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(±)-Hexestrol, Analog of a Synthetic Estrogen

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Abstract. Monoclinic, space group $P2_1/c$, $a=7{\cdot}707$ (2), $b=18{\cdot}013$ (7), $c=13{\cdot}888$ (4) Å, $\beta=125{\cdot}75$ (2)°, $Z=4$, $M=270{\cdot}37$, $D_c=1{\cdot}14$ g cm^{-3}, and $D_m=1{\cdot}15$ g cm^{-3}. The atoms in the six-carbon alkyl group form a zigzag chain, and the molecule has a bent conformation which differs from the conformation of the highly active artificial estrogen diethylstilbestrol. The oxygen–oxygen distance is 8·63 Å.

Introduction. A crystal with dimensions of approximately $0{\cdot}2\times0{\cdot}2\times0{\cdot}25$ mm was used to measure the lattice parameters and intensities. The data showed systematic absences of $k=2n+1$ for $0k0$ and $l=2n+1$ for $h0l$ indicating space group $P2_1/c$, and the cell constants were determined by least-squares analysis of the angular settings of 30 reflections [at 20°C; λ(Cu $K\alpha_1$) = 1·54051 Å]. The intensities of 2729 reflections (1589 reflections had $I>2\sigma$) with $2\theta<125°$ were measured on a G.E. XRD-5 diffractometer using Cu $K\alpha$ radiation monochromated by balanced nickel and cobalt filters. After the usual Lorentz and polarization corrections had been applied, normalized structure factor amplitudes were computed, and the structure was solved by direct methods using quadruples of calculated cosine invariants (Hauptman, 1972, chapter X).

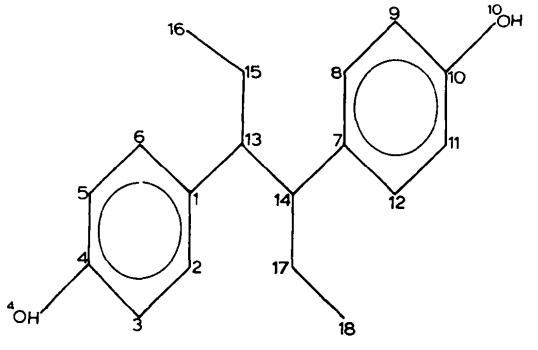

Fig. 1. Atomic numbering for (±)-hexestrol.

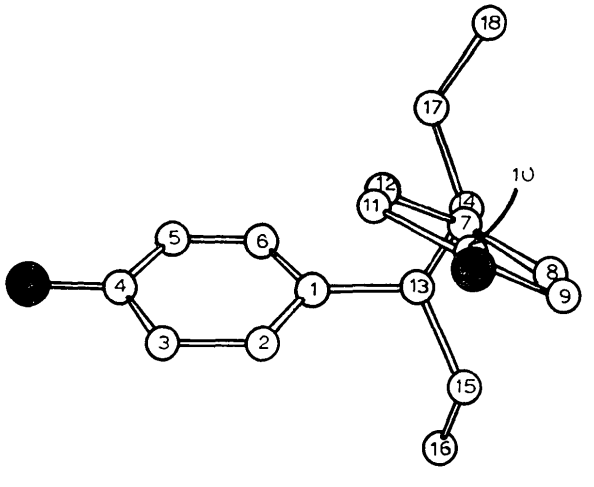

Fig. 2. Crystallographically observed conformation of (±)-hexestrol. ● = oxygen atom.

The positional and anisotropic thermal parameters of the non-hydrogen atoms and the positional parameters of 20 hydrogens (B_{iso} fixed at 4·0) located by Fourier difference syntheses were refined by block-diagonal least-squares using all data for which $\sin\theta/\lambda > 0{\cdot}15$. Data for which $|F_c|/|F_o|$ was less than 0·6 were not allowed to influence the refinement. Weights were chosen such that $\langle w\Delta^2\rangle$ would be independent of $|F_o|$ where $w^{-1}=\{1+[(|F_o|-b)/a]^2\}^{1/2}$ and the constants a and b were both taken to be 10e, and refinement was terminated when all shifts were less than $\frac{1}{3}$ of their respective standard deviations. The R index was defined as $\sum(||F_o|-|F_c||)/\sum|F_o|$, and its final value was 8·6% for the 1589 reflections with $I>2\sigma$ and 12·3% for all data. The final refined positional and thermal parameters are given in Table 1, and a list of the structure factors is obtainable.*

Discussion. The structural formula for (±)-hexestrol is shown in Fig. 1. The interatomic distances and valency angles among non-hydrogen atoms are given in Table 2, and there are no unusual values. The conformation of the molecule is shown in Fig. 2 and expressed quantitatively in Table 3 in terms of the torsional angles centered about the bonds where free rotation might be presumed to exist. The atoms in the six-carbon aliphatic chain are arranged in approximate *trans* orientations about the three central bonds [C(13)–C(15), C(13)–C(14), and C(14)–C(17) bonds] as shown by the torsional angles of −161·6, 169·1, and −169·8°. The deviations of the six atoms from a least-

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Table 1.

(*a*) Final atomic coordinates and anisotropic thermal parameters for the non-hydrogen atoms.

The thermal parameters are of the form $\exp[-2\pi^2(U_{11}h^2a^{*2}+2U_{12}hka^*b^*+\cdots)]$. The standard deviations of the last two figures are given in parentheses.

	x/a	*y/b*	*z/c*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	−0·23783 (61)	0·18709 (21)	−0·11561 (32)	0·0549 (22)	0·0482 (22)	0·0444 (20)	−0·0013 (18)	0·0317 (18)	0·0054 (17)
C(2)	−0·38806 (67)	0·15521 (24)	−0·10248 (33)	0·0677 (25)	0·0644 (26)	0·0473 (22)	−0·0146 (21)	0·0411 (21)	−0·0079 (19)
C(3)	−0·54978 (71)	0·11079 (24)	−0·18765 (37)	0·0646 (26)	0·0649 (27)	0·0535 (23)	−0·0060 (21)	0·0402 (22)	0·0060 (20)
C(4)	−0·56912 (64)	0·09572 (23)	−0·29187 (32)	0·0551 (23)	0·0608 (24)	0·0359 (19)	−0·0053 (20)	0·0239 (18)	0·0003 (18)
C(5)	−0·42333 (72)	0·12703 (27)	−0·30821 (37)	0·0707 (28)	0·0832 (31)	0·0492 (23)	−0·0056 (24)	0·0422 (22)	−0·0035 (22)
C(6)	−0·26387 (67)	0·17254 (26)	−0·22133 (34)	0·0597 (24)	0·0770 (29)	0·0461 (22)	−0·0101 (22)	0·0344 (20)	0·0031 (21)
C(7)	0·11280 (59)	0·14339 (21)	0·15559 (31)	0·0471 (20)	0·0537 (23)	0·0409 (19)	−0·0046 (18)	0·0276 (17)	−0·0049 (17)
C(8)	0·17158 (59)	0·17061 (21)	0·26365 (32)	0·0484 (21)	0·0487 (22)	0·0448 (20)	−0·0029 (18)	0·0254 (18)	−0·0078 (17)
C(9)	0·15308 (61)	0·12934 (22)	0·34078 (30)	0·0540 (21)	0·0560 (23)	0·0344 (18)	0·0002 (19)	0·0252 (17)	−0·0055 (17)
C(10)	0·07222 (63)	0·05796 (22)	0·30936 (33)	0·0515 (22)	0·0576 (24)	0·0448 (21)	−0·0049 (19)	0·0297 (19)	−0·0027 (18)
C(11)	0·00524 (75)	0·03027 (24)	0·20022 (38)	0·0776 (29)	0·0519 (25)	0·0555 (24)	−0·0128 (22)	0·0409 (23)	−0·0120 (20)
C(12)	0·02578 (71)	0·07223 (23)	0·12550 (34)	0·0741 (27)	0·0569 (24)	0·0445 (22)	−0·0126 (21)	0·0398 (21)	−0·0174 (19)
C(13)	−0·05363 (66)	0·23484 (23)	−0·02015 (34)	0·0659 (26)	0·0526 (24)	0·0531 (23)	−0·0132 (20)	0·0395 (22)	−0·0063 (19)
C(14)	0·14620 (64)	0·18987 (24)	0·07610 (34)	0·0562 (23)	0·0648 (26)	0·0482 (22)	−0·0067 (20)	0·0351 (20)	−0·0017 (20)
C(15)	−0·12048 (76)	0·29159 (25)	0·03527 (39)	0·0766 (30)	0·0601 (27)	0·0577 (25)	−0·0054 (23)	0·0385 (24)	−0·0106 (21)
C(16)	0·26366 (84)	0·35137 (28)	−0·05046 (50)	0·0719 (31)	0·0659 (31)	0·0897 (35)	0·0026 (25)	0·0388 (28)	−0·0014 (27)
C(17)	0·23791 (76)	0·14433 (28)	0·02214 (39)	0·0711 (28)	0·0837 (32)	0·0588 (26)	−0·0061 (25)	0·0457 (24)	−0·0041 (24)
C(18)	0·45362 (88)	0·11006 (38)	0·11274 (49)	0·0817 (35)	0·1322 (52)	0·0814 (35)	0·0215 (35)	0·0586 (31)	0·0073 (34)
O(4)	−0·72809 (52)	0·05110 (19)	−0·37940 (25)	0·0771 (21)	0·0848 (23)	0·0468 (16)	−0·0263 (18)	0·0315 (16)	−0·0156 (16)
O(10)	0·05509 (49)	0·01346 (17)	0·38431 (24)	0·0800 (20)	0·0671 (19)	0·0517 (16)	−0·0125 (16)	0·0412 (16)	0·0041 (14)

Table 1 (*cont.*)

(*b*) Final positional parameters for the experimentally observed hydrogen atoms

Standard deviations are in parentheses. The hydroxyl hydrogens were not found.

	x/a	*y/b*	*z/c*
H(2)	−0·3872 (57)	0·1644 (21)	−0·0301 (32)
H(3)	−0·6627 (60)	0·0971 (21)	−0·1852 (33)
H(5)	−0·4462 (59)	0·1167 (20)	−0·3881 (32)
H(6)	−0·1753 (58)	0·1936 (21)	−0·2378 (32)
H(8)	0·2309 (59)	0·2207 (21)	0·2951 (32)
H(9)	0·1963 (59)	0·1475 (20)	0·4153 (32)
H(11)	−0·0477 (59)	−0·0223 (20)	0·1825 (33)
H(12)	−0·0255 (60)	0·0541 (21)	0·0513 (33)
H(13)	−0·0019 (59)	0·2607 (21)	−0·0678 (33)
H(14)	0·2534 (59)	0·2303 (21)	0·1286 (32)
H(15*A*)	−0·0097 (58)	0·3222 (21)	0·0972 (32)
H(15*B*)	−0·1811 (59)	0·2642 (20)	0·0759 (33)
H(16*A*)	−0·3933 (57)	0·3298 (21)	−0·1276 (31)
H(16*B*)	−0·1833 (58)	0·3747 (20)	−0·0850 (32)
H(16*C*)	−0·3185 (59)	0·3956 (20)	−0·0268 (32)
H(17*A*)	0·2468 (59)	0·1786 (20)	−0·0276 (32)
H(17*B*)	0·1335 (59)	0·1084 (20)	−0·0329 (32)
H(18*A*)	0·4581 (60)	0·0799 (20)	0·1714 (33)
H(18*B*)	0·5569 (59)	0·1493 (20)	0·1771 (33)
H(18*C*)	0·4936 (59)	0·0841 (21)	0·0751 (33)

squares plane passed through this group are: C(13), −0·25 Å; C(14), −0·17 Å; C(15), −0·08 Å; C(16), 0·29 Å; C(17), −0·06 Å; and C(18), 0·26 Å. There are two hydrogen bonds involving the hydroxyl group; these bonds have lengths of 2·74 and 2·76 Å. There is only one other intermolecular distance between non-hydrogen atoms which measures less than 3·5 Å, and this is a contact of 3·48 Å between O(10) and C(16).

Table 2. *Interatomic distances and angles between the non-hydrogen atoms*

Standard deviations are in parentheses.

(*a*) Distances

C(1)–C(2)	1·397 (6) Å	C(8)—C(9)	1·379 (5) Å
C(1)–C(6)	1·386 (5)	C(9)—C(10)	1·384 (6)
C(1)–C(13)	1·522 (6)	C(10)–C(11)	1·378 (6)
C(2)–C(3)	1·368 (6)	C(10)–O(10)	1·380 (5)
C(3)–C(4)	1·393 (6)	C(11)–C(12)	1·366 (6)
C(4)–C(5)	1·390 (6)	C(13)–C(14)	1·553 (6)
C(4)–O(4)	1·373 (5)	C(13)–C(15)	1·539 (6)
C(5)–C(6)	1·381 (6)	C(14)–C(17)	1·535 (6)
C(7)–C(8)	1·380 (5)	C(15)–C(16)	1·504 (7)
C(7)–C(12)	1·393 (6)	C(17)–C(18)	1·512 (8)
C(7)–C(14)	1·523 (5)		

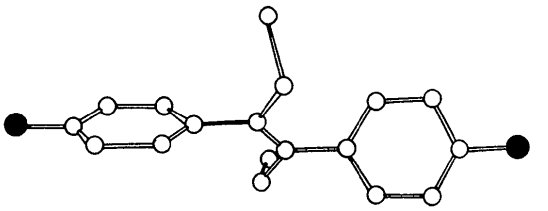

Fig. 3. Conformation of diethylstilbestrol in the triclinic diethylstilbestrol.methanol.water complex (Busetta & Hospital, 1969*b*).

Table 2 (*cont.*)

(*b*) Angles

C(2)—C(1)–C(6)	116·3 (2)°	C(8)—C(9)—C(10)	119·2 (4)°
C(2)—C(1)–C(13)	122·8 (5)	C(9)—C(10)–C(11)	119·6 (2)
C(6)—C(1)–C(13)	120·9 (3)	C(9)—C(10)–O(10)	121·7 (2)
C(1)—C(2)–C(3)	122·3 (2)	C(11)–C(10)–O(10)	118·7 (3)
C(2)—C(3)–C(4)	120·2 (3)	C(10)–C(11)–C(12)	120·0 (4)
C(3)—C(4)–C(5)	119·0 (4)	C(7)—C(12)–C(11)	122·0 (4)
C(3)—C(4)–O(4)	122·2 (2)	C(1)—C(13)–C(14)	114·0 (2)
C(5)—C(4)–O(4)	118·8 (3)	C(1)—C(13)–C(15)	113·4 (2)
C(4)—C(5)–C(6)	119·4 (2)	C(14)–C(13)–C(15)	111·7 (4)
C(1)—C(6)–C(5)	122·8 (3)	C(7)—C(14)–C(13)	114·1 (2)
C(8)—C(7)–C(12)	116·6 (2)	C(7)—C(14)–C(17)	112·4 (2)
C(8)—C(7)–C(14)	120·4 (3)	C(13)–C(14)–C(17)	111·5 (4)
C(12)–C(7)–C(14)	123·0 (5)	C(13)–C(15)–C(16)	112·7 (5)
C(7)—C(8)–C(9)	122·4 (3)	C(14)–C(17)–C(18)	114·1 (3)

Table 3. *Torsional angles*

C(2)—C(1)—C(13)–C(14)	−85·1°
C(2)—C(1)—C(13)–C(15)	44·3
C(6)—C(1)—C(13)–C(14)	94·5
C(6)—C(1)—C(13)–C(15)	−136·2
C(8)—C(7)—C(14)–C(13)	95·4
C(8)—C(7)—C(14)–C(17)	−136·3
C(12)–C(7)—C(14)–C(13)	−85·4
C(12)–C(7)—C(14)–C(17)	42·9
C(1)—C(13)–C(14)–C(7)	68·0
C(1)—C(13)–C(14)–C(17)	−60·7
C(15)–C(13)–C(14)–C(7)	−62·2
C(15)–C(13)–C(14)–C(17)	169·1
C(1)—C(13)–C(15)–C(16)	68·0
C(14)–C(13)–C(15)–C(16)	−161·6
C(7)—C(14)–C(17)–C(18)	60·6
C(13)–C(14)–C(17)–C(18)	−169·8

The structure of (±)-hexestrol, which is estrogenically inactive, was solved in order to determine what conformational differences exist between it and the structurally similar, highly potent artificial estrogen, diethylstilbestrol (Smiley & Rossmann, 1969; Busetta & Hospital, 1969*a*,*b*; Weeks, Cooper & Norton, 1970). A specific distance between terminal oxygen atoms has long been regarded as essential for estrogenic activity, and X-ray analysis has shown this distance to be about 11 Å in the natural steroidal estrogens (Cooper, Hauptman & Norton, 1969) and 12 Å in diethylstilbestrol. In contrast, the oxygen–oxygen distance in (±)-hexestrol is only 8·63 Å. This short distance results from the conformation about the C(13)–C(14) bond. A planar, zigzag chain arrangement of the six-carbon aliphatic group may be achieved when the C(1)–C(13)–C(14)–C(7) torsional angle is 60° (actual value 68·0°). In diethylstilbestrol (Fig. 3), the C(13)–C(14) bond is unsaturated, and this angle is restrained to be 180°.

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