

The Structure of the Crystalline Complex Estradiol.Urea (1:1)

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The crystal data for the complex estradiol.urea (1:1), $C_{18}H_{24}O_2 \cdot CON_2H_4$, are $a=24.631(1)$, $b=7.951(1)$, $c=9.302(1)$ Å, orthorhombic $P2_12_12_1$, $Z=4$, $D_x=1.20$, $D_m=1.20$ g.cm⁻³. Three-dimensional data were collected on a single-crystal counter diffractometer. The structure was solved from a set of phases derived from two-dimensional structure invariants, with phasing extended by application of the tangent formula. Refinement by a block-diagonal least-squares procedure resulted in a final R of 6.3% for 1886 observed reflections. All hydrogen atoms were located in difference electron density syntheses, and their coordinates were refined by least-squares methods. The basic packing pattern observed in numerous steroid crystals, infinite chains of steroids hydrogen-bonded head to tail, is retained in the complex. The urea molecules bind the steroids together with an extensive hydrogen-bonding network in which each urea is hydrogen-bonded to four different steroid chains. Comparison of the thermal motion of the urea molecule in the complex with that of urea crystallized in a tetragonal space group, suggests that the nonrigid body motion observed in the complex is a result of differences in hydrogen-bonding to the two nitrogen atoms and the absence of crystallographically imposed symmetry.

Introduction

As part of an investigation of steroid complex formation and crystallization, the stable crystalline complexes cortisol.urea (1:1) and estradiol.urea (1:1) have been prepared. The crystal-structure study of the estrogen complex was undertaken in order to determine the configuration of the complex, the extent of hydrogen bonding in the crystal structure, and the alteration, if any, of the steroid packing pattern as a result of complex formation. A schematic representation of the steroid molecule, showing the numbering of atoms and ring designations, is given in Fig. 1. Hydrogen atoms are omitted from the diagram, but are given the same numbering as the carbon atoms to which they are attached. Where appropriate, the hydrogen atoms are also designated β or α , depending on their orientation relative to the top (β) or under (α) side of the molecule.

Experimental

Large columnar crystals of estradiol.urea (1:1) were grown from a benzene solution containing a 1:10 molar ratio of steroid to urea. A cuboid crystal, 0.2 mm on an edge, was used for data collection. All X-ray measurements were made on a General Electric single-crystal counter diffractometer. The crystal was mounted with the c axis parallel to the ϕ axis of the instrument. The systematic extinctions ($h00$, $h=2n+1$; $0k0$, $k=2n+1$; $00l=2n+1$) indicate the orthorhombic space group $P2_12_12_1$. The unit-cell dimensions were obtained from a least-squares calculation, based on 2θ measurements of 35 hkl α_1 and α_2 reflections having

$2\theta > 85^\circ$. The density was measured by flotation in an aqueous potassium iodide solution. The crystal data are presented in Table 1.

Table 1. Crystal data for estradiol.urea (1:1)

$C_{18}H_{24}O_2 \cdot CON_2H_4$	F.W.332.4
Orthorhombic	Space group $P2_12_12_1$
$a=24.631(1)$ Å	$Z=4$
$b=7.951(1)$	$F(000)=720$
$c=9.302(1)$	$D_m=1.20$ g.cm ⁻³
$\lambda(Cu K\alpha_1)=1.54051$ Å	$D_x=1.20$
$\lambda(Cu K\alpha_2)=1.54438$	

The intensities of 2088 independent reflections, with 2θ less than 145° , were measured by the stationary-crystal stationary-counter technique. The background was a uniform function of 2θ above 45° , and a background correction curve was constructed from balanced nickel-cobalt measurements of 15% of the data in this range. Reflections were considered unobserved

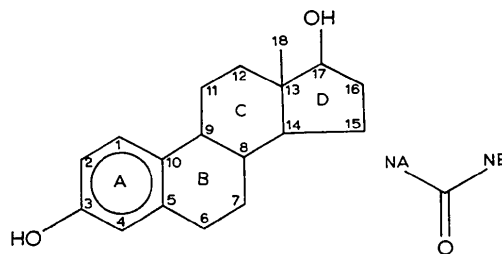


Fig. 1. Schematic representation of the steroid molecule showing the numbering of atoms and ring designation.

if the net count was less than twice the standard deviation of the background. Cobalt-filtered background measurements were made for all data with 2θ less than 45°. Calibrated nickel filters were used in the measurement of the most intense reflections. No significant

changes were observed in the intensities of five standard reflections measured daily during the period of data collection. The intensity of the 006 reflection (χ=90°, 2θ=59.6°) varied up to a maximum of ±2.0% from its mean value within the φ range in which data were

Table 2. Comparison of the observed structure factor amplitudes with those calculated (×10) from the refined atomic parameters for the structure of estradiol.urea (1:1)

Table with multiple columns of numerical data representing structure factor amplitudes and calculated values for estradiol.urea (1:1). The table is organized into several groups of columns, each with sub-headers for different indices (H, K, L, P, O, F, C).

collected. Intensities were corrected for Lorentz and polarization factors but not for absorption ($\mu R=0.07$).

Structure determination

The structure was determined by a phasing procedure, based on the two-dimensional structure invariants $\cos(\varphi_1 + \varphi_2 + \varphi_3)$ whose values were calculated by a recently developed formula. The phasing process is described fully in the preceding paper (Duax, Weeks & Hauptman, 1971). A structure-factor calculation, based on positional parameters for the 24 nonhydrogen atoms taken from the *E* map, resulted in an *R* index ($R = \sum ||F_o| - |F_c|| / \sum |F_o|$) of 0.46. After five cycles of refinement of the positional parameters and anisotropic thermal parameters of the nonhydrogen atoms, *R* was lowered to 0.11. A three-dimensional Fourier difference synthesis, calculated without the contributions of the hydrogen atoms to the structure factors, produced well-defined electron densities corresponding to the 28 hydrogen atoms. Introduction of these atoms into the structure-factor calculations lowered *R* to 0.08. Three more refinement cycles were performed, which included refinement of the positional and isotropic thermal parameters of the hydrogen atoms. The scattering factors used throughout the refinement were taken from *International Tables for X-ray Crystallography* (1962). The refined thermal parameters for the hydrogen atoms ranged from 0.5 for hydrogen atoms of the bridgehead carbon atoms to 5.0 for the hydrogen atoms of carbon atoms having the largest anisotropic motion. This variation of thermal motion was considered to be largely spurious, and the hydrogen thermal parameters were held constant at 2.5 in the last three cycles of refinement. The calculated intensities of the two most intense reflections were 25% higher than the observed intensities. This was assumed to be due to extinction and these reflections were not included in the final refinement. In the last refinement cycles, a weighting scheme in which $1/w = [(|F_o| - 15) / 15^2 + 1]^{1/2}$ was used in order that $\langle w\Delta^2 \rangle$ remain invariant with $|F_o|$. Refinement was terminated when all

parameter shifts were less than one-half their standard deviations and the minimization function, $\sum_w (|F_o| - |F_c|)^2 / (m - n)$, was 0.80. The final *R* values were 0.07 for all reflections and 0.063 for the 1886 observed reflections. Table 2 lists the final observed and calculated structure factor amplitudes. Final atomic positional and thermal parameters are given in Tables 3 and 4.

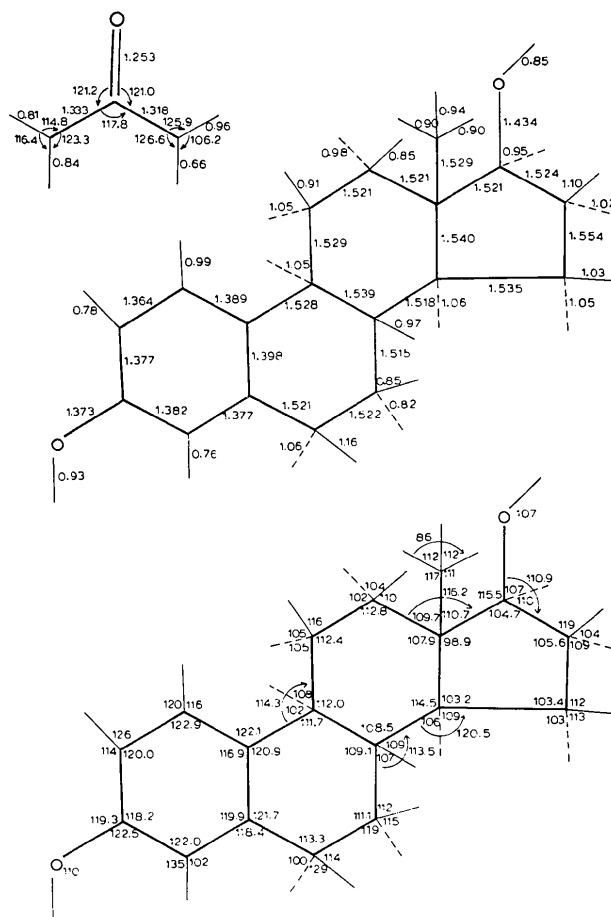


Fig. 2. Interatomic distances and angles. Dashed lines are used to designate α -face hydrogen atoms.

Table 3. Positional and thermal parameters of the nonhydrogen atoms, at the end of the least-squares refinement

Temperature factors are of 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)	0.0836 (1)	0.4431 (4)	0.4110 (4)	0.0329(19)	0.0217(18)	0.0384(22)	-0.0055(16)	-0.0032(18)	-0.0056(18)
C(2)	0.1350 (1)	0.3799 (4)	0.4060 (4)	0.0361(20)	0.0188(18)	0.0465(24)	-0.0008(17)	-0.0016(19)	-0.0059(19)
C(3)	0.1789 (1)	0.4457 (5)	0.4219 (4)	0.0293(18)	0.0293(20)	0.0345(21)	0.0031(16)	-0.0009(17)	-0.0021(19)
C(4)	0.1690 (1)	0.6537 (5)	0.4496 (5)	0.0269(20)	0.0637(30)	-0.0064(17)	-0.0028(15)	-0.0021(20)	-0.0076(22)
C(5)	0.1172 (1)	0.7173 (4)	0.4595 (5)	0.0310(19)	0.0212(18)	0.0544(28)	-0.0045(16)	0.0031(20)	-0.0047(20)
C(6)	0.1101 (1)	0.9019 (5)	0.4979 (8)	0.0290(20)	0.0225(20)	0.1319(54)	-0.0021(18)	0.0060(29)	-0.0204(32)
C(7)	0.0535 (1)	0.9889 (4)	0.4657 (6)	0.0306(20)	0.0170(18)	0.0850(38)	-0.0032(16)	0.0036(23)	-0.0051(23)
C(8)	0.0102 (1)	0.8479 (4)	0.5172 (4)	0.0249(17)	0.0147(17)	0.0416(22)	-0.0018(15)	-0.0025(17)	-0.0006(18)
C(9)	0.0149 (1)	0.6824 (4)	0.4321 (4)	0.0243(17)	0.0217(18)	0.0368(20)	-0.0028(15)	-0.0012(17)	0.0000(18)
C(10)	0.0726 (1)	0.6118 (4)	0.4360 (4)	0.0261(17)	0.0293(18)	0.0311(19)	-0.0016(15)	-0.0021(16)	0.0017(17)
C(11)	-0.0292 (1)	0.5964 (4)	0.4747 (5)	0.0304(19)	0.0260(18)	0.0681(32)	-0.0061(17)	0.0008(21)	-0.0005(22)
C(12)	-0.0859 (1)	0.6309 (5)	0.4546 (5)	0.0288(19)	0.0255(19)	0.0645(30)	-0.0073(17)	-0.0024(20)	-0.0077(22)
C(13)	-0.0919 (1)	0.7930 (4)	0.5499 (4)	0.0241(17)	0.0296(19)	0.0333(21)	-0.0051(16)	-0.0021(16)	0.0011(18)
C(14)	-0.0471 (1)	0.9149 (4)	0.5003 (5)	0.0247(17)	0.0144(17)	0.0494(24)	-0.0015(15)	0.0025(18)	0.0012(20)
C(15)	-0.0636 (1)	1.0822 (5)	0.5702 (7)	0.0333(22)	0.0321(22)	0.1115(47)	-0.0029(20)	0.0078(29)	-0.0170(32)
C(16)	-0.1267 (1)	1.0757 (6)	0.5690 (7)	0.0325(22)	0.0322(23)	0.0322(23)	-0.0018(20)	0.0073(29)	-0.0110(32)
C(17)	-0.1413 (1)	0.9005 (5)	0.5147 (5)	0.0231(17)	0.0327(20)	0.0496(25)	-0.0015(16)	0.0006(18)	-0.0002(22)
C(18)	-0.0895 (1)	0.7544 (7)	0.7107 (5)	0.0407(24)	0.0830(40)	0.0353(25)	-0.0025(28)	0.0022(21)	0.0127(29)
C(19)	0.2443 (1)	-0.0046 (6)	0.1365 (4)	0.0283(16)	0.0261(14)	0.0691(22)	0.0052(12)	0.0030(15)	-0.0046(17)
O(1)	0.2304 (1)	0.4213 (3)	0.4106 (3)	0.0254(13)	0.0344(16)	0.0336(20)	-0.0040(12)	0.0032(18)	-0.0078(16)
O(17)	-0.1916 (1)	0.0645 (3)	0.5757 (3)	0.0621(22)	0.0361(20)	0.0401(21)	0.0068(19)	0.0074(20)	0.0014(21)
U(19)	0.2248 (1)	-0.0474 (3)	0.0206 (3)	0.0725(27)	0.0385(20)	0.0801(21)	0.0142(21)	-0.0124(21)	0.0008(19)
N(A)	0.2807 (1)	-0.1636 (3)	0.1507 (4)	0.1243(43)	0.0445(24)	0.0374(22)	0.0179(29)	-0.0055(27)	-0.0075(21)
N(B)	0.2505 (2)	0.0966 (5)	0.2475 (4)	0.0543(18)	0.0398(17)	0.0387(17)	0.0147(15)	-0.0051(15)	-0.0019(15)

Table 4. Positional parameters for the hydrogen atoms in estradiol.urea (1:1)

Values are $\times 10^3$.

	X	Y	Z
H(1)	52 (2)	372 (8)	382 (6)
H(2)	143 (2)	288 (7)	387 (6)
H(4)	185 (2)	726 (7)	478 (6)
H(6A)	131 (2)	957 (8)	410 (7)
H(6B)	121 (2)	902 (9)	620 (7)
H(7A)	42 (1)	970 (6)	382 (5)
H(7B)	51 (1)	1062 (6)	509 (5)
H(8)	17 (1)	826 (6)	618 (5)
H(9)	9 (1)	710 (6)	322 (5)
H(11A)	-26 (2)	458 (8)	398 (7)
H(11B)	-20 (1)	508 (5)	560 (5)
H(12A)	-90 (2)	642 (9)	361 (8)
H(12B)	-110 (2)	561 (8)	488 (6)
H(14)	-54 (1)	921 (6)	387 (4)
H(15A)	-47 (1)	1173 (6)	499 (5)
H(15B)	-48 (2)	1092 (9)	673 (7)
H(16A)	-141 (1)	1165 (6)	501 (6)
H(16B)	-141 (2)	1114 (9)	676 (7)
H(17)	-146 (1)	906 (6)	413 (4)
H(18A)	-86 (2)	849 (7)	762 (6)
H(18B)	-56 (2)	726 (8)	746 (7)
H(18C)	-117 (2)	684 (8)	745 (6)
H(N1A)	245 (2)	-230 (7)	98 (6)
H(N1B)	273 (1)	-202 (6)	227 (5)
H(N2A)	239 (1)	212 (6)	252 (5)
H(N2B)	256 (1)	74 (6)	314 (5)
H(17O)	-199 (1)	750 (6)	536 (5)
H(30)	255 (2)	507 (6)	394 (5)

Steroid geometry

The intramolecular bond distances and valency angles (Fig. 2) are in good agreement with values observed in determinations of similar steroid structures. The estimated standard deviations in bond lengths are 0.006 and 0.06 Å for bonds involving nonhydrogen and hydrogen atoms, respectively. E.s.d.'s in valency angle are 0.4, 2.5, and 4.0° for angles of the types C-C-C, C-C-H, and H-C-H respectively. The average $C(sp^3)-C(sp^3)$ bond length in this determination is 1.528 Å as compared with expected values of 1.533 Å (Bonham & Bartell, 1959) or 1.526 Å (Lide, 1962). Only the C(15)-C(16) bond length is more than two standard deviations away from either of these expected values. A lengthening of bond distances in the *D* ring is common in steroids. The average of the C-C bond lengths in the aromatic *A* ring is 1.381 Å, which is

slightly shorter than the values of 1.390 and 1.394 Å observed for the two estriol molecules (Cooper, Norton & Hauptman, 1969). The bond lengths and valency angles in the urea molecule are within 0.015 Å and 0.2° of the values observed in crystalline urea by Caron & Donohue (1964).

The bonds and angles involving hydrogen atoms are within three standard deviations of standard values. Because of strains imposed at ring junctions, some deviations from theoretical values would be expected, particularly in valency angles. The average C-H bond distance is 0.96 Å and the average C-C-H bond angle is 108.7°. The most questionable hydrogen position is that of H(N2b) of the urea molecule, which results in the short N-H distance of 0.66 Å. The Newman projections (Fig. 3) illustrate the orientation of the hydrogen atom of the angular methyl group over the *C/D* junction, and the relative orientation of hydrogen atoms on adjacent carbon atoms in the bonds C(6)-C(7), C(11)-C(12), and C(15)-C(16). The hydrogen atoms of the methyl groups are oriented in the expected *gauche* positions relative to the bonds to C(13). Staggered conformations are also observed for the hydrogen atoms on the carbon atoms of the C(6)-C(7) and the C(11)-C(12) bonds. These bonds occur in the half-chair conformation *B* ring and the normal-chair conformation *C* ring respectively. The hydrogen atoms on the carbon atoms of the C(15)-C(16) bond in the β -envelope *D* ring are almost fully eclipsed. Such hydrogen atoms are not always eclipsed. One example of a structure with a twisted β -envelope conformation *D* ring, in which the hydrogen atoms of C(15) and C(16) are staggered, is 2,4-dibromoestradiol [Fig. 3(e)] (Cody, DeJarnette, Duax & Norton, 1971).

Steroid conformation

In Fig. 4 the conformation of the molecule is illustrated in two *ORTEP* drawings (Johnson, 1965). The torsional angles, a sensitive quantitative index of ring conformation, are presented in Table 5.

The *D* ring conformation is a distorted β -envelope and can be described by the parameters $\Delta = 48.99$ and $\varphi_m = 22.31$ (Altona, Geise & Romers, 1968). The *C* ring is in the normal-chair conformation. The average of the absolute values of the torsional angle in the *C*

Table 5. Torsional angles in the rings*

Ring A		Ring B		Ring C		Ring D	
Bond	$\varphi(A-B)^\dagger$	Bond	$\varphi(A-B)$	Bond	$\varphi(A-B)$	Bond	$\varphi(A-B)$
C(1)-C(2)	-2.2	C(5)-C(6)	-17.0	C(8)-C(9)	-53.6	C(13)-C(14)	48.1
C(2)-C(3)	3.0	C(6)-C(7)	45.4	C(9)-C(11)	53.3	C(14)-C(15)	-33.6
C(3)-C(4)	-0.9	C(7)-C(8)	-64.2	C(11)-C(12)	-54.2	C(15)-C(16)	5.9
C(4)-C(5)	-2.1	C(8)-C(9)	52.5	C(12)-C(13)	54.1	C(16)-C(17)	24.3
C(5)-C(10)	2.9	C(9)-C(10)	-25.1	C(13)-C(14)	-57.7	C(13)-C(17)	-44.3
C(1)-C(10)	-0.8	C(5)-C(10)	7.2	C(8)-C(14)	57.6		

* The sign convention for torsional angles is that of Klyne & Prelog (1960).

† $\varphi(A-B)$ 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.

ring is 55.1° , indicating typical flattening of the ring due to junction strain. The *B* ring is in the half-chair conformation, which is the most common form observed in the 1,3,5(10)-estratriene series (*e.g.* Cooper, Norton & Hauptman, 1969; Norton, Kartha & Lu, 1964; Busetta & Hospital, 1969). The algebraic sum of the torsional angles C(9)–C(10)–C(5)–C(6) and C(10)–C(5)–C(6)–C(7) for this structure is 10° , indicating a half-chair conformation. When the sum of these torsional angles in a 1,3,5(10)-estratriene molecule is 0° , the conformation is 'sofa', as in one of the three molecules of 2,4-dibromoestradiol (Cody *et al.*, 1971). The deviations of individual atoms of the phenolic *A* ring from the least-squares plane of atoms C(1), C(2), C(3), C(4), C(5), and C(10) are given in Table 6.

Table 6. The deviations, *D*, of individual atoms from the least-squares plane through (a) atoms C(1), C(2), C(3), C(4), C(5), and C(10) in the phenolic *A* ring of estradiol, and (b) through atoms C(19), O(19), N(19A), and N(19B) of the urea molecule

(a)	
	<i>D</i>
C(1)	–0.004 Å
C(2)	0.017
C(3)	–0.014
C(4)	–0.004
C(5)	0.018
C(10)	–0.013
O(3)	–0.048
C(6)	0.100
C(9)	–0.130
H(1)	–0.14
H(2)	–0.02
H(4)	0.15
H(O3)	–0.33
C(7)	–0.265
C(8)	0.405

(b)	
	<i>D</i>
C(19)	–0.007 Å
O(19)	0.003
N(A)	0.002
N(B)	0.002
H(NA1)	–0.32
H(NA2)	–0.03
H(NB1)	–0.01
H(NB2)	–0.10

The deviations of individual atoms from the least-squares plane of the nonhydrogen atoms of the urea molecule are given in Table 6(b). Only one of the hydrogen atoms deviates appreciably from the plane of the molecule.

Thermal vibration analysis

Analysis of the thermal motion of estriol (Cooper, Norton & Hauptman, 1969) and 12α -bromo- 11β -hydroxyprogesterone (Cooper & Norton, 1968) showed these steroids to behave as rigid bodies, with some

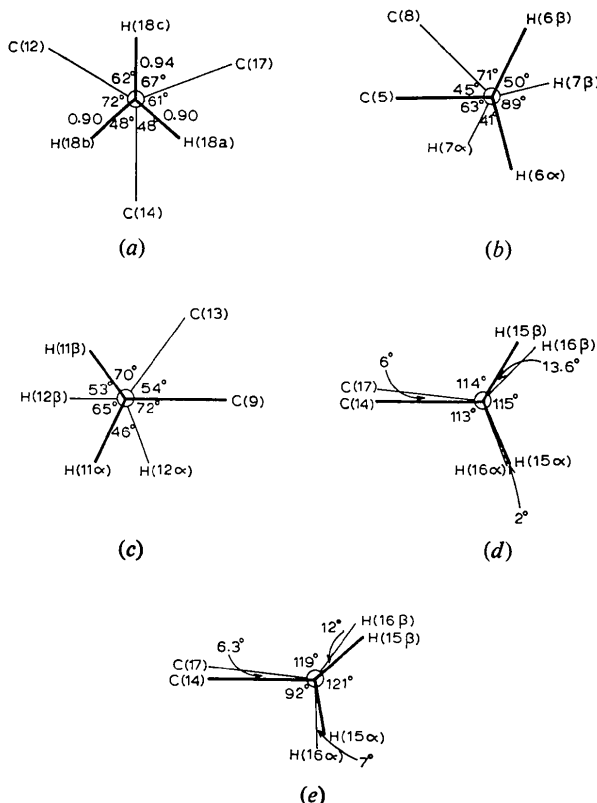


Fig. 3. Newman projections, illustrating the conformations of hydrogen atoms about selected bonds in estradiol [(a), (b), (c), (d)] and $6x$ -fluorocortisol [(e)].

Table 7. Comparison of the rigid-body vibrational parameters for urea in the tetragonal lattice and the estradiol complex

	Tetragonal			Orthorhombic complex			
	Eigen-values	Direction of eigenvectors		Eigen-values	Direction cosines of eigenvectors		
T_1	0.202 Å	a + b		0.174 Å	–0.5371	0.7465	0.3928
T_2	0.188	a – b		0.217	–0.8420	–0.4461	–0.3035
T_3	0.141	c		0.182	–0.0512	–0.4937	0.8681
ω_1	13.13°	c		8.15°	–0.1624	0.0015	–0.9867
ω_2	6.08	a + b		10.72	–0.2214	0.9744	0.0379
ω_3	2.70	a – b		3.26	–0.9616	–0.2246	0.1579

independent motion of atoms not in closest packing contact with other molecules in the lattice. Similar analysis of the estradiol thermal motion in the urea complex suggested that in this case the molecule does not behave as a rigid body. When the 17 atoms of the steroid nucleus were included in rigid-body calculations (Schomaker & Trueblood, 1968), the root-mean-square difference between the observed U_{ij} 's and the U_{ij} 's calculated from \mathbf{T} and ω was found to be 0.009 \AA^2 . Although the librational motion about axes perpendicular to the general plane of the steroid ($\omega_2 = 1.4^\circ$) and parallel to the length of the steroid ($\omega_1 = 3.7^\circ$) were similar to those observed in the structures cited above, libration about the third axis [ω_3 , Fig. 5(a)] was calculated as $(-5.26)^{1/2}$. This suggests that the molecule is not a rigid body but flaps in the center where molecular packing is least dense.

The thermal motion of urea in its tetragonal crystalline form has been thoroughly studied (Caron & Donohue, 1964). In the tetragonal structure, the principal axes of \mathbf{T} and ω are fixed in the directions $\mathbf{a} + \mathbf{b}$, $\mathbf{a} - \mathbf{b}$, and \mathbf{c} by symmetry requirements. Despite the lack of space-group-imposed symmetry, the librational motion of urea in the orthorhombic complex is similar to that in the tetragonal structure. The magnitudes and directional cosines of \mathbf{T} and ω for the urea molecules in the two crystals are compared in Table 7. The r.m.s. difference between the observed U_{ij} 's and the U_{ij} 's calculated from \mathbf{T} and ω in the complex is 0.001 \AA^2 . Translational motion in the complex is nearly isotropic, and the principal axes are not coincident with either the cell sides or the axes of inertia of the molecule. The axis about which there is least

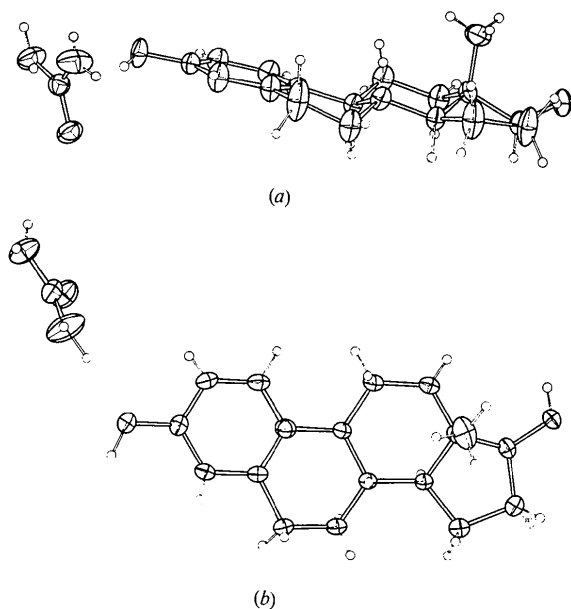


Fig. 4. Perspective views of estradiol, showing 50% probability thermal vibrational ellipsoids (a) rotated 77° about the C(13)–C(10) vector and (b) parallel to the cross product of the vectors C(13)–C(10) and C(12)–C(14).

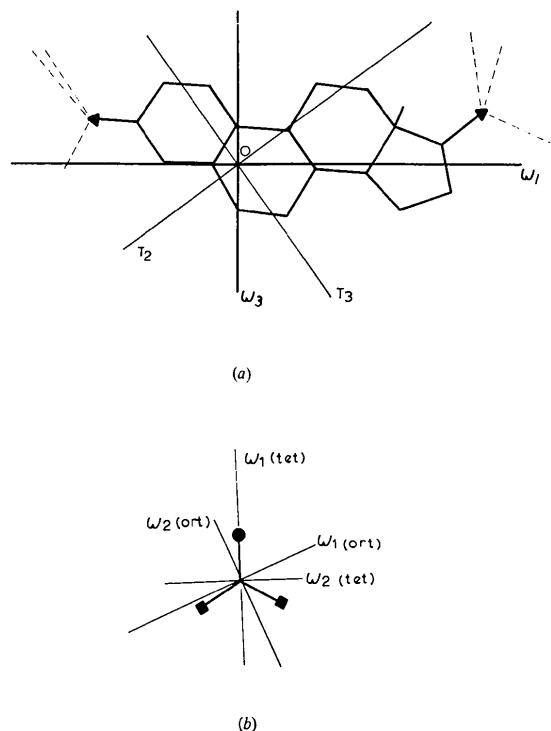


Fig. 5. (a) The principal axes of \mathbf{T} and ω in the estradiol nucleus viewed parallel to the axis about which there is least rotation (ω_2). (b) The principal axes of libration of the urea molecule in the tetragonal lattice, and in the estradiol complex viewed parallel to the axis of least librational freedom (ω_3).

librational is nearly coincident in the two structures and is perpendicular to the plane of the molecule. The other librational axes in the tetragonal structure are parallel and perpendicular to the carbon–oxygen double bond. In the complex, these axes are rotated 20° from this orientation [Fig. 5(b)]. The coordinates of the unweighted centroid are $x = 0.2451$, $y = -0.0059$, $z = 0.1389$.

Molecular packing and hydrogen bonding

The spatial arrangement of molecules can best be described as a partitioned packing system, with alternate layers of steroid and urea molecules. The planes of the steroid molecules are roughly perpendicular to the planes of the urea molecules, as shown in Fig. 6. The characteristic pattern observed in estrogen crystal structures is an arrangement of infinite chains of steroid molecules, hydrogen-bonded head to tail. This pattern is retained in the complex, with the additional feature that all bonding to lateral chains is *via* the urea molecules. The only intermolecular contacts of less than 2.7 \AA are listed in Table 8. The absence of contacts of less than 2.5 \AA distance (with the exception of those hydrogen atoms involved in hydrogen bonding) is due to the rigid hydrogen-bonding arrangement. Distor-

tions of hydrogen positions due to packing forces are probably at a minimum.

Table 8. *Intermolecular distances less than 2.7 Å between hydrogen atoms*

Contact	Position*	Distance
H(1)—H(14)	4/ $\bar{1}\bar{1}0$	2.54 Å
H(2)—H	1/0 $\bar{1}0$	2.65
H(6 β)—H(18C)	4/ $\bar{1}01$	2.57
H(7 α)—H(11 α)	4/ $\bar{1}00$	2.64
H(7 β)—H(18B)	4/ $\bar{1}01$	2.62
H(11 α)—H(15 α)	1/0 $\bar{1}0$	2.51
H(NB1)—H(O17)	3/000	2.324
H(O17)—H(O3)	3/ $\bar{1}10$	2.317

* Equivalent position nomenclature: the symbol 4/ $\bar{1}\bar{1}0$ is taken to mean that the second atom mentioned in the contact is in the molecule at equivalent position 4, translated $\bar{1}$, $\bar{1}$, and 0 unit cells in the a , b , and c directions, respectively. The equivalent positions are 1 = (x , y , z); 2 = ($\frac{1}{2}-x$, $-y$, $\frac{1}{2}+z$); 3 = ($\frac{1}{2}+x$, $\frac{1}{2}-y$, $-z$); 4 = ($-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$).

Fig. 7 illustrates the hydrogen-bonding system viewed parallel to the a axis, and Table 9 summarizes the geometry of the hydrogen bonds. All hydrogen bonds have acceptable geometries. The longest hydrogen bond (3.151 Å) has the most favorable N—H \cdots O angle (173°), while the smallest N—H \cdots O angle occurs in conjunction with a shorter N \cdots O distance of 3.039 Å. The 2.85 Å, N \cdots O (carbonyl) bond is very strong, when compared to the average N—H \cdots O bond of 3.01 Å observed in the tetragonal urea structure. The other N—H \cdots O (hydroxyl) bonds in this structure are of a length and geometry comparable to the N—H \cdots O (water) hydrogen bonds observed in arginine hydrochloride monohydrate (Dow, Jensen, Mazumdar, Srinivasan & Ramachandran, 1970), as shown in Table 9. The only hydrogen bond between urea molecules forms infinite chains extending in the direction of the c axis. Each urea molecule is hydrogen-bonded to four different estradiol molecules, resulting

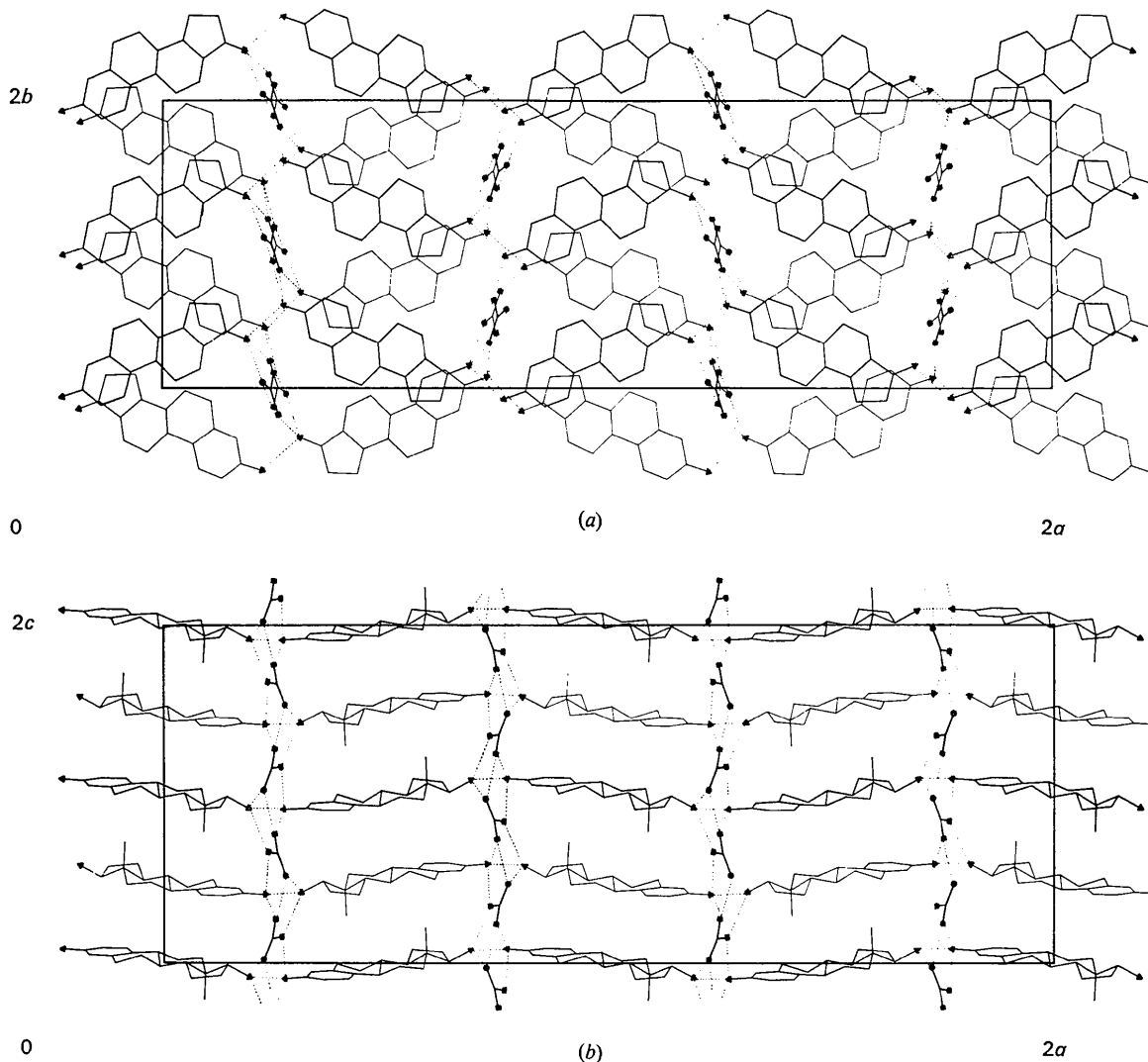


Fig. 6. Projection of four unit cells (a) onto the (001) plane and (b) onto the (010) plane.

Table 9. (a) Summary of the geometry of the hydrogen bonding in estradiol.urea, and (b) selected hydrogen bonds in arginine hydrochloride monohydrate

	Hydrogen bond $X-H \cdots Y$	$X-H$	Distance $H \cdots Y$	Distance $X \cdots Y$	Angle $X-H \cdots Y$
(a)	O(3)—H \cdots O(17)	0.93	1.78 Å	2.679 Å	161°
	O(17)—H \cdots O(19)	0.85	1.81	2.652	170
	N(A)—H(A1) \cdots O(3)	0.83	2.39	3.039	138
	N(A)—H(A2) \cdots O(17)	0.83	2.31	3.151	173
	N(B)—H(B1) \cdots O(3)	0.96	2.23	3.034	156
	N(B)—H(B2) \cdots O(19)	0.66	2.20	2.854	169
(b)	N(8)—H(31) \cdots O(3)	0.79	2.26	3.03	164
	N(8)—H(32) \cdots O(3)	0.83	2.06	2.88	169
	N(4)—H(14) \cdots O(6)	0.87	2.11	2.97	169
	N(4)—H(15) \cdots O(6)	0.88	2.03	2.90	167

in a strong interlocking of the steroid chains. At first glance, the alternate layers of steroid and urea molecules suggest similarities to the urea clathrate structures (Smith, 1950; Schlenk, 1951). However, the urea's primary interaction is to bind the steroid's chains together, rather than to surround or isolate the steroid molecules.

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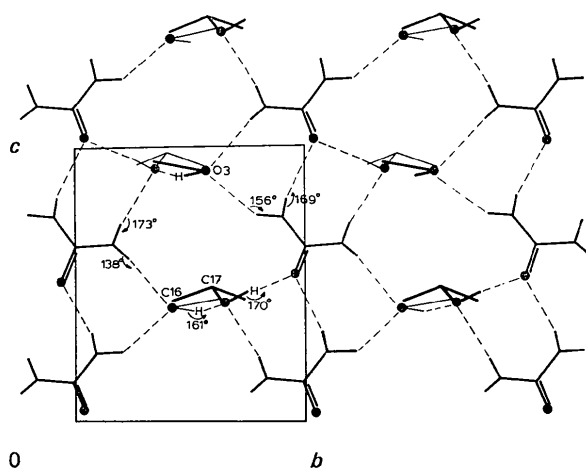


Fig. 7. Hydrogen-bonding in a plane perpendicular to the a axis in estradiol.urea (1:1).