

APPENDIX

The conditional probability distribution
of $\cos(\varphi_h + \varphi_k + \varphi_{-h-k})$

Let the vector h be fixed and assume that k ranges uniformly throughout reciprocal space. Denote by $P(x|E_k, |E_{h+k}|)$ the conditional probability distribution of the random variable $X = \cos(\varphi_h + \varphi_k + \varphi_{-h-k})$, given that $|E_k|$ and $|E_{h+k}|$ have specified, fixed values. By means of an analysis to be published at a later date we find

$$P(x|E_k, |E_{h+k}|) \simeq \begin{cases} \frac{\exp Ax}{\pi I_0(A)\sqrt{1-x^2}} & \text{if } |x| < 1, \\ 0 & \text{if } |x| > 1, \end{cases} \quad (1)$$

where

$$A = \frac{2}{N^{1/2}} |E_h E_k E_{h+k}|, \quad (2)$$

I_0 is the Bessel function of imaginary argument, and N is the number of atoms, assumed identical, in the

unit cell.* Since, as explained in § 3, this distribution was needed in order to evaluate the structure invariants $\cos(\varphi_1 + \varphi_2 + \varphi_3)$, (1) has been tabulated for appropriate values of A . This function is readily computed with the aid of modern computers and the tabulation is, therefore, not reproduced here.

References

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* A related probability distribution, from which (1) may be derived, is given by Cochran (1955).

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Estrogenic Steroids. III. The Crystal and Molecular Structure of Estriol

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Crystal data for estriol ($C_{18}H_{24}O_3$) are: $a = 9.270$, $b = 23.001$, $c = 7.560$ Å, $\beta = 110.90$. Space group $P2_1$ with two molecules in the asymmetric unit. The structure was solved from a set of phases derived initially by application of a phase determining formula of the type

$$K|E_1 E_2 E_3| \cos(\varphi_1 + \varphi_2 + \varphi_3) = \langle (|E_k|^p - \langle |E|^p \rangle) \rangle \langle (|E_{h_1+k}|^p - \langle |E|^p \rangle) \rangle \langle (|E_{-h_3+k}|^p - \langle |E|^p \rangle) \rangle_k + R$$

and extended by application of the tangent formula. The structure was refined by block diagonal least-squares with anisotropic thermal parameters for the non-hydrogen atoms, to $R = 5.6\%$. All hydrogen atoms were located. Standard deviations of non-hydrogen distances and angles are 0.007 Å and 0.4° respectively.

Differences in hydrogen bonding, packing environment and intramolecular steric effects cause the two molecules in the asymmetric unit to be non-identical. The two molecules are hydrogen bonded head-to-tail *via* the 3-hydroxyl oxygen of one molecule and the 16 α -hydroxyl hydrogen of another, in such a way that the 18-methyl group of the first lies under the A ring of the second, producing distortion of this aromatic ring. Steric hindrance between the C ring equatorial hydrogen atom at C(11), and the hydrogen atom at C(1) produces twisting about the C(9)–C(10) bond, in opposite directions in the two molecules, causing the B ring to take up a half chair conformation in the first and a twist boat conformation in the second.

The molecules pack with molecules of the first kind and molecules of the second kind, hydrogen bonded in separate chains parallel to b . These chains are cross linked *via* the asymmetric unit and *via* weaker hydrogen bonds involving all three hydroxyl groups. Three distinct types of hydrogen bond exist in which the O...H–O angles are 159–177°, 136°, and 128°.

Introduction

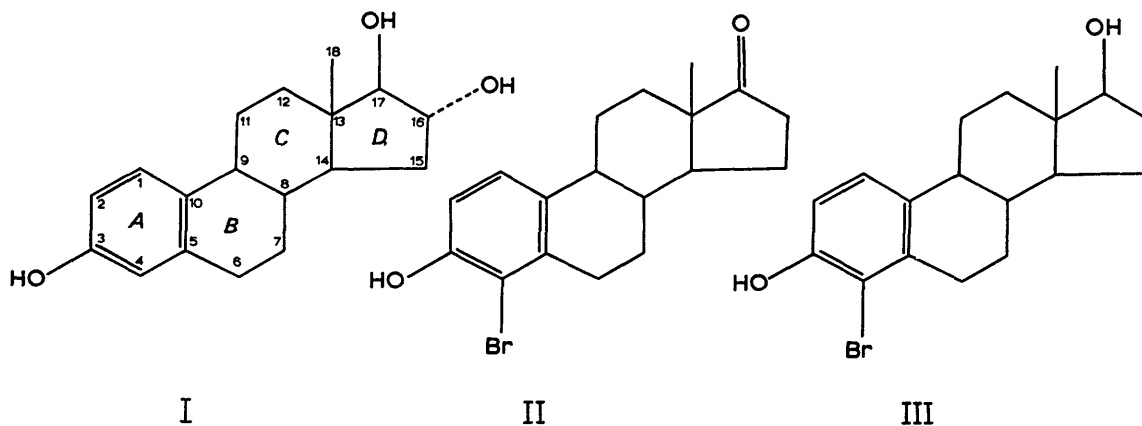
The estrogens, of which the principal members are estradiol, estrone and estriol, are essential for the

development and maintenance of the secondary female sex characteristics. They are produced mainly by the ovary and to a small extent by the adrenal cortex but during pregnancy, the placenta produces relatively

large amounts of estriol. It is of interest to note that, large concentrations of estrogenic hormones have been isolated from males suffering from feminizing adrenal carcinoma (Dempsey & Richardson Hall, 1963). Both estradiol and estrone are metabolized to estriol, which is often the principal estrogen recoverable from human urine; the only other reported natural source of estriol is female willow catkins (Skarzynski, 1933); however, Jacobsohn, Frey & Hochberg (1965) could not confirm this finding.

There is evidence of the possibility that the estrogens affect the energy turnover of cells *in vitro* by acting in concert with enzyme systems responsible for hydrogen transport (Talalay, Hurlock & Williams-Ashman, 1958). For example, in the presence of pyridine nucleotides, 17β -estradiol acts as a coenzyme in which it is alternately oxidized and reduced, promoting a reversible hydrogen transfer between the pyridine nucleotides. Whereas estradiol appears to act mainly on the endometrium, estriol acts specifically on the cervix and the vagina (Puck, 1957). These hormones, therefore, show such unique specificities for particular intracellular locations, that minor molecular structure variations could alter not only the magnitude of their biological activities but also the quantitative nature of the responses they elicit.

We have previously reported the results of X-ray crystallographic structure determinations of brominated estrone (II) and estradiol (III) (Norton, Lu & Kartha, 1963, 1964), and we now complete the series of principal estrogens by reporting the crystal structure of estriol (I).



Experimental

Crystals of estriol, grown by slow evaporation of a solution in isopropyl alcohol were tabular with (010) dominating, and showed cleavage on (100). The space group was determined as $P2_1$ ($0k0$, for $k=2n$ only) and the crystal data are:

Estriol ($C_{18}H_{24}O_3$)₂, $M=(288.37)$ ₂, $a=9.261 \pm 0.003$
 $b=23.025 \pm 0.002$, $c=7.561 \pm 0.002$ Å, $\beta=111.00 \pm 0.03^\circ$

(at $20 \pm 2^\circ\text{C}$, $\text{Cu } K\alpha=1.54051$ Å), $V=1505.04$ Å³,
 $D_m=1.268$ g.cm⁻³ (by flotation), $Z=4$, $D_c=1.273$
 g.cm⁻³. Space group $P2_1$, C_2^2 no.4.

An 0.2 mm equidimensional crystal was ground to a spherical shape and was mounted on a General Electric single crystal orienter, with its b axis parallel to the φ axis of the instrument. The intensities of 3193 independent reflections with 2θ less than 150° were measured by the stationary-crystal stationary-counter method, with use of $\text{Cu } K\alpha$ radiation monochromatized by balanced nickel and cobalt filters. Each reflection was measured for ten seconds with each filter. No corrections were applied for extinction or for absorption of X-rays in the specimen. A number of $0kl$ reflections were also measured, as a consistency test for comparison with the $0kl$ intensities. These 131 additional intensities were included in the structure refinement and, where appropriate, the pairs of $0kl$ and $0\bar{k}l$ reflections are also included in Table 1. For the purposes of the phase determination procedures however, the corresponding average intensities were used.

Structure determination

The phase determination described in detail in the previous paper, is briefly summarized here. The values of 1805 structure invariants,

$$\cos(\varphi_1 + \varphi_2 + \varphi_3), \varphi_i = \Phi_{h_i};$$

$$i=1,2,3; \mathbf{h}_1 + \mathbf{h}_2 + \mathbf{h}_3 = 0,$$

were found by means of a variant of equation (5.12)

(Hauptman, 1964). Once the values of three suitable phases and the sign of one structure invariant, $\varphi_1 + \varphi_2 + \varphi_3$, were arbitrarily specified, thus fixing the origin and enantiomorph, these 1805 structure invariants led directly, by means of a least-squares technique, to the values of 103 phases. By the use of these 103 phases and employing the Tangent Formula, equation (5.62) (Karle & Hauptman, 1956) the values of all 1023 phases were determined whose corresponding normalized structure factor magnitudes $|E|$ were

Table 1. Comparison of the observed structure amplitudes with those calculated from the refined parameters for this structure

The values are tabulated on ten times absolute scale.

M K L F0BS FCAL					M K L F0BS FCAL					M K L F0BS FCAL					M K L F0BS FCAL					M K L F0BS FCAL					M K L F0BS FCAL														
0 0 1	195	191	0	4	-2	255	242	0 19 4	12	14	1	3	6	58	60	0 112	5	238	242	1 23	4	95	79	2 6	-3	162	137	2 15	-7	12	12	3 1	1	209	208	3 10	0	170	174
0 0 -1	200	191	0	4	2	255	242	0 19 4	12	14	1	3	7	51	88	0 112	-5	238	242	1 23	4	95	79	2 6	4	67	87	2 16	0	40	41	3 1	1	375	390	3 10	0	167	151
0 0 2	296	284	0	4	-4	310	284	0 19 4	12	14	1	3	4	41	43	0 112	10	109	103	1 23	4	95	79	2 6	-4	87	107	2 17	0	40	41	3 1	1	272	273	3 10	0	172	187
0 0 0	237	234	0	4	0	19	5	89	81	1 3	-8	40	44	1 12	6	74	74	2 1	24	0	51	45	2 6	-5	94	105	2 16	-1	193	187	3 1	2	92	89	3 10	-2	292	288	
0 0 0	3 255	253	0	4	-4	110	97	4	39	1	3	8	49	40	1 12	6	74	74	2 1	24	0	51	45	2 6	5	72	65	2 16	-2	93	86	3 1	3	123	118	3 10	0	170	187
0 0 -1	255	253	0	4	4	25	22	0	20	5	42	45	39	1	3	-8	47	53	1 12	-6	74	74	2 1	4	38	34	2 16	2	134	134	3 1	0	267	278	3 10	0	181	185	
0 0 4	217	201	0	4	0	72	22	0	20	10	147	177	1	4	0	413	530	1 12	-8	72	60	2 6	-6	262	271	2 16	3	82	73	3 1	4	67	60	3 10	3	24	24		
0 0 -4	217	201	0	4	0	72	22	0	20	10	147	177	1	4	0	413	530	1 12	-8	72	60	2 6	6	262	271	2 16	-3	82	73	3 1	-4	67	60	3 10	-3	24	24		
0 0 0	5	62	61	0	4	-6	32	25	20	0	-154	177	1	4	-1	500	514	1 13	1	0	60	97	2 6	7	47	60	2 16	4	0	0	3 1	-5	223	222	3 10	4	88	86	
0 0 0	5	59	61	0	4	-7	56	46	20	-2	295	258	1	4	-2	249	235	1 13	-1	0	237	237	2 6	-8	73	66	2 16	-4	214	224	3 1	5	37	30	3 10	5	94	96	
0 0 0	5	56	61	0	4	-7	58	46	20	-2	295	258	1	4	-2	249	235	1 13	-1	0	237	237	2 6	-8	73	66	2 16	-4	214	224	3 1	5	37	30	3 10	5	94	96	
0 0 0	5	53	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	340	325	1 13	2	0	189	189	2 6	-9	80	74	2 16	-5	36	33	3 1	-6	59	53	3 10	-6	69	67	
0 0 0	5	53	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	340	325	1 13	2	0	189	189	2 6	-9	80	74	2 16	-5	36	33	3 1	-6	59	53	3 10	-6	69	67	
0 0 0	5	49	61	0	4	-7	58	42	20	-2	295	258	1	4	-2	441	441	1 13	3	0	140	140	2 6	-10	87	81	2 16	-6	49	45	3 1	-7	67	63	3 10	-7	82	79	
0 0 0	5	49	61	0	4	-7	58	42	20	-2	295	258	1	4	-2	441	441	1 13	3	0	140	140	2 6	-10	87	81	2 16	-6	49	45	3 1	-7	67	63	3 10	-7	82	79	
0 0 0	5	46	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-11	94	87	2 16	-7	56	53	3 1	-8	74	71	3 10	-8	91	88	
0 0 0	5	43	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-11	94	87	2 16	-7	56	53	3 1	-8	74	71	3 10	-8	91	88	
0 0 0	5	43	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-11	94	87	2 16	-7	56	53	3 1	-8	74	71	3 10	-8	91	88	
0 0 0	5	40	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-12	101	94	2 16	-8	63	60	3 1	-9	81	78	3 10	-9	98	95	
0 0 0	5	37	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-13	108	101	2 16	-9	70	67	3 1	-10	88	85	3 10	-10	105	102	
0 0 0	5	37	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-13	108	101	2 16	-9	70	67	3 1	-10	88	85	3 10	-10	105	102	
0 0 0	5	34	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-14	115	108	2 16	-10	77	74	3 1	-11	95	92	3 10	-11	112	109	
0 0 0	5	34	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-14	115	108	2 16	-10	77	74	3 1	-11	95	92	3 10	-11	112	109	
0 0 0	5	31	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-15	122	115	2 16	-11	84	81	3 1	-12	102	99	3 10	-12	119	116	
0 0 0	5	31	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-15	122	115	2 16	-11	84	81	3 1	-12	102	99	3 10	-12	119	116	
0 0 0	5	28	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-16	129	122	2 16	-12	91	88	3 1	-13	109	106	3 10	-13	126	123	
0 0 0	5	28	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-16	129	122	2 16	-12	91	88	3 1	-13	109	106	3 10	-13	126	123	
0 0 0	5	25	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-17	136	129	2 16	-13	98	95	3 1	-14	116	113	3 10	-14	133	130	
0 0 0	5	25	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-17	136	129	2 16	-13	98	95	3 1	-14	116	113	3 10	-14	133	130	
0 0 0	5	22	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-18	143	136	2 16	-14	105	102	3 1	-15	123	120	3 10	-15	140	137	
0 0 0	5	22	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-18	143	136	2 16	-14	105	102	3 1	-15	123	120	3 10	-15	140	137	
0 0 0	5	19	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-19	150	143	2 16	-15	92	89	3 1	-16	130	127	3 10	-16	147	144	
0 0 0	5	19	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-19	150	143	2 16	-15	92	89	3 1	-16	130	127	3 10	-16	147	144	
0 0 0	5	16	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-20	157	150	2 16	-16	79	76	3 1	-17	137	134	3 10	-17	154	151	
0 0 0	5	16	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-20	157	150	2 16	-16	79	76	3 1	-17	137	134	3 10	-17	154	151	
0 0 0	5	13	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-21	164	157	2 16	-17	66	63	3 1	-18	144	141	3 10	-18	161	158	
0 0 0	5	13	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-21	164	157	2 16	-17	66	63	3 1	-18	144	141	3 10	-18	161	158	
0 0 0	5	10	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-22	171	164	2 16	-18	53	50	3 1	-19	151	148	3 10	-19	168	165	
0 0 0	5	10	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-22	171	164	2 16	-18	53	50	3 1	-19	151	148	3 10	-19	168	165	
0 0 0	5	7	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-23	178	171	2 16	-19	40	37	3 1	-20	158	155	3 10	-20	175	172	
0 0 0	5	7	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-23	178	171	2 16	-19	40	37	3 1	-20	158	155	3 10	-20	175	172	
0 0 0	5	4	61	0	4	-7	56	42	20	-2	295	258	1	4	-2	500	500	1 13	3	0	140	140	2 6	-24	185	178	2 16	-20	27	24	3 1	-21							

Table 1 (cont.)

H	K	L	F0BS	FCAL	H	K	L	F0BS	FCAL	H	K	L	F0BS	FCAL	H	K	L	F0BS	FCAL	H	K	L	F0BS	FCAL						
8 19 -3	21	25	9 0 -3	53	63	9 0 -3	37	41	9 0 -4	32	34	9 12 -2	25	23	9 17 -2	32	32	10 1 -1	22	34	10 6 -7	19	22	10 11 -2	34	36	11 2 -4	15	17	
8 19 -4	59	54	9 0 -4	36	30	9 0 -5	39	43	9 0 -7	51	46	9 12 -3	47	41	9 17 -3	17	10	10 1 -2	33	34	10 7 0	36	31	10 11 -3	58	52	11 3 -1	21	21	
8 19 -5	22	68	9 0 -5	58	64	9 0 -6	49	50	9 0 0	43	40	9 12 -4	69	56	9 17 -4	15	10	10 1 -3	33	34	10 7 0	36	31	10 11 -4	25	19	11 3 -2	31	40	
8 20 -1	31	28	9 0 1	37	37	9 0 2	31	37	9 0 1	18	18	9 12 -5	29	24	9 18 -2	16	10	10 1 -4	31	34	10 7 1	36	33	10 11 -5	67	68	11 3 -3	16	17	
8 20 -2	17	17	9 0 2	54	47	9 0 3	57	29	14 0	9 1 -1	12	12	9 12 -6	50	60	9 18 -3	11	27	10 1 -5	32	42	10 7 -1	42	40	10 12 -1	29	32	11 3 -4	18	10
8 20 -3	25	29	9 0 4	34	34	9 0 5	34	34	9 0 2	32	36	9 12 -7	22	22	9 18 -4	10	20	10 1 -6	31	34	10 7 -2	41	38	10 12 -2	30	32	11 3 -5	37	48	
8 20 -4	-4	51	9 0 6	1	24	9 0 7	1	42	9 0 3	2	36	9 13 1	16	22	9 18 -5	10	10	10 1 -7	31	34	10 7 -3	41	38	10 12 -3	40	36	11 4 -1	18	74	
9 0 0	34	26	9 1 1	52	49	9 1 2	49	46	9 1 1	76	81	9 13 2	1	63	10 0 0	1	17	10 1 -8	31	34	10 7 -4	52	42	10 12 -4	70	74	11 4 -2	32	43	
9 0 -1	58	92	9 1 3	1	37	9 1 4	1	37	9 1 2	46	46	9 13 3	1	51	10 0 1	1	35	10 1 -9	31	34	10 7 -5	56	54	10 12 -5	36	11	11 4 -3	36	13	
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9 0 -2	54	60	9 1 7	3	21	9 1 8	3	21	9 1 4	43	43	9 13 5	1	31	10 0 3	1	10	10 1 -11	31	34	10 7 -7	10	9	10 12 -7	25	38	11 4 -5	32	31	
9 0 -3	2	28	9 1 9	4	27	9 1 10	4	27	9 1 5	52	49	9 13 6	1	22	10 0 4	1	10	10 1 -12	31	34	10 7 -8	10	9	10 12 -8	11	10	11 4 -6	11	16	
9 0 -4	112	108	9 1 11	47	47	9 1 12	47	47	9 1 6	44	39	9 13 7	1	16	10 0 5	1	10	10 1 -13	31	34	10 7 -9	24	22	10 12 -9	40	41	11 4 -7	54	38	
9 0 -5	24	16	9 1 13	51	26	9 1 14	51	26	9 1 7	52	42	9 13 8	1	10	10 0 6	1	10	10 1 -14	31	34	10 7 -10	24	22	10 12 -10	13	11	11 4 -8	54	38	
9 0 -6	112	109	9 1 15	37	35	9 1 16	37	35	9 1 8	39	30	9 13 9	1	10	10 0 7	1	10	10 1 -15	31	34	10 7 -11	24	22	10 12 -11	13	11	11 4 -9	54	38	
9 0 -7	24	25	9 1 17	11	21	9 1 18	11	21	9 1 9	42	42	9 13 10	1	10	10 0 8	1	10	10 1 -16	31	34	10 7 -12	24	22	10 12 -12	13	11	11 4 -10	54	38	
9 0 -8	12	29	9 1 19	107	101	9 1 20	107	101	9 1 10	42	42	9 13 11	1	10	10 0 9	1	10	10 1 -17	31	34	10 7 -13	24	22	10 12 -13	13	11	11 4 -11	54	38	
9 1 0	36	34	9 1 21	50	50	9 1 22	50	50	9 1 11	38	33	9 13 12	1	10	10 1 0	1	10	10 1 -18	31	34	10 7 -14	24	22	10 12 -14	13	11	11 4 -12	54	38	
9 1 1	30	34	9 1 23	91	74	9 1 24	91	74	9 1 12	38	33	9 13 13	1	10	10 1 1	1	10	10 1 -19	31	34	10 7 -15	24	22	10 12 -15	13	11	11 4 -13	54	38	
9 1 -1	70	70	9 1 25	76	85	9 1 26	76	85	9 1 13	42	42	9 13 14	1	10	10 1 2	1	10	10 1 -20	31	34	10 7 -16	24	22	10 12 -16	13	11	11 4 -14	54	38	
9 1 -2	40	64	9 1 27	115	104	9 1 28	115	104	9 1 14	42	42	9 13 15	1	10	10 1 3	1	10	10 1 -21	31	34	10 7 -17	24	22	10 12 -17	13	11	11 4 -15	54	38	
9 1 2	32	22	9 1 29	4	56	9 1 30	4	56	9 1 15	42	42	9 13 16	1	10	10 1 4	1	10	10 1 -22	31	34	10 7 -18	24	22	10 12 -18	13	11	11 4 -16	54	38	
9 1 -3	41	60	9 1 31	54	62	9 1 32	54	62	9 1 16	42	42	9 13 17	1	10	10 1 5	1	10	10 1 -23	31	34	10 7 -19	24	22	10 12 -19	13	11	11 4 -17	54	38	
9 1 -4	58	57	9 1 33	4	18	9 1 34	4	18	9 1 17	42	42	9 13 18	1	10	10 1 6	1	10	10 1 -24	31	34	10 7 -20	24	22	10 12 -20	13	11	11 4 -18	54	38	
9 1 -5	54	68	9 1 35	4	40	9 1 36	4	40	9 1 18	42	42	9 13 19	1	10	10 1 7	1	10	10 1 -25	31	34	10 7 -21	24	22	10 12 -21	13	11	11 4 -19	54	38	
9 1 -6	115	110	9 1 37	4	22	9 1 38	4	22	9 1 19	42	42	9 13 20	1	10	10 1 8	1	10	10 1 -26	31	34	10 7 -22	24	22	10 12 -22	13	11	11 4 -20	54	38	
9 1 -7	90	83	9 1 39	4	75	9 1 40	4	75	9 1 20	42	42	9 13 21	1	10	10 1 9	1	10	10 1 -27	31	34	10 7 -23	24	22	10 12 -23	13	11	11 4 -21	54	38	
9 1 -8	110	110	9 1 41	4	24	9 1 42	4	24	9 1 21	42	42	9 13 22	1	10	10 1 10	1	10	10 1 -28	31	34	10 7 -24	24	22	10 12 -24	13	11	11 4 -22	54	38	
9 2 0	90	77	9 1 43	5	58	9 1 44	5	58	9 1 22	42	42	9 13 23	1	10	10 1 11	1	10	10 1 -29	31	34	10 7 -25	24	22	10 12 -25	13	11	11 4 -23	54	38	
9 2 -1	17	8	9 1 45	1	58	9 1 46	1	58	9 1 23	42	42	9 13 24	1	10	10 1 12	1	10	10 1 -30	31	34	10 7 -26	24	22	10 12 -26	13	11	11 4 -24	54	38	
9 2 -2	18	13	9 1 47	1	58	9 1 48	1	58	9 1 24	42	42	9 13 25	1	10	10 1 13	1	10	10 1 -31	31	34	10 7 -27	24	22	10 12 -27	13	11	11 4 -25	54	38	
9 2 -3	26	29	9 1 49	5	52	9 1 50	5	52	9 1 25	42	42	9 13 26	1	10	10 1 14	1	10	10 1 -32	31	34	10 7 -28	24	22	10 12 -28	13	11	11 4 -26	54	38	
9 2 -4	44	41	9 1 51	9	52	9 1 52	9	52	9 1 26	42	42	9 13 27	1	10	10 1 15	1	10	10 1 -33	31	34	10 7 -29	24	22	10 12 -29	13	11	11 4 -27	54	38	
9 2 -5	24	24	9 1 53	9	52	9 1 54	9	52	9 1 27	42	42	9 13 28	1	10	10 1 16	1	10	10 1 -34	31	34	10 7 -30	24	22	10 12 -30	13	11	11 4 -28	54	38	

Table 2(a). Positional and thermal parameters of the non-hydrogen atoms, at the end of the least-squares refinement. The atoms of the two molecules are distinguished by the prefixes 1 and 2 respectively. Thermal parameters are listed in the form $\exp \{-2\pi^2(U_{11}h^2a^*{}^2 + 2U_{12}hk a^*b^* + \dots)\}$.

	X/A	Y/B	Z/C	U11	U22	U33	U12	U13	U23
1C 1	0.97161(71)	0.73168(25)	0.45922(71)	0.0643(40)	0.0397(31)	0.0232(22)	0.0029(29)	0.0227(24)	0.0030(22)
1C 2	0.94607(71)	0.67349(24)	0.41653(70)	0.0669(39)	0.0361(31)	0.0203(20)	-0.0020(28)	0.0155(23)	-0.0028(21)
1C 3	0.90256(59)	0.53493(23)	0.58051(72)	0.0364(29)	0.0326(23)	0.0260(21)	0.0005(24)	0.0121(20)	0.0000(20)
1C 4	1.00058(62)	0.65378(21)	0.74570(72)	0.0438(30)	0.0264(24)	0.0235(19)	0.0048(24)	0.0130(20)	0.0038(19)
1C 5	1.02421(60)	0.71320(22)	0.78852(65)	0.0386(29)	0.0318(23)	0.0172(18)	0.0072(23)	0.0092(19)	0.0014(18)
1C 6	1.05861(88)	0.75120(27)	0.95044(77)	0.0922(53)	0.0407(33)	0.0205(22)	0.0069(35)	0.0110(28)	0.0008(22)
1C 7	0.79485(61)	0.73747(24)	1.01535(64)	0.0395(29)	0.0332(21)	0.0155(17)	-0.0012(23)	0.0125(23)	0.0000(20)
1C 8	0.99594(63)	0.83172(22)	0.86425(66)	0.0448(32)	0.0294(24)	0.0192(17)	-0.0057(24)	0.0133(20)	0.0013(19)
1C 9	1.04100(59)	0.81709(21)	0.69145(64)	0.0392(29)	0.0331(23)	0.0202(18)	-0.0023(24)	0.0136(19)	0.0074(19)
1C10	1.01086(59)	0.75327(22)	0.62445(68)	0.0581(35)	0.0319(27)	0.0155(20)	-0.0023(23)	0.0129(23)	0.0002(18)
1C11	0.96651(60)	0.85876(22)	0.52744(69)	0.0657(39)	0.0285(28)	0.0216(20)	0.0081(28)	0.0215(23)	0.0068(20)
1C12	0.99464(68)	0.82275(22)	0.58092(70)	0.0605(38)	0.0304(29)	0.0245(20)	0.0032(26)	0.0194(23)	0.0022(19)
1C13	0.94132(58)	0.93702(21)	0.74302(66)	0.0329(28)	0.0294(26)	0.0217(19)	-0.0025(22)	0.0086(19)	0.0017(18)
1C14	1.02827(65)	0.89823(21)	0.90800(69)	0.0490(34)	0.0255(27)	0.0246(20)	-0.0062(25)	0.0150(22)	0.0015(19)
1C15	0.98998(84)	0.92080(25)	1.07589(77)	0.0891(52)	0.0368(35)	0.0290(25)	-0.0141(33)	0.0264(25)	-0.0085(23)
1C16	0.97346(69)	0.98654(24)	1.03711(75)	0.0555(35)	0.0292(28)	0.0300(22)	-0.0071(26)	0.0223(23)	-0.0049(20)
1C17	0.99509(63)	0.99533(21)	0.84743(72)	0.0449(32)	0.0285(27)	0.0288(24)	-0.0001(24)	0.0164(21)	-0.0000(20)
1C18	0.78546(61)	0.93247(27)	0.65010(68)	0.0458(36)	0.0457(35)	0.0159(20)	-0.0005(23)	0.0139(23)	-0.0129(22)
1O 3	0.95831(45)	0.57631(15)	0.51673(50)	0.0046(25)	0.0230(17)	0.0336(15)	-0.0004(18)	0.0248(17)	-0.0045(14)
1O16	1.07893(55)	1.01994(17)	1.18647(52)	0.0743(50)	0.0384(21)	0.0340(16)	-0.0080(21)	0.0173(18)	-0.0148(16)
1O17	0.91269(50)	1.04514(16)	0.75197(56)	0.0745(59)	0.0295(19)	0.0439(18)	0.0118(20)	0.0301(19)	0.0068(16)
2C 1	0.56982(67)	0.63261(23)	1.03267(68)	0.0577(36)	0.0346(30)	0.0200(17)	0.0050(27)	0.0127(22	

Table 2(b) (cont.)

	X/A	Y/B	Z/C
1H(12A)	1.1138	0.9328	0.6343
1H(12B)	0.9343	0.9443	0.4675
1H(14)	1.1517	0.9047	0.9499
1H(15A)	0.8878	0.9028	1.0753
1H(15B)	1.0866	0.9123	1.2010
1H(16)	0.8578	1.0018	0.9999
1H(17)	1.1114	0.9981	0.8778
1H(18A)	0.7346	0.8927	0.6391
1H(18B)	0.7386	0.9382	0.7924
1H(18C)	0.7135	0.9616	0.5728
1H(O3)	0.9865	0.5567	0.6427
1H(O16)	1.1854	1.0011	1.1840
1H(O17)	0.9439	1.0633	0.6434
2H(1)	0.6157	0.8065	1.1381
2H(2)	0.5955	0.9059	1.2073
2H(4)	0.3997	0.9363	0.6324
2H(6A)	0.2800	0.8308	0.4379
2H(6B)	0.4076	0.8622	0.4324
2H(7A)	0.4140	0.7675	0.3334
2H(7B)	0.5926	0.7834	0.4722
2H(8)	0.3538	0.7227	0.5912
2H(9)	0.6703	0.7532	0.8263
2H(11A)	0.6237	0.7184	1.0774
2H(11B)	0.4683	0.7037	0.9490
2H(12A)	0.7317	0.6474	0.9270
2H(12B)	0.6189	0.6281	1.0068
2H(14)	0.6484	0.6783	0.6112
2H(15A)	0.3391	0.6475	0.3202
2H(15B)	0.4953	0.6536	0.2669
2H(16)	0.4104	0.5539	0.3887
2H(17)	0.7110	0.5867	0.6632
2H(18A)	0.3124	0.6405	0.7248
2H(18B)	0.2855	0.5947	0.5582
2H(18C)	0.3654	0.5709	0.8109
2H(O3)	0.5008	1.0032	0.8902
2H(O16)	0.7126	0.5629	0.4062
2H(O17)	0.5784	0.5074	0.8230

Table 2(c). Positional parameters of the non-hydrogen atoms, after correction for libration of the individual molecules

These corrected parameters were used for all intramolecular geometry calculations.

	X/A	Y/B	Z/C
1C(1)	0.97161	0.73168	0.45922
1C(2)	0.94588	0.67348	0.41544
1C(3)	0.96246	0.63449	0.56022
1C(4)	1.00069	0.65362	0.74631
1C(5)	1.02446	0.71308	0.78913
1C(6)	1.05897	0.73104	0.99169
1C(7)	1.09517	0.79371	1.03346
1C(8)	0.99601	0.83168	0.86478
1C(9)	1.04131	0.81712	0.69113
1C(10)	1.01101	0.75325	0.64412
1C(11)	0.96613	0.85887	0.52128
1C(12)	0.99464	0.92290	0.57983
1C(13)	0.94105	0.93713	0.74246
1C(14)	1.02852	0.89624	0.90960
1C(15)	0.99001	0.92077	1.07681
1C(16)	0.97338	0.98658	1.03789
1C(17)	0.99511	0.99545	0.84718
1C(18)	0.76448	0.93257	0.67938
1O(3)	0.93789	0.57618	0.51646
1O(16)	1.07936	1.01996	1.18772
1O(17)	0.91227	1.04532	0.75110

Table 2(c) (cont.)

	X/A	Y/B	Z/C
2C(1)	0.56976	0.83245	1.03358
2C(2)	0.54685	0.88980	1.07788
2C(3)	0.48000	0.92759	0.93239
2C(4)	0.42987	0.90924	0.74380
2C(5)	0.45387	0.85118	0.70318
2C(6)	0.39972	0.83301	0.49755
2C(7)	0.47396	0.77727	0.46311
2C(8)	0.46686	0.73043	0.60353
2C(9)	0.56601	0.75001	0.80509
2C(10)	0.52546	0.81217	0.84937
2C(11)	0.56712	0.70469	0.95628
2C(12)	0.62262	0.64464	0.91280
2C(13)	0.52374	0.62422	0.71329
2C(14)	0.52840	0.67249	0.56888
2C(15)	0.46032	0.64226	0.37609
2C(16)	0.51073	0.57882	0.41783
2C(17)	0.59503	0.57595	0.63234
2C(18)	0.35962	0.60736	0.69937
2O(3)	0.46287	0.98511	0.97231
2O(16)	0.60875	0.55829	0.31526
2O(17)	0.59930	0.51811	0.70545

Thermal vibration analysis*

Fig. 1 gives identical views of the molecules in the asymmetric unit, and shows the shapes and orientations of the thermal vibration ellipsoids. When the thermal motion of the molecules in the asymmetric unit are analyzed separately in terms of the rigid body motion of the steroid nucleus, C(1)–C(17), we find that these molecules do in fact behave very nearly as rigid bodies. The root mean square differences between the observed U_{ij} terms and those calculated from the derived T and ω tensors are only 0.0035 Å² for the seventeen atoms comprising the nuclei of each of molecules 1 and 2. The substituent methyl and hydroxyl groups, however, have a small amount of additional independent motion, approximately perpendicular to the plane of the nucleus, for the hydroxyl groups, and approximately parallel to the plane of the nucleus, for the methyl groups. The rigid body motions are principally translational, and are almost isotropic with an average amplitude of translation of 0.17 Å. Rotational motion is limited by the close packing of the irregularly shaped molecules, and amounts to only five to six degrees about the long axis of each molecule. Using Cruickshank's (1961) method, the positional parameters of the non-hydrogen atoms of the two molecules were corrected for the librational motions of the separate molecules, and these corrected parameters, which are listed in Table 2(c), were used in all intramolecular geometry calculations.

For comparison, we also calculated the rigid body parameters for atoms C(1)–C(17) for both molecules considered together. The results of these calculations and of those for the separate molecules are given in Table 3, from which we can see that the eigenvalues of

* All rigid body calculations were carried out by use of Schomaker & Trueblood's (1968) program. The significance of the thermal motions of the atoms in this structure and in other steroids will be the subject of another communication.

represent a more anisotropic translation of the whole asymmetric unit than for the separate nuclei, and that the rotational motion is quite negligible. The fit of the calculated U_{ij} terms to those observed, however, was not as consistent as for the molecules considered separately.

Intramolecular geometry

A quick perusal of the intramolecular bond distances and angles in Fig. 2 shows that the two molecules in the asymmetric unit are not identical. The major differences exist in the regions of the 3- and the 16 α -hydroxyl groups, at the *C/D* ring junction, about atoms C(9) and C(11), and about atom C(7).

In molecule 1, the *A* ring shows typical aromaticity and delocalization of the π electrons to produce an average bond length of 1.395 ± 0.012 Å. Molecule 2 shows similar aromaticity except that bond C(2)–C(3) is considerably shortened to 1.365 Å. Such an effect has been frequently observed in phenol structures, but there has usually been an additional *ortho* substituent (e.g. *o*-fluorobenzoic acid, Krause & Dunken, 1966; salicylic acid, Sundaralingam & Jensen, 1965). In the present case, the distortion of the *A* ring in molecule 2 is attributed to the interaction between this ring and the C(18) methyl group of the associated molecule 1. This effect is easily seen on the right-hand side of Fig. 3, in which the top molecule is molecule 2. The interaction

has produced a folding of the *A* ring of molecule 2 about the line C(2)–C(4) such that atoms C(1), C(2), C(4), C(5) and C(10) and atoms C(2), C(3), C(4) and O(3) are separately planar, with a dihedral angle of 2.6° . Both the 3-hydroxyl bonds are shortened by the aromatic *A* rings, but not as much as in salicylic acid, where the bond is 1.358 Å.

The distortions in the *B* and *C* rings of both molecules are mainly a result of a twisting about the C(9)–C(10) bond to accommodate the strong interaction between the aromatic hydrogen atom H(1) and the equatorial *C* ring hydrogen atom H(11)*A*. In the two molecules, the respective distances between these two hydrogen atoms are 2.04 and 2.09 Å. The projections along the C(9)–C(10) bond of rings *A*, *B* and part of ring *C* of the two molecules are given in Fig. 4. In the schematic representations of the torsional angles given in Fig. 4(c), we can see that steric hindrance between H(1) and H(11)*A* has been reduced by a rotation about the C(9)–C(10) bond, in a clockwise direction in molecule 1, and in an anticlockwise direction in molecule 2. Such a rotation would require excessive energy in a fully saturated system, but the Δ^{5-10} bond introduces a degree of flexibility into the *B* ring at atoms C(6) and C(7) so that comparatively little energy is required to change this ring from a half chair to a boat conformation. The flexibility about the C(6)–C(7) bond in molecule 1 brings the π electrons of these two atoms

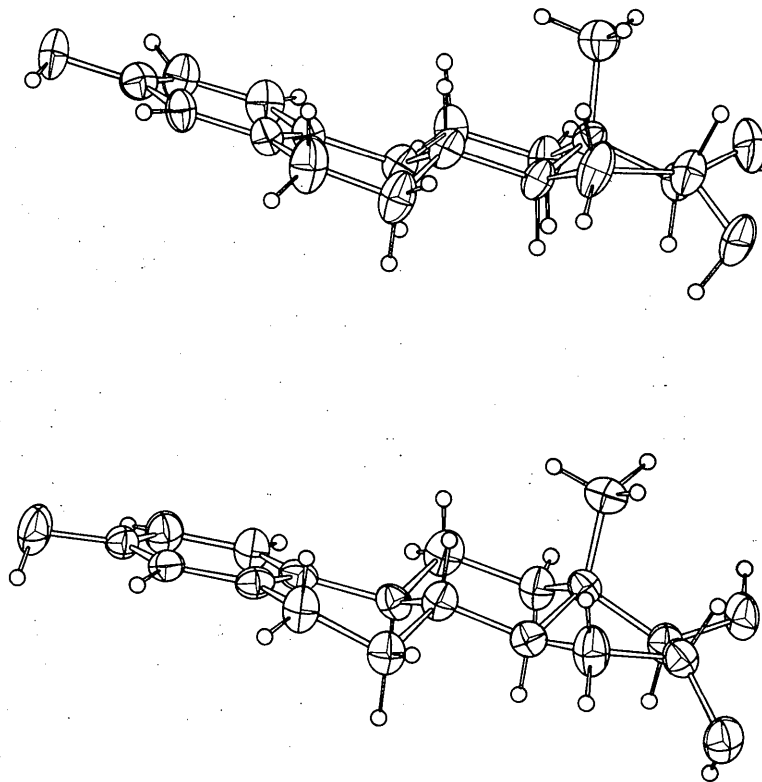


Fig. 1. Perspective views of the two molecules, showing 50% probability thermal vibration ellipsoids. Above, molecule 1; below molecule 2.

ated ring in attempting to minimize the steric hindrance between the equatorial hydrogen atom at C(11) and atom H(1).

The different environments of the *D* rings of the two molecules in terms of hydrogen bonding (as will be discussed later), effect totally different distributions of strain in this highly strained system involving the fusion of the cyclohexane and cyclopentane rings. Consequently, we observe somewhat different geometries for the two *D* rings. In both cases, however, the *D* rings have β -envelope configurations, as shown by the torsional angles in Table 4. The C(17)–OH bond lengths in both molecules agree with the expected value of 1.43 Å, as does the C(16)–OH bond in molecule 1. The C(16)–OH bond in molecule 2, which is involved in strong hydrogen bonding with atom O(3) of molecule 1, however, is lengthened to 1.468 Å, a distance which is similar to that observed for the C–O distance in epoxides (Gopalakrishna, Cooper & Norton, 1968), thus indicating the stability of this hydrogen bond and consequently, its role in the formation of the bimolecular asymmetric unit in this structure. Further evidence for the different affects of hydrogen bonding on the two *D* rings is obtained from the different torsional angles between the 16 α - and 17 β -hydroxyl oxygen atoms in molecules 1 and 2. These angles are 85° and 78° ($\pm 0.5^\circ$) respectively, and the distances between the oxygen atoms O(16) and O(17) are 3.161 Å and 3.123 Å respectively.

Gross geometry of the steroid nucleus

Reference will be made in this discussion to the subdivisions of the steroid nucleus as laid out in Tables 5(a), 5(b) and 5(c). Both molecules (excluding the axial methyl groups) may be regarded as being represented by essentially planar surfaces, lying almost parallel to the (100) crystal face, with the r.m.s. deviations of the atoms from their respective planes being 0.279 Å (1)

and 0.200 Å (2)*. These deviations from the least-squares planes through the two separate nuclei are illustrated in Fig. 5. Both molecules are slightly twisted about their long axes, as shown by the angle which the nucleus to methyl bond, C(13)–C(18), makes with the nuclear plane, *viz.* 5.4° (1) and 4.3° (2). The normals to the two nuclear planes are 12.1° apart. The *B/C* and *C/D* inter-ring junctions have been flattened from 120° (for cyclohexane) to around 130° [Table 5(c)], producing an overall nuclear length, C(3)–C(16), of

* The numbers in parentheses refer to molecules 1 and 2.

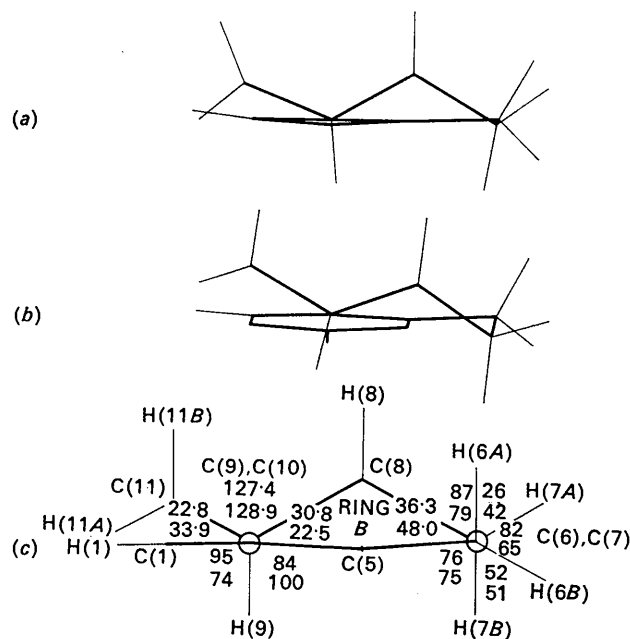


Fig. 4. Projections along the C(9)–C(10) bond of rings *A*, *B* and part of ring *C* of (a) molecule 1 and (b) molecule 2. (c) is a schematic representation of these projections, showing torsion angles and identifying the atoms. Angles for molecule 1 above those for molecule 2.

Table 4. Torsional angles in the rings

ϕ_{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	ϕ_{A-B}^*	Bond	ϕ_{A-B}^*	Bond	ϕ_{A-B}^*	Bond	ϕ_{A-B}^*
C(1)–C(2)	–1.3†	C(5)–C(6)	–6.4	C(8)–C(9)	–51.9	C(13)–C(14)	48.2
	–1.1		–18.7		–56.7		47.9
C(2)–C(3)	1.6	C(6)–C(7)	36.3	C(9)–C(11)	52.0	C(14)–C(15)	–32.2
	2.5		48.0		56.1		–32.6
C(3)–C(4)	–0.7	C(7)–C(8)	–64.0	C(11)–C(12)	–55.0	C(15)–C(16)	2.7
	–2.3		–64.8		–55.6		3.5
C(4)–C(5)	–0.6	C(8)–C(9)	59.9	C(12)–C(13)	57.8	C(16)–C(17)	27.8
	0.7		51.1		55.7		27.8
C(5)–C(10)	0.9	C(9)–C(10)	–30.8	C(13)–C(14)	–61.5	C(13)–C(17)	–46.0
	0.7		–22.5		–60.0		–45.9
C(1)–C(10)	0.1	C(5)–C(10)	3.8	C(8)–C(14)	58.0		
	–0.5		5.8		59.3		

* 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.

8.853 Å (1) and 8.964 Å (2), compared with 8.97 Å in bromoestrone (II) and 8.99 Å in bromoestradiol (III). The shorter effective length of estriol molecule 1 is due to an *upward* bowing of the molecule [cf. Fig. 5(a)] contrary to the usual observation in steroids of slight downward bowing.

Table 5(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 a , b and c^* .

Plane	Atom	l	m	n	p
B2	C(6), C(7), C(9), C(10)	0.9759	-0.1584	0.1498	5.371*
		0.9083	0.4131	0.0655	10.372
B3C1	C(7), C(8), C(9), C(11)	0.6725	0.6711	0.3122	19.430
		-0.8902	0.4457	0.0942	5.482
C2	C(8), C(11), C(12), C(14)	0.9665	-0.1458	0.2114	5.182
		0.9054	0.4083	0.1164	9.814
C3D1	C(12), C(13), C(14), C(15)	0.7194	0.6303	0.2919	20.019
		-0.9339	0.3574	0.0082	2.345
D2	C(13), C(15), C(16), C(17)	0.9623	-0.0996	0.2530	5.748
		0.9005	0.4203	0.1114	9.334
D3	C(14), C(15), C(16), C(17)	0.8566	0.1395	0.4967	12.122
		0.9731	0.1787	-0.1453	5.440
A	C(1), C(2), C(3), C(4), C(5), C(10)	0.9831	-0.1126	0.1440	6.205
		0.9692	0.2446	-0.0298	6.883
B	C(5), C(6), C(7), C(8), C(9), C(10)	0.9815	0.0212	0.1904	8.731
		0.9708	0.2392	0.0205	7.071
C	C(8), C(9), C(11), C(12), C(13), C(14)	0.9450	0.1584	0.2863	11.530
		0.9934	0.1074	0.0412	4.909
D	C(13), C(14), C(15), C(16), C(17)	0.9526	0.1034	0.2860	10.449
		0.9708	0.2237	0.0864	6.807
C1-C17		0.9775	0.0541	0.2038	9.164
		0.9821	0.1841	0.0388	6.130

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

Table 5(b). *Deviations (Å) from the least-squares planes*

	A	B	C	D	B2	B3C1	C2	C3D1	D2	D3	C(1)-C(17)
C(1)	0.003*										0.000
	-0.001										0.126
C(2)	-0.009										-0.252
	-0.010										0.055
C(3)	0.007										-0.324
	0.014										-0.048
C(4)	0.001										-0.177
	-0.007										-0.134
C(5)	-0.006	-0.090			0.056						0.061
	-0.003	-0.043			0.138						-0.065
C(6)		-0.032			-0.017						0.154
		-0.121			-0.081						-0.146
C(7)		0.274			0.017	0.051					0.510
		0.325			0.083	0.005					0.376
C(8)		-0.390	-0.231		-0.753	-0.047	-0.012				-0.139
		-0.344	-0.248		-0.701	-0.005	-0.014				-0.221
C(9)		0.242	0.204		-0.017	-0.057	0.636				0.461
		0.157	0.232		-0.081	-0.005	0.675				0.286
C(10)	0.004	-0.004			0.016						0.163
	0.007	0.025			0.080						0.075
C(11)			-0.213			0.053	0.012				0.035
			-0.231			0.005	0.014				-0.255
C(12)			0.239				-0.013	0.064			0.303
			0.236				-0.014	0.084			0.099
C(13)			-0.264	-0.318			-0.722	-0.068	-0.101	-0.753	-0.360
			-0.248	-0.316			-0.712	-0.090	-0.100	-0.754	-0.414
C(14)			0.265	0.265			0.013	-0.057	0.638	0.011	0.182
			0.259	0.265			0.014	-0.075	0.643	0.014	0.177
C(15)				-0.109				0.062	0.103	-0.016	-0.337
				-0.116				0.081	0.099	-0.021	-0.113
C(16)				-0.078					-0.165	0.016	-0.359
				-0.073					-0.162	0.021	-0.022
C(17)				0.240					0.163	-0.011	0.077
				0.240					0.162	-0.014	0.224

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

Table 5(c). *Interplanar angles*

Plane 1	Plane 2	Angle*
B3C1	B2	126.6 128.2
B3C1	C2	128.2 127.8
C3D1	C2	131.7 134.3
C3D1	D2	134.7 133.6
C3D1	D3	148.1 147.8
A	B	171.9 177.1
B	C	170.2 172.2
C	D	176.8 172.7
C(1)-C(17)	(100)	167.8 169.2
C(1)-C(17)	(010)	93.1 100.6
C(1)-C(17)	(001)	101.8 92.2

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

With the exceptions of atoms C(7) and C(8), all atoms of rings *A* and *B* are nearly coplanar, with r.m.s. deviations from these planes of 0.019 Å (1) and 0.032 Å (2) for the two molecules. The decreased overall *A*-*B* planarity for the second molecule is due to the interaction between its *A* ring and the methyl group of molecule 1, as described in the section on intramolecular geometry. If one takes the mean plane through the *A* ring of molecule 2, atoms C(2), C(3), C(4) and O(3) deviate from this plane by 0.010, 0.014, 0.007 and 0.071 Å, respectively. By comparison, the greatest deviation from the plane of the *A* ring of molecule 1 is 0.009 Å at C(2).

In molecule 1, the *B* ring has a sofa conformation, with C(8) lying 0.69 Å above, and C(7) 0.06 Å below the plane of atoms C(5), C(6), C(9) and C(10). In molecule 2, these distances are 0.37 Å and 0.39 Å, respectively, so that the *B* ring has a conformation intermediate between a half chair and a boat (Figs. 1 and 5).

The *D* rings of both molecules have only slightly distorted β -envelope conformations.

Hydrogen bonding

Three distinct classes of hydrogen bonds exist in this structure, as summarized in Table 6. These are depicted in Fig. 6 which shows all hydrogen bonding to the

Table 6. *Summary of the geometry of the hydrogen bonding between the molecules*

	Hydrogen bond	Position of O	Distance H...O	Distance O...O	Angle O-H...O
I	1O(17)-H...1O(3)	2/100*	1.92 Å	2.926 Å	159°
	2O(16)-H...1O(3)	1/000	1.98	2.915	162
	2O(17)-H...2O(3)	2/011	1.80	2.809	177
II	1O(3)-H...1O(16)	2/111	1.82	2.645	137
	1O(16)-H...2O(17)	2/101	1.91	2.799	136
III	2O(3)-H...2O(16)	2/000	1.99	2.647	128

* Equivalent position nomenclature: 2O(17)-2C(3) 2/011 is taken to mean atom 2O(17) at equivalent position 1 to atom 2C(3) at equivalent position 2, translated 0, -1 and 1 unit cells in the *a*, *b* and *c* directions respectively. The equivalent positions are: 1 = *x*, *y*, *z*; 2 = 1 - *x*, $\frac{1}{2}$ + *y*, 1 - *z*.

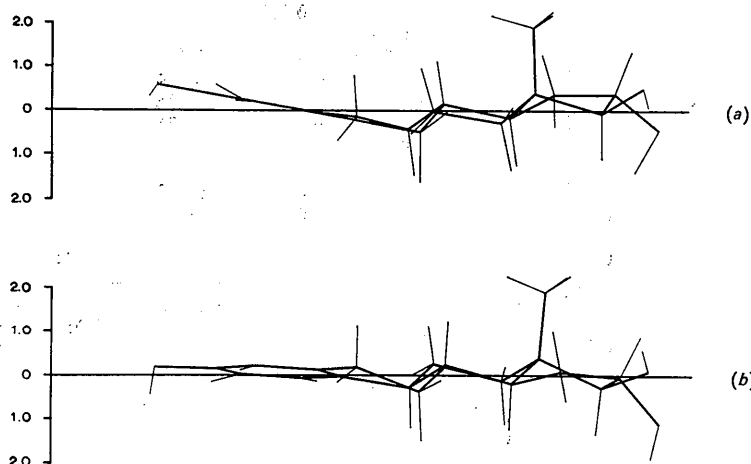


Fig. 5. Projections parallel to the least-squares planes through (a) molecule 1 and (b) molecule 2. The scales show the deviations, in Å units, of the atoms from these planes.

asymmetric unit, *viz.* molecules 1 and 2. Each hydroxyl group is involved in two hydrogen bonds and acts both as a proton donor and as a proton acceptor. Molecule 1 takes part in an additional hydrogen bond at 1O(3), in which this hydroxyl group exhibits tetrahedral coordination.

I. Linear bonds

Molecules 1, which are related by the screw axis at $(x, z=0, \frac{1}{2})$ are hydrogen bonded head-to-tail *via* $1O(3) \cdots H-1O(17)$. Molecules 2, related by the screw axis at $(x, z=\frac{1}{2}, 0)$ are similarly bonded *via* $2O(3) \cdots H-2O(16)$.

II. Non-linear bonds

Molecules 1, which are related by the screw axis at $(x, z=0, 0)$ are hydrogen bonded head-to-tail *via* $1O(16) \cdots H-1O(3)$ and these molecules are further bonded to molecules 2, as produced by the same screw axis, *via* $2O(17) \cdots H-1O(16)$.

III.

Molecules 2, related by the screw axis at $(x, z=\frac{1}{2}, \frac{1}{2})$ are weakly hydrogen bonded *via* $2O(16) \cdots H-2O(3)$. This bond, in which the $O \cdots H-O$ angle is 128° , is extremely distorted, and it is probable that it is not an hydrogen bond in the true sense of the word, since the oxygen atoms are almost in van der Waals contact. It is clear, however, that owing to their close approach, some interaction must occur between the hydrogen atom and the non-bonded oxygen atom. The most distorted interaction actually attributed to hydrogen bonding, which has been reported to date, is that in ethyl-1-thio- α -D-glucofuranoside, with an angle $O \cdots H-O$ of 138° and a distance O-O of 2.718 Å (Parthasarathy & Davis, 1967).

Intermolecular geometry

Since the joint distribution of the motions of the molecules is unknown, only the distances between the mean positions of the atoms in different molecules are meaningful, and consequently, the *non-libration* corrected atomic coordinates have been used in calculations of *intermolecular geometry*.

Of the eighteen intermolecular C-C distances less than 3.8 Å, between molecules 1 and molecules 1 and between molecules 2 and molecules 2, only one does not involve one of the hydroxyl groups. On the other hand, seven of the fourteen distances between molecules 1 and molecules 2 are between non-hydrogen atoms and of these, five involve the methyl groups. When hydrogen atoms are considered, there are twenty six close intermolecular distances between hydrogen atoms (less than 2.5 Å) and between carbon and hydrogen atoms (less than 3.0 Å). Of these, only six are between nonhydroxyl group atoms. These distances are summarized in Table 7. If we eliminate from these lists all contacts between atoms brought into juxtaposition through their lying adjacent to hydrogen bonded atoms, the total is reduced from fifty eight to eighteen, of which nine are to the methyl groups. The remaining nine contacts are to atoms C(6), C(7), C(11) and C(12) or to the hydrogen atoms attached to these carbon atoms.

Table 7(a). Intermolecular distances less than 3.8 Å, between non-hydrogen atoms

Molecule 1-Molecule 1		
1O(3)-1O(16)	2/1 $\bar{1}$ 1*	2.645 Å
-1O(17)	2/1 $\bar{1}$ 0	2.926
-1C(12)	2/1 $\bar{1}$ 0	3.707
-1C(16)	2/1 $\bar{1}$ 1	3.787
-1C(17)	2/1 $\bar{1}$ 0	3.557
1O(16)-1C(3)	2/101	3.360
-1C(4)	2/101	3.249
1O(17)-1C(2)	2/100	3.640
-1C(3)	2/100	3.620
1C(11)-1C(15)	1/00 $\bar{1}$	3.745
Molecule 1-Molecule 2		
1O(3)-2O(16)	1/000	2.915
-2C(16)	1/000	3.761
-2C(17)	1/000	3.588
-2C(18)	1/100	3.726
1O(16)-2O(17)	2/101	2.799
-2C(17)	2/101	3.121
2O(16)-1C(3)	1/000	3.596
1C(3)-2C(18)	1/100	3.510
1C(4)-2C(18)	1/100	3.635
1C(7)-2C(6)	1/101	3.759
1C(12)-2C(4)	1/100	3.790
1C(18)-2C(3)	1/000	3.775
-2C(4)	1/000	3.357
-2C(5)	1/000	3.499

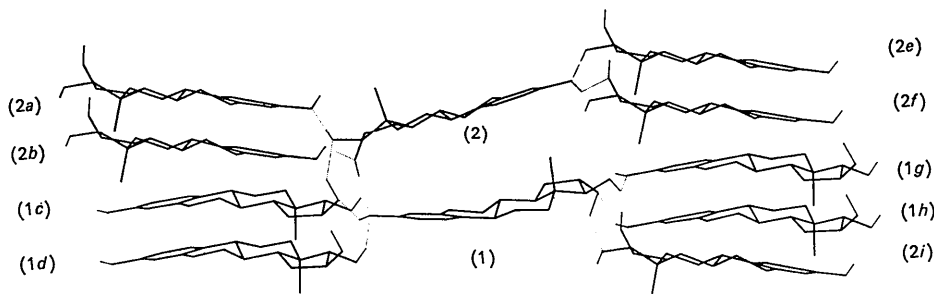


Fig. 6. Projection along the [104] direction, of all molecules hydrogen bonded to the asymmetric unit comprised of molecules 1 and 2. The letters indicate the positions of the various molecules, which, in the nomenclature of Table 7 are: (a)=2/0 $\bar{1}$ 1, (b)=2/0 $\bar{1}$ 0, (c)=2/1 $\bar{1}$ 1, (d)=2/1 $\bar{1}$ 0, (e)=2/001, (f)=2/000 (g)=2/100, (h)=2/101, (i)=2/101.

Table 7(a) (cont.)

Molecule 2—Molecule 2		
2O(3)—2O(16)	2/000	2.647
—2O(17)	2/001	2.808
—2C(16)	2/000	3.737
—2C(18)	2/001	3.730
2O(16)—2C(3)	2/0 $\bar{1}$ 0	3.488
—2C(4)	2/0 $\bar{1}$ 0	3.466
—2C(12)	1/00 $\bar{1}$	3.686
2O(17)—2C(3)	2/0 $\bar{1}$ 1	3.725

* Equivalent position nomenclature: 2O(17)—2C(3) 2/0 $\bar{1}$ 1 is taken to mean atom 2O(17) at equivalent position 1 to atom 2C(3) at equivalent position 2, translated 0, -1 and 1 unit cells in the *a*, *b* and *c* directions respectively. The equivalent positions are: $1 = x, y, z$; $2 = 1 - x, \frac{1}{2} + y, 1 - z$.

Table 7(b). Intermolecular distances less than 2.5 Å between hydrogen atoms

1H(1)—1H(7)A	1/00 $\bar{1}$ *	2.34 Å
1H(7)B—2H(7)A	1/101	2.44
1H(11)A—2H(6)A	1/100	2.50
1HO(3)—1HO(17)	2/1 $\bar{1}$ 0	2.47
1HO(16) 2H(17)	2/101	2.31
2HO(17)	2/101	2.21
1HO(17) 2H(18)B	2/000	2.25

* Equivalent position nomenclature: 2O(17)—2C(3) 2/0 $\bar{1}$ 1 is taken to mean atom 2O(17) at equivalent position 1 to atom 2C(3) at equivalent position 2, translated 0, -1 and 1 unit cells in the *a*, *b* and *c* directions respectively. The equivalent positions are: $1 = x, y, z$; $2 = 1 - x, \frac{1}{2} + y, 1 - z$.

Table 7(c). Intermolecular distances less than 3.0 Å between hydrogen and non-hydrogen atoms

Molecule 1—Molecule 1		
1C(2)—1HO(17)	2/1 $\bar{1}$ 0*	2.83 Å
1C(3)—1HO(17)	2/110	2.60
1C(16)—1HO(3)	2/101	2.82
1O(3)—1HO(17)	2/1 $\bar{1}$ 0	1.92
1O(16)—1H(4)	2/101	2.47
—1HO(3)	2/101	1.82
Molecule 1—Molecule 2		
1C(3)—2HO(16)	1/000	2.74 Å
1C(4)—2H(17)	1/000	2.96
—2H(18)A	1/100	2.97
1O(3)—2HO(16)	1/000	1.98
1O(16)—2H(17)	2/101	2.42
1O(17)—2H(16)	2/000	2.81
Molecule 2—Molecule 2		
2C(3)—2HO(17)	2/001	2.80 Å
2C(11)—2H(15)B	1/001	2.91
2C(16)—2HO(3)	2/0 $\bar{1}$ 0	2.88
2O(3)—2H(18)C	2/001	2.70
—2HO(17)	2/001	1.80
2O(16)—2H(4)	2/0 $\bar{1}$ 0	2.84
—2HO(3)	2/0 $\bar{1}$ 0	1.99

* Equivalent position nomenclature: 2O(17)—2C(3) 2/0 $\bar{1}$ 1 is taken to mean atom 2O(17) at equivalent position 1 to atom 2C(3) at equivalent position 2, translated 0, -1 and 1 unit cells in the *a*, *b* and *c* directions respectively. The equivalent positions are: $1 = x, y, z$; $2 = 1 - x, \frac{1}{2} + y, 1 - z$.

The picture which emerges is one involving an extensively hydrogen-bonded bilayer structure, in which the top-to-bottom packing of the layers is disturbed by the axial methyl groups, C(18). The side-to-side packing is determined by the equatorial hydrogen atoms at C(6), C(7), C(11) and C(12). Fig. 7 illustrates these modes of packing.

Relation of this structure to the theories of interaction of steroid hormones with cell membranes

Steroid hormones interact very specifically with some type or types of molecule at the cell surface, and the steroid molecules orient horizontally with respect to this surface (Munch, 1957; Gershfeld & Heftmann, 1963). Since the area of specific attachment to the receptor surface is small, van der Waals forces will play little part in determining this interaction (2–4 kcal.mole⁻¹, Munch, Scott & Engel, 1957), and the major energy of interaction is probably provided by hydrogen bonding (Bush, 1962).

Estriol consists of an effectively planar, lipophilic nucleus, containing three hydrophilic groups. It is, therefore, reasonable to assume that, in agreement with what has been said above, estriol lies horizontally at the interface of the cell and the surrounding aqueous phase. Two alternative modes of interaction then present themselves; either the steroid α -surface or the steroid β -surface interacts with the receptor surface. In this context it is interesting to note that 17 β -estradiol is a potent estrogen, whereas 17 α -estradiol shows only weak estrogenic activity. From the present structure investigation, it would appear that the closest approach of a steroid β -surface to a reasonably flat receptor surface is the same as the distance between molecules 1 and 2 of the asymmetric unit, or about 4.5 Å between the carbon atoms comprising the two surfaces. The α -surface could presumably approach a suitably flat surface to within the sum of the van der Waals radii of the atoms in the surfaces, or about 4.0 Å.

As well as the phenolic hydroxyl group, at least one other 'active' oxygen function is required for estrogenic activity. The distance between these two oxygen functions has been given by Keading & Schuler (1950) as 14.5 Å. This distance is surprisingly long, especially since the longest dimension of the steroid nucleus is only about 9 Å. In view of our work on the three estrogens, we can now give accurate dimensions for this 'critical' distance for evaluating possible estrogen activity. We have summarized in Table 8 the intramolecular 3–16 α and 3–17 β oxygen–oxygen distances as found in estrone, estradiol and estriol. The average distance is 10.98 Å. This distance is very close to two turns of the α -helix, (2×5.38 Å), and with 3.60 amino acid residues per turn of α -helix, the oxygen–oxygen distance in the estrogens corresponds to 7.5 residues in the α -helix.

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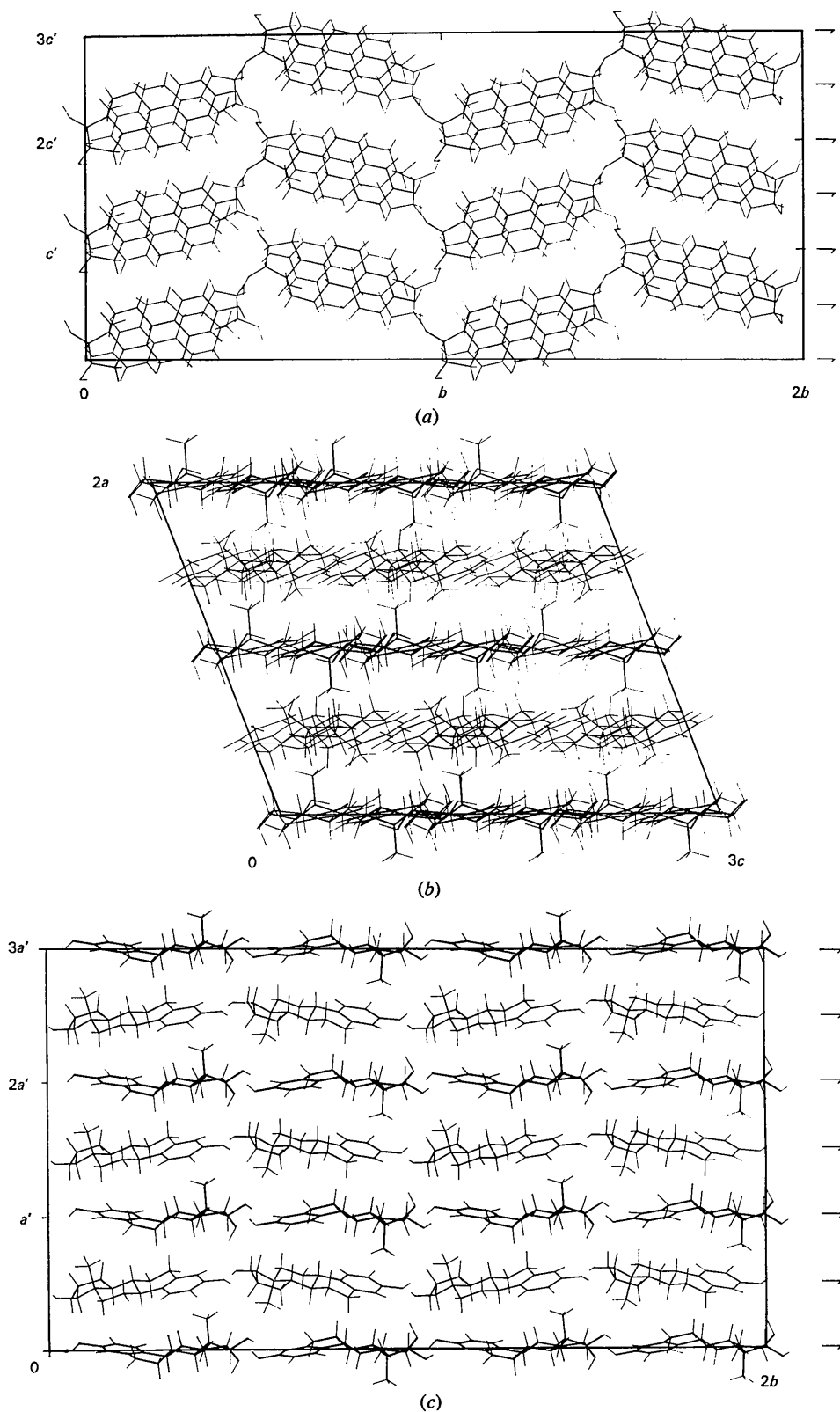


Fig. 7. Projections of six unit cells along (a) [100], (b) [101], (c) [001]. a' and c' are the projections of a and c respectively, where indicated. The heavier molecules in each case are molecules 1.

Table 8. *Intramolecular oxygen-oxygen distances in the estrogens*

4-Bromo-17 β -estradiol	10.95 \pm 0.04 Å	
4-Bromo-estrone	10.78 \pm 0.04	
Estriol (3-17 β), molecule 1	10.952 \pm 0.007	(11.66 \pm 0.05)*
Estriol (3-17 β), molecule 2	11.085 \pm 0.007	(11.45 \pm 0.05)*
Estriol (3-16 α), molecule 1	11.266 \pm 0.007	(10.92 \pm 0.05)*
Estriol (3-16 α), molecule 2	10.859 \pm 0.007	(11.18 \pm 0.05)*

* Distances between the hydroxyl hydrogen atoms.

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Die Kristallstruktur eines substituierten Cyclohexanonoxims

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2-(*cis*-4-Bromo-1-methylcyclohexyl)-3-(4-hydroxyimino-1-methylcyclohexyl)-*trans*-2-butene, C₁₈H₃₀NOBr, crystallizes in space group *P*2₁/*c* with *a* = 15.47, *b* = 8.65, *c* = 13.79 Å, β = 96.7°, and four molecules in the unit cell. The structure has been determined by the use of 778 three-dimensional photographic intensity data. Both cyclohexane rings in the molecule have the same chair conformation with the methyl groups in equatorial position. The molecules are linked into pairs by intermolecular hydrogen bonds between adjacent oxime groups.

Im Zusammenhang mit den Versuchen von Inhoffen und Mitarbeitern (siehe z. B. Inhoffen, Müller & Brendler, 1966) zum Aufbau von neuartigen, nicht-steroiden Verbindungen mit androgener Wirksamkeit interessierte die Konformation des Kohlenstoffgerüsts von 2,3-Bis-(4-oxo-1-methylcyclohexyl)-*trans*-2-buten, (I).

