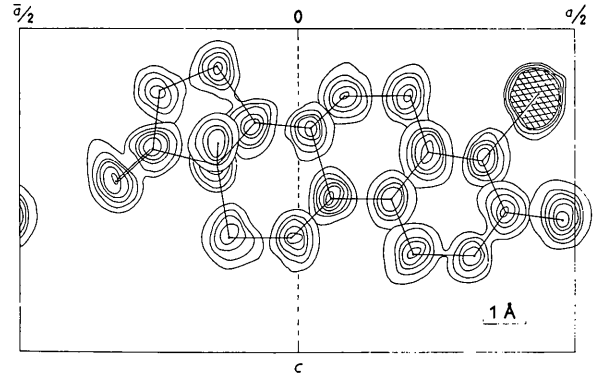

Fig. 2. Sections through the three dimensional electron density in the neighborhood of the center of each atom projected onto the a–c plane.

Table 4. *Bond lengths and bond angles in 4-bromoestrone*

Bond lengths		Bond angles	
$C_1{-}C_2$	1·39 Å	$C_1{-}C_2{-}C_3$	121°
$C_2{-}C_3$	1·34	$C_2{-}C_3{-}C_4$	119
$C_3{-}C_4$	1·42	$C_3{-}C_4{-}C_5$	122
$C_3{-}O_1$*	1·37	$C_4{-}C_5{-}C_{10}$	116
$C_4{-}C_5$	1·43	$C_5{-}C_{10}{-}C_1$	121
$C_4{-}Br$	1·92	$C_{10}{-}C_1{-}C_2$	121
$C_5{-}C_{10}$	1·40	$C_3{-}C_4{-}Br$	119
$C_{10}{-}C_1$	1·42	$Br{-}C_4{-}C_5$	119
$C_5{-}C_6$	1·46	$C_2{-}C_3{-}O_1$*	122
$C_6{-}C_7$	1·56	$C_4{-}C_3{-}O_1$	119
$C_7{-}C_8$	1·53	$C_{10}{-}C_5{-}C_6$	123
$C_8{-}C_9$	1·56	$C_5{-}C_6{-}C_7$	117
$C_9{-}C_{10}$	1·55	$C_6{-}C_7{-}C_8$	108
$C_9{-}C_{11}$	1·58	$C_7{-}C_8{-}C_9$	108
$C_{11}{-}C_{12}$	1·61	$C_8{-}C_9{-}C_{10}$	109
$C_{12}{-}C_{13}$	1·55	$C_9{-}C_{10}{-}C_5$	118
$C_{13}{-}C_{14}$	1·49	$C_8{-}C_{14}{-}C_{13}$	112
$C_{14}{-}C_8$	1·50	$C_{14}{-}C_{13}{-}C_{12}$	108
$C_{14}{-}C_{15}$	1·57	$C_{13}{-}C_{12}{-}C_{11}$	106
$C_{15}{-}C_{16}$	1·56	$C_{12}{-}C_{11}{-}C_9$	106
$C_{16}{-}C_{17}$	1·57	$C_{11}{-}C_9{-}C_8$	111
$C_{17}{-}C_{13}$	1·53	$C_9{-}C_8{-}C_{14}$	106
$C_{17}{-}O_2$	1·20	$C_{12}{-}C_{13}{-}C_{18}$	113
$C_{13}{-}C_{18}$	1·58	$C_{14}{-}C_{15}{-}C_{16}$	102
		$C_{15}{-}C_{16}{-}C_{17}$	102
		$C_{16}{-}C_{17}{-}C_{13}$	108
		$C_{17}{-}C_{13}{-}C_{18}$	101
		$C_{17}{-}C_{13}{-}C_{14}$	103
		$C_{13}{-}C_{14}{-}C_{15}$	106
		$C_{16}{-}C_{17}{-}O_2$†	124
		$C_{13}{-}C_{17}{-}O_2$†	127
		$C_7{-}C_8{-}C_{14}$	112
		$C_8{-}C_{14}{-}C_{15}$	118
		$C_{12}{-}C_{13}{-}C_{17}$	114
		$C_1{-}C_{10}{-}C_9$	121
		$C_4{-}C_3{-}C_6$	120
		$C_{10}{-}C_9{-}C_{11}$	109
		$C_{18}{-}C_{13}{-}C_{14}$	116

* O_1 = hydroxyl oxygen.

† O_2 = ketone oxygen.

Table 5. *Coefficients a, b, c, d in the equations* ($ax+by+cz=d$) *of the mean planes of 4-bromoestrone*

	a	*b*	*c*	*d*
Entire molecule	0·01	0·93	0·37	3·16
A	0·18	0·91	0·38	3·68
B*	0·06	0·95	0·32	3·32
B1	0·18	0·93	0·29	3·51
B2	0·26	0·90	0·35	3·74
B3	−0·67	0·73	0·16	1·89
C	−0·11	0·95	0·27	3·07
C1	−0·64	0·75	0·14	1·93
C2	0·23	0·92	0·33	2·95
C3	−0·72	0·69	0·07	2·89
D	−0·04	0·90	0·43	3·20
D1	−0·54	0·77	0·34	3·51
D2	0·14	0·89	0·43	2·61
B3–C1	−0·66	0·74	0·15	1·92
C3–D1	−0·65	0·72	0·22	3·40

* B designates the entire ring B, C the entire C-ring, D the entire D-ring.

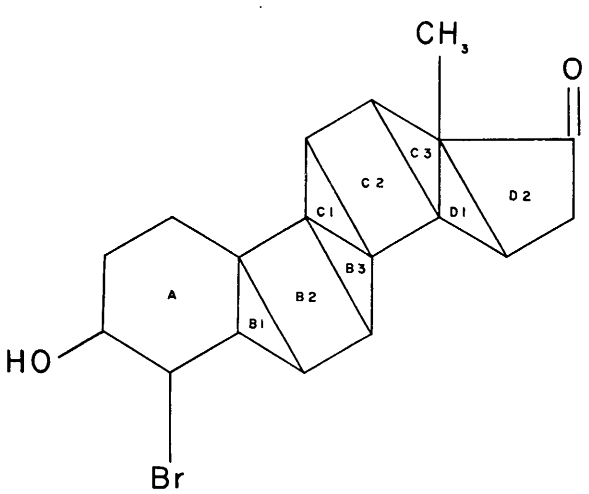

Table 6. *The root mean square distance* (λ) *of the atoms from the mean planes*

	λ
Entire molecule	0·26 Å
A	0·02
B	0·29
B1	0·00
B2	0·02
B3	0·00
C	0·27
C1	0·00
C2	0·00
C3	0·00
D	0·18
D1	0·00
D2	0·01

for these reflections. Table 3 lists the final fractional co-ordinates, standard deviations in Ångström units (calculated using the Cruickshank formula), and isotropic temperature factors for each atom. Fig. 2 shows sections through the electron density in the neighborhood of each atom in 4-bromoestrone projected onto the *a*–*c*-plane. A list of observed and calculated structure factors is available from the authors upon request.

Discussion

The bond lengths obtained from the final coordinates of the atoms in 4-bromoestrone are listed in Table 4. A statistical treatment of the carbon–carbon single bonds yields 1·55 Å as the average value with a standard deviation of 0·04 Å. It is interesting to note that the standard deviation obtained by statistical treatment ($\sigma^2=\overline{X^2}-\overline{X}^2$) is about twice as large as the value obtained using the Cruickshank method. The distribution curve of the single bond values shows

Table 7. *The perpendicular distance* (Å) *of individual atoms from one or more of the mean planes*

	A	B	B1	B2	B3	C	C1	C2	C3	D	D1	D2	Entire molecule
C_1	0·00	—	—	—	—	—	—	—	—	—	—	—	+0·05
C_2	−0·01	—	—	—	—	—	—	—	—	—	—	—	−0·18
C_3	+0·03	—	—	—	—	—	—	—	—	—	—	—	−0·27
C_4	−0·03	—	—	—	—	—	—	—	—	—	—	—	−0·23
C_5	+0·02	−0·07	0·00	—	—	—	—	—	—	—	—	—	+0·05
C_6		−0·04	0·00	−0·01	—	—	—	—	—	—	—	—	+0·04
C_7	—	+0·33	—	+0·02	0·00	—	—	—	—	—	—	—	+0·45
C_8	—	−0·37	—	—	0·00	−0·26	0·00	0·00	—	—	—	—	−0·15
C_9	—	+0·24	—	−0·02	0·00	+0·20	—	—	—	—	—	—	+0·52
C_{10}	0·00	−0·06	0·00	+0·02	—	—	—	—	—	—	—	—	+0·16
C_{11}	—	—	—	—	—	−0·31	0·00	0·00	—	—	—	—	+0·02
C_{12}	—	—	—	—	—	+0·24	—	0·00	0·00	—	—	—	+0·34
C_{13}	—	—	—	—	—	+0·33	—	—	0·00	−0·20	0·00	+0·01	−0·42
C_{14}	—	—	—	—	—	+0·25	0·00	0·00	0·00	+0·26	0·00	—	−0·17
C_{15}	—	—	—	—	—	—	—	—	—	−0·21	0·00	−0·01	−0·03
C_{16}	—	—	—	—	—	—	—	—	—	+0·09	—	+0·01	−0·07
C_{17}	—	—	—	—	—	—	—	—	—	+0·05	—	−0·01	−0·21
C_{18}	—	—	—	—	—	—	—	—	—	−1·76	−1·32	−1·53	−1·99
Br	−0·05	—	—	—	—	—	—	—	—	—	—	—	−0·45
O_1*	−0·01	—	—	—	—	—	—	—	—	—	—	—	−0·49
O_2†	—	—	—	—	—	—	—	—	—	+0·23	—	−0·01	−0·02

* O_1 = hydroxyl oxygen. † O_2 = ketone oxygen.

that most of the values are clustered about 1·55 Å. Since only one third of the points lie outside the sigma region (1·55 ± 0·04 Å), as would be expected in a normal Gaussian distribution, the bond lengths 1·61, 1·46, 1·48, and 1·50 Å do not differ significantly from the value 1·54 Å predicted by Pauling and others. The bond angles calculated from these bond lengths (Table 4) have a standard deviation of 1·20°.

The equations of the mean planes of 4-bromoestrone (Table 5) were calculated using the method of Schomaker *et al.* (1959). If the entire molecule is referred to one plane $(0{\cdot}01x+0{\cdot}93y+0{\cdot}37z-3{\cdot}16=0)$ the root mean square distance of carbon atoms (C_{18} excluded) from this plane is 0·26 Å. If the molecule is referred to four planes A, B, C, D, the root mean square distances are respectively 0·02, 0·29, 0·28, and 0·18 Å units. Shorter root mean square distances are obtained by further subdividing the ring system (with the exception of ring A) as shown in Table 6. Table 7 lists the perpendicular distances of each atom from the one or more mean planes which contain it.

Considering the data presented in the discussion thus far the following points are evident.

(*a*) The bromine atom is attached to carbon four, as deduced by the chemical methods of establishing molecular configuration. Since it is at a distance of 0·05 Å from the mean plane of ring A, it may be said to lie essentially in this plane.

(*b*) The hydroxyl oxygen is at a perpendicular distance of 0·01 Å from the mean plane of ring A, hence also lies in this plane.

(*c*) From Table 7 it is seen that the perpendicular distance of C_{18} to the mean plane of the entire molecule is 1·99 Å. It is interesting to note that this distance is equal to the sum of the C_{13}–C_{18} bond length (1·58 Å) plus the perpendicular distance of C_{13} (0·42 Å) to the mean plane of the entire molecule. The methyl group, therefore, has an axial conformation.

(*d*) The ketone oxygen is at a perpendicular distance of 0·01 Å from the mean plane of ring D2, hence lies in this plane.

The angles between the mean planes of 4-bromo-

Table 8. *The angles between mean planes*

Planes	Angle
A–B	170°
A–B1	170
B1–B2	171
B2–B3	122
B3–C	144
B3–C1	177
B–C	170
C1–C2	127
C2–C3	119
C3–D	133
C3–D1	160
C–D	170
D1–D2	148

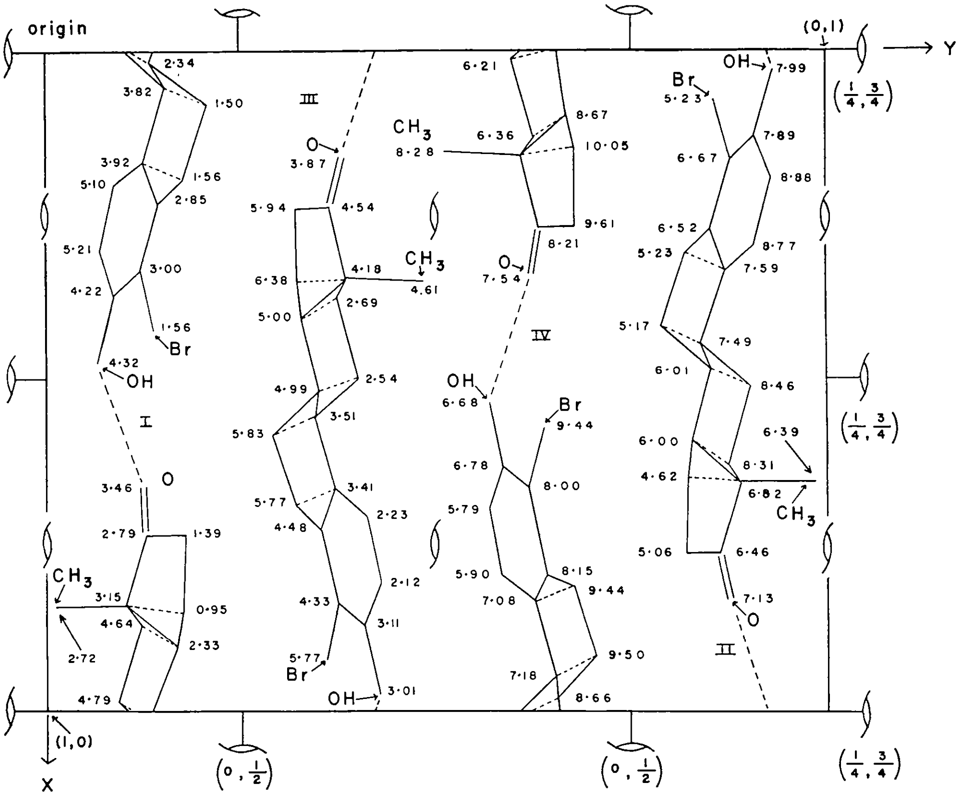

Fig. 3. Stacking diagram.

estrone have been calculated, and are shown in Table 8. Since the angle between B3 and C1 (177°) is so close to 180°, it is seen that B3 and C1 are almost the same plane. That this is so is further demonstrated by the fact that the root mean square distance of atoms C_7, C_8, C_9, and C_{11} from the mean plane B3–C1 $(-0\cdot66x+0\cdot74y+0\cdot15z-1\cdot92=0)$ is 0·02 Å. The planes C3 and D1, on the other hand, are quite different, as is indicated by the angle of 160° between them, and more fully by a 0·13 Å root mean square deviation of atoms C_{12}, C_{13}, C_{14}, and C_{15} from the mean plane C3–D1 $(-0\cdot65x+0\cdot72y+0\cdot22z-3\cdot40=0)$.

Table 9. *Van der Waals distances in the y-direction less than* 4·50 Å

I	II	*d*	IV	II	*d*
C_7	O_2	3·72 Å	C_{12}	Br	3·95 Å
C_9	O_2	3·78	C_{16}	C_5	4·16
C_6	C_{16}	4·48	C_{16}	C_{10}	3·71
C_5	C_{16}	4·17	C_{17}	C_5	3·88
C_{10}	C_{16}	3·80	C_{17}	C_6	4·26
C_1	C_{16}	3·79	O_2	C_6	3·94
C_3	C_{15}	4·34	O_2	C_7	3·72
C_2	C_{15}	4·25	C_3	C_{14}	3·95
C_4	C_{14}	3·98	C_3	C_{15}	4·34
C_3	C_{14}	3·95	C_2	C_{14}	4·34
C_2	C_{14}	4·34	C_2	C_{15}	4·25
O_2	C_7	3·72	C_4	C_{14}	3·99
C_{17}	C_6	4·26	C'	C_{16}	4·16
C_{16}	C_5	4·16	C_{10}	C_{16}	3·80
C_{17}	C_5	3·88	C_6	O_2	3·94
C_{12}	C_4	4·06	C_7	O_2	3·72
C_{13}	C_4	4·41			
C_{14}	C_5	3·98			
C_{14}	C_3	3·95			

III	IV	*d*
O_2	C_{18}	3·73 Å
C_{1r}	C_{18}	4·42
C_1	C_3	4·50
C_{10}	C_2	3·93
C_1	C_2	4·36
C_4	C_1	3·73

Fig. 3 shows the stacking of four molecules of 4-bromoestrone. The numbers beside each atom represent the height of the atom along *z*. It can be seen from Fig. 3 that the molecules are held together in the *x*-direction by hydrogen bonding with –O–H–O- distances of 2·76 Å. In the *y*-direction the molecules are held together by van der Waals forces. Table 9 lists all van der Waals distances in the *y*-direction less than 4·50 Å. In the *z*-direction the molecules are also held together by van der Waals forces of the same order of magnitude as those in the *y*-direction. None of the van der Waals distances are unusually small.

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