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Crystal chemistry of some synthetic 2-oxa-steroids: conformation, packing motifs and isostructurality

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The crystal structures of six synthetic 2-oxa-steroids (*A*-ring lactone steroids) have been determined by single-crystal X-ray diffraction. The conformation and hydrogen bonding in these oxa-steroids is compared with packing motifs in the natural steroids and the anabolic agent, Anavar®. O—H···O hydrogen bonding with lactone carbonyl O is the preferred arrangement in molecules with a C—OH group. The donor H atoms of *A*, *B* and *D* rings participate in C—H···O interactions with lactone carbonyl O and *D*-ring hydroxyl/ketone O acceptor atoms. The conformation of the lactone ring in these analogues is different from the natural androgens because replacement of the C2-methylene group by an O atom changes the geometry of the *A* ring. Two structurally related lactone steroids provide the first example of O—H···O/C—H···O interaction mimicry and furthermore the two components form a binary solid solution. The O—H···O and C—H···O hydrogen bonds in 2-oxa-steroid crystal structures are analysed and the observed preferences discussed in terms of geometric and chemical factors.

1. Introduction

Naturally occurring steroid hormones, such as androstanes, cholestanes, estranes, pregnanes and their synthetic derivatives, have been well used in clinical therapy for over four decades now (Duax *et al.*, 1994; Fuhrhop & Penzlin, 1994; Hanson, 1995; Makin & Gower, 1996; Leake, 1996; Blickenstaff, 1996). The beneficial properties of steroidal drugs and hormones are occasionally accompanied by unwanted side effects, and this curtails their prolonged administration in the treatment of cancer and hormone regulation (Pappo, 1969; Zurer, 1984). Androgenic steroids produce side effects such as acne, changes in liver function and decreased sperm population in male patients when used in clinical therapy. Testosterone (1) exhibits androgenic or male physical-characteristic promoting and anabolic or muscle-building activity. Since anabolic agents are also potent androgens, they cause facial hair growth, male pattern baldness, deepening of the voice and menstrual irregularities in female athletes. To overcome these and related problems with steroidal drugs, synthetic analogues have been examined by the Searle group. Nilevar® (2), 17α-ethyl-17-hydroxy-19-nor-4-androstene-3-one, norethandrolone (Colton *et al.*, 1957), and Anavar® (3), 17β-hydroxy-17-methyl-2-oxa-5α-androstane-3-one, oxandrolone (Pappo & Jung, 1962, 1968), are anabolic agents with negligible androgenic side effects (Fig. 1). The crystal structure of Anavar® (3) was examined by Rendle & Trotter (1975) to study the

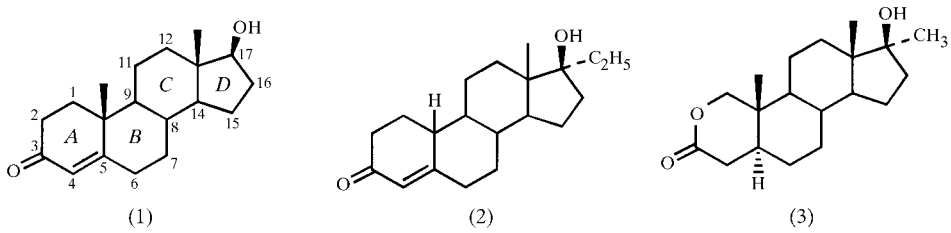


Figure 1
Anabolic steroids: Testosterone (1), Nilevar® (2) and Anavar® (3). Steroid atom numbering and ring labels are shown in (1).

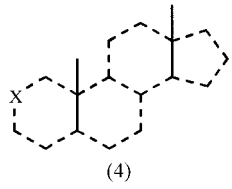


Figure 2
Fragment (4) used to search 2-heterosteroids in the CSD. The dotted lines indicate 'any bond' and X = O, N or S.

structure–activity relationship and the effect of C2-methylene on O-atom replacement in lactone steroids. The *A*-ring in (3) has a flattened chair conformation, the *D* ring is in an envelope conformation and the *B* and *C* rings are in the normal chair conformation. The molecules are connected by O17—H···O3 hydrogen bonds. The possibility of C—H···O hydrogen bonding in the crystal was ruled out based on the long H—O distance (> 2.9 Å).

A search of the Cambridge Structural Database (CSD, version 5.16, October 1998, 190 307 entries; Kennard & Allen, 1993) for fragment (4) (Fig. 2) in the organic structures (screen 57) furnished six steroid analogues (Fig. 3) with a heteroatom at C2 and a carbonyl group at C3.[1] Of these six structures, five are lactone steroids (ANSTER10, GAKFIH, TASVOY, WORMAN, WORTBZ) and one is a lactam (BEXPID). Inspection of the five 2-oxa-steroids in Fig. 3 shows that three structures are derivatives of wortmannin [(7), (8) and (9)] and one is an epoxidation rearrangement product (6). On perusal of the literature, it becomes clear that the primary motivation for carrying out the X-ray crystal structure determination in these cases was to confirm the molecular structure and/or the stereochemistry. Anavar® (3) is the only 2-oxa-steroid for which the conformation and hydrogen bonding in the crystal have been studied (Rendle & Trotter, 1975). The medicinal importance of 2-oxa-steroids together with the paucity of structural data on these molecules led to the present study on some analogues of Anavar®. In this paper, the crystal structures of 2-oxa-4-androstene-3,17-dione (10), 2-oxa-5α-androstane-3,17-dione (11), 17β-hydroxy-2-oxa-4-androstene-3-one (12), 6α-hydroxy-2-oxa-4-androstene-3,17-dione (13), 6α-hydroxy-2-oxa-5β-androstane-3,17-dione (14) and 6α,17β-dihydroxy-2-oxa-4-androstene-3-one (15) (Fig. 4) are analysed with a view to understanding their conformation and hydrogen-bonding patterns. The complexity of functional groups in the *A*, *B* and *D* rings is gradually varied: four molecules have strong (O—H···O) and weak (C—H···O) hydrogen-bonding groups [(12)–(15)], while two molecules have only weak donor atoms [(10) and (11)]. The crystal structures of these lactone steroids are discussed in three parts:

(i) packing motifs of the individual molecules;
(ii) conformation in the crystal;
(iii) crystal structure comparison and isostructurality.

2. Experimental

2.1. Synthesis

The synthesis of 2-oxa-steroids (13) and (14), and (15) from dehydroisoandrosterone was recently reported by Nangia & Anthony (1996, 1997). The saturated *B*-ring oxa-steroids, (10) and (11), and (12) were synthesized from the C17-ketal of (18) (Childers *et al.*, 1988). All compounds were characterized by their satisfactory ^{1}H and ^{13}C NMR and IR spectra, and recrystallized under ambient conditions from a mixture of ethyl acetate and hexane.

2.2. X-ray data

The single-crystal X-ray data for the structures are summarized in Table 1.[2] Space group and unit-cell determination as well as all intensity measurements were carried out on a KM-4 diffractometer (KUMA) using graphite-monochromatic Cu $K\alpha$ radiation (λ = 1.54178 Å). The reflection intensities were collected at 293 (2) K and measured using a variable θ–2θ scan by the background–peak–background method. Two standard reflections monitored during data collection at short intervals showed insignificant (< 2.5%) intensity fluctuation. The structures were solved by direct methods using *SHELXS*86 (Sheldrick, 1985). In all cases the best *E*-maps revealed all non-H atoms. The structures were refined by least-squares minimization of $\Sigma w(F_o^2 - F_c^2)^2$ in *SHELXL*93 (Sheldrick, 1993) using all reflections. The positions of O—H hydrogen atoms were obtained from the difference-density maps and the C—H hydrogen atoms were generated geometrically and allowed to ride on their carriers, except for the methyl H atoms which formed rigid groups with adjustable rotation around the C—CH_3 bonds. The final refinement included anisotropic displacement parameters for the non-H atoms and isotropic displacement parameters for all H atoms. Neutron-normalized H-atom positions (C—H

[1] A total of 11 structures were retrieved, of which five do not belong to the steroid skeleton and are not discussed.

[2] Supplementary data for this paper are available from the IUCr electronic archives (Reference: KA0049). Services for accessing these data are described at the back of the journal.

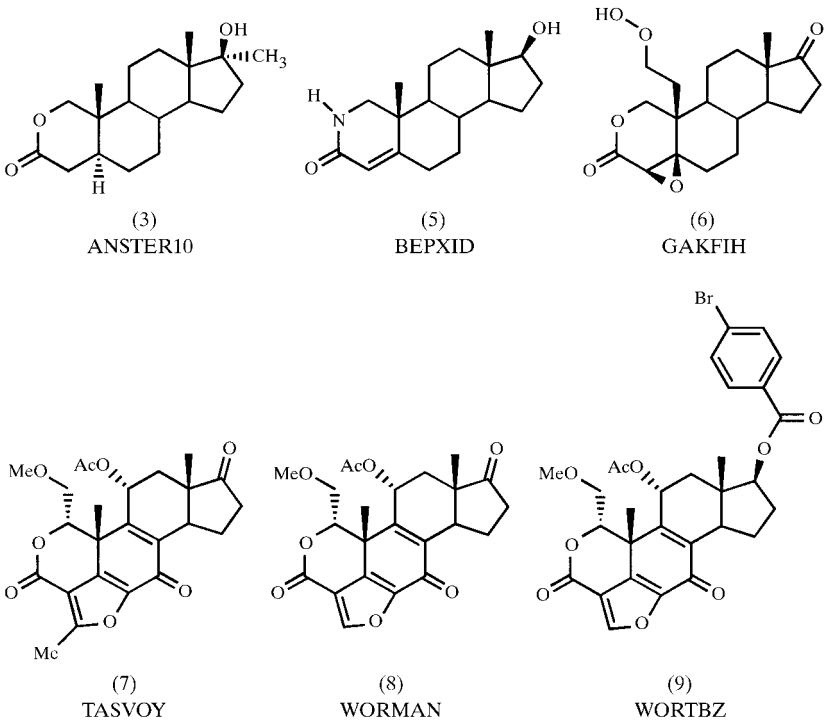


Figure 3
Six 2-heterosteroids retrieved from the CSD and their Refcodes.

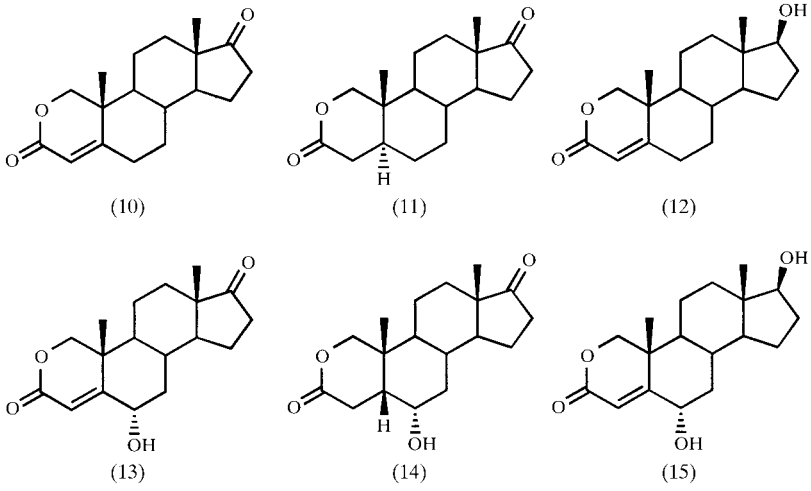


Figure 4
The synthetic 2-oxa-steroids analysed in this study.

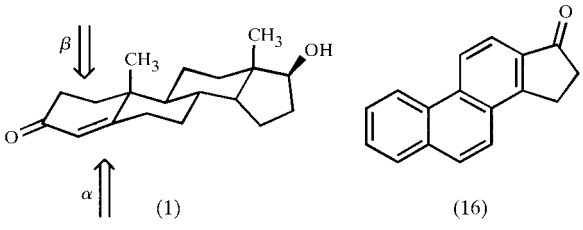


Figure 5
Comparison of testosterone (1) with cyclopentaphenanthrene (16). α and β refer to the concave and convex faces of the steroid skeleton, respectively.

1.083 Å) are used for the hydrogen-bond geometries in Table 2 and the C—H···O contacts displayed in Fig. 6.

3. Results and discussion

3.1. CSD results

Steroids have donor and acceptor atoms on the periphery of the tetracyclic skeleton that form O—H···O hydrogen bonds (Duax & Norton, 1975; Duax *et al.*, 1976, 1994), as in testosterone (1), and in this respect they are similar to cyclopenta[*a*]phenanthrene (16), which has the same carbon core except that the *A*/*B*/*C* rings are aromatic (Fig. 5). The crystal structure of (16) is stabilized by the numerous C—H···O hydrogen bonds between the relatively acidic, aromatic sp^2 C—H donors and the O17 acceptor atom (Desiraju *et al.*, 1993). In steroids, however, the C atoms are sp^3 hybridized and as such inactivated, except when they are in the proximity of a carbonyl or alkene group (Pedireddi & Desiraju, 1992). Moreover, the C—H···O bond-forming ability of methylene donor groups could vary depending on whether the H atoms are on the convex (β) or the concave (α) face owing to steric factors. The methyl groups are inactivated, but more accessible because they extend out on the convex face of the steroid skeleton. Thus, it may reasonably be expected that the C—H···O interactions (Desiraju, 1996; Steiner, 1997; Desiraju & Steiner, 1999) in steroids will show significant geometric variability, depending on the position and stereochemistry of the donor C—H group.

All steroid crystal structures (class 6) were surveyed in the CSD (organic only, screen 57) and a sub-database created of error-free and ordered structures (screens 33 and 35) with $R \leq 0.10$ (screen 88). This sub-database of 1088 entries was searched for C—H···O contacts in the H···O distance range (d) 2.0–2.8 Å and C—H···O angle (θ) 110–180°. All C—H distances were neutron-normalized to 1.083 Å (HNORM). No constraints were imposed on the hybridization of the acceptor group, that is sp^2 (carbonyl) and sp^3 (hydroxyl, ether) O atoms were considered together.

The distance–angle scatter plots of C—H···O contacts at C1, C2, C4, C6 and C16 were next examined. The C1—H···O and C16—H···O contacts displayed in Fig. 6 show the inverse d–θ correlation characteristic of a hydrogen bond (Desiraju, 1996), suggesting that these weak interactions could be important in the stabilization of steroid crystal structures. On the other hand, the d–θ scatter plots of C18 and C19 methyl H atoms show a random distribution of points (not shown in the figure), indicating that these short contacts are probably a

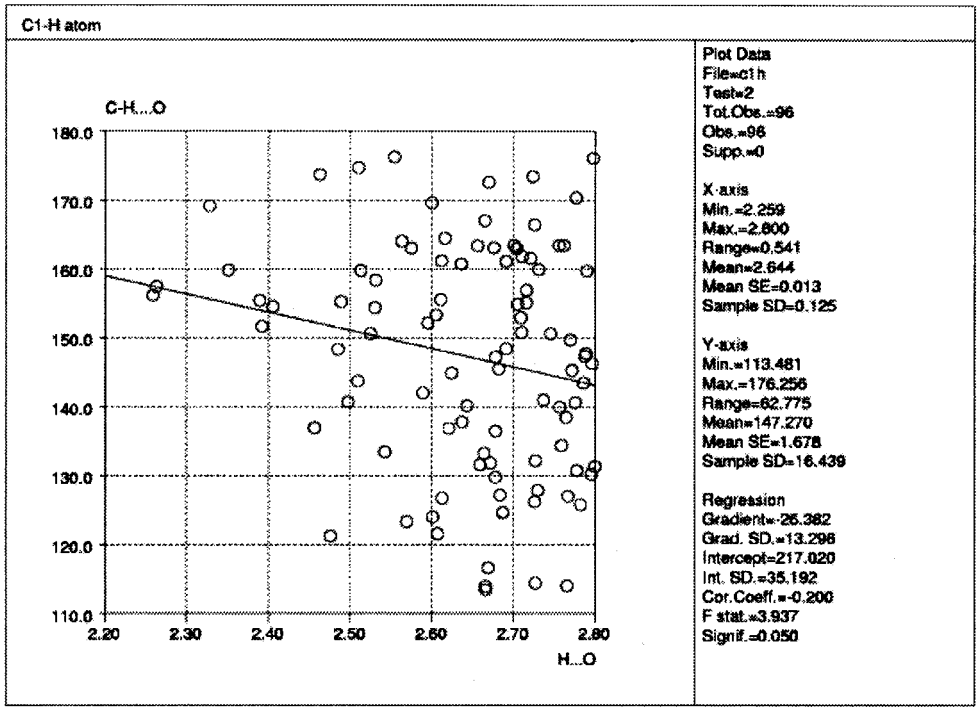
result of other intermolecular interactions in the crystal. The replacement of C2-methylene by an O atom alters the *A* ring:

(i) two C—H donors are replaced by an sp^3 O acceptor;

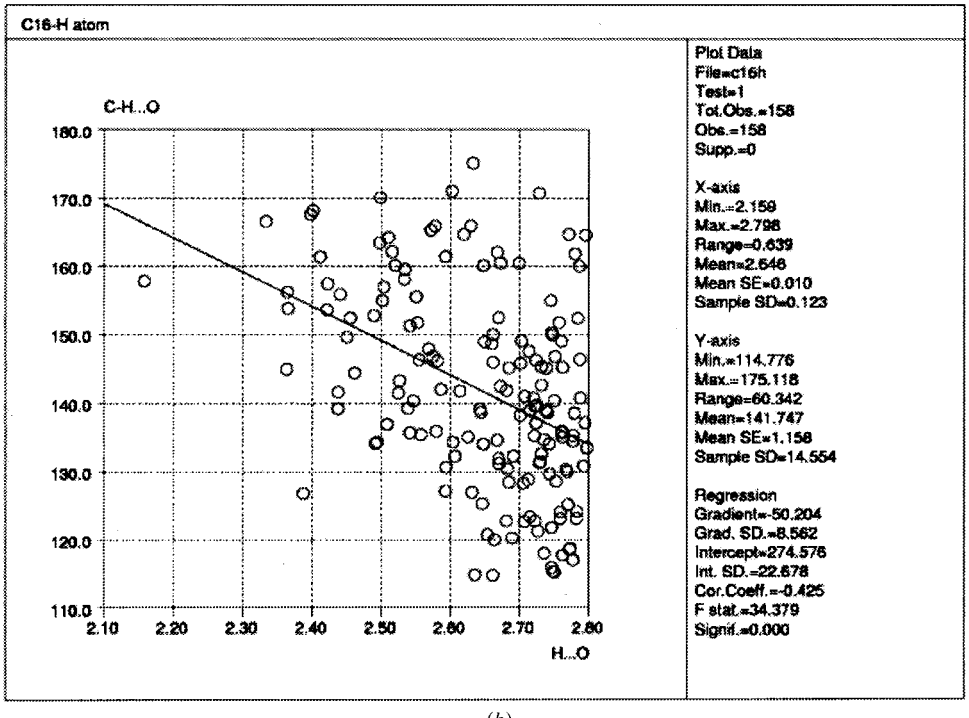
(ii) the acidity of C1–H is enhanced due to the proximal electronegative atom;

(iii) the conformation of the ring and the acceptor ability of O3 are changed.

Thus, the geometry and hydrogen-bonding patterns in 2-oxa-steroid crystal structures should be different, and yet related, to the natural androgenic steroids.



(*a*)



(*b*)

Figure 6
Distance–angle (d–θ) scatterplot for C—H···O contacts in steroids retrieved from the CSD. (*a*) C1—H···O; (*b*) C16—H···O.

3.2. Crystal structure analysis

A common aggregation motif in steroid crystal structures is the O—H···O hydrogen bond between C17-hydroxy donor and C3-ketone or -hydroxy acceptor groups (Duax & Norton, 1975). In this way, the molecules are connected in a head-to-tail fashion and crystallize in $P2_1$ or $P2_12_12_1$ space groups. Keeping this packing motif in mind, the crystal structures of oxa-steroids (12) and (15) are discussed.

In the crystal structure of 17-hydroxy lactone (12), space group $P2_12_12_1$, the molecules form a head-to-tail chain of O—H···O [H···*A* distance, *D*—H···*A* angle: 1.97 (3) Å, 171 (3)°] hydrogen bonds along [100] between screw-axis related molecules (Fig. 7). Such translation-related chains are connected by C6—H···O17 and C12—H···O3 hydrogen bonds to form a corrugated sheet in (110). Adjacent screw-axis related layers are stacked along [001] and connected by a C18—H···O17 hydrogen bond. The crystallographic data and metrics of O—H···O and C—H···O hydrogen bonds for the six structures are summarized in Tables 1 and 2.

In 6,17-dihydroxy lactone (15) ($P2_12_12_1$), translation-related molecules form O17—H···O3 [1.91 (3) Å, 167 (3)°] hydrogen-bonded chains along [110], which in turn are connected through O6—H···O17 [1.70 (5) Å, 166 (3)°] bonds between screw-axis related molecules (Fig. 8). The interlayer region between successive (110) planes is connected through C—H···O hydrogen bonds originating from donor groups on the β face of the

Table 1
Experimental details.

(*a*)

	(10)	(11)	(12)	(13)	(14)
Crystal data					
Chemical formula	$C_{18}H_{24}O_3$	$C_{18}H_{26}O_3$	$C_{18}H_{26}O_3$	$C_{18}H_{24}O_4$	$C_{18}H_{26}O_4$
Chemical formula weight	288.37	290.39	290.39	304.37	306.39
Cell setting	Monoclinic	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a (Å)	6.2321 (3)	6.3180 (4)	14.241 (2)	6.2214 (7)	6.335 (1)
b (Å)	9.9264 (6)	6.4489 (5)	9.4401 (9)	12.050 (1)	9.482 (1)
c (Å)	12.8120 (8)	38.841 (3)	11.648 (2)	10.888 (1)	27.245 (6)
β (°)	97.079 (5)	–	–	103.07 (1)	–
V (Å^3)	786.54 (8)	1582.5 (2)	1565.9 (4)	795.10 (13)	1636.6 (5)
Z	2	4	4	2	4
D_x (Mg m^{-3})	1.218	1.219	1.232	1.271	1.244
Radiation type	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$
Wavelength (Å)	1.54178	1.54178	1.54178	1.54178	1.54178
No. of reflections for cell parameters	62	91	41	43	56
θ range (°)	19–51	14–51	18–63	25–50	16–42
μ (mm^{-1})	0.647	0.644	0.651	0.717	0.697
Temperature (K)	293 (2)	293 (2)	293 (2)	293 (2)	293 (2)
Crystal form	Cubic	Prism	Prism	Plate	Plate
Crystal size (mm)	0.45 × 0.30 × 0.20	0.45 × 0.40 × 0.10	0.70 × 0.70 × 0.25	0.40 × 0.40 × 0.20	0.3 × 0.2 × 0.10
Crystal colour	Colourless	Colourless	Colourless	Brown	Colourless
Melting point (K)	458–459	433–435	473–475	517–519	508–511
Data collection					
Diffractometer	KM-4	KM-4	KM-4	KM-4	KM-4
Data collection method	ω–2θ scans	ω–2θ scans	ω–2θ scans	ω–2θ scans	ω–2θ scans
Absorption correction	None	None	None	None	None
No. of measured reflections	1685	1736	1722	1624	1586
No. of independent reflections	1597	1736	1722	1596	1586
No. of observed reflections	1434	1567	1592	1458	913
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0137	0.0000	0.0000	0.0312	0.0000
θ_{max} (°)	70.09	70.15	70.14	70.10	65.13
Range of h, k, l	$0 \rightarrow h \rightarrow 7$ $0 \rightarrow k \rightarrow 12$ $-15 \rightarrow l \rightarrow 15$	$-7 \rightarrow h \rightarrow 7$ $-7 \rightarrow k \rightarrow 7$ $-47 \rightarrow l \rightarrow 44$	$0 \rightarrow h \rightarrow 17$ $0 \rightarrow k \rightarrow 11$ $0 \rightarrow l \rightarrow 14$	$-7 \rightarrow h \rightarrow 2$ $-14 \rightarrow k \rightarrow 14$ $-13 \rightarrow l \rightarrow 13$	$0 \rightarrow h \rightarrow 7$ $0 \rightarrow k \rightarrow 10$ $0 \rightarrow l \rightarrow 32$
No. of standard reflections	2	2	2	2	2
Frequency of standard reflections	Every 100 reflections	Every 100 reflections	Every 100 reflections	Every 100 reflections	Every 100 reflections
Refinement					
Refinement on	F^2	F^2	F^2	F^2	F^2
$R[F^2>2\sigma(F^2)]$	0.0342	0.0307	0.0305	0.0359	0.0344
$wR(F^2)$	0.0919	0.0886	0.0959	0.1013	0.1042
S	1.056	1.045	1.068	1.075	0.982
No. of reflections used in refinement	1597	1736	1722	1512	1586
No. of parameters used	190	219	222	228	231
H-atom treatment	Riding (C—H 0.93–0.96 Å)	Riding (C—H 0.93–0.96 Å)	Riding (C—H 0.93–0.96, O—H 0.82 Å)	Riding (C—H 0.93–0.96, O—H 0.82 Å)	Riding (C—H 0.93–0.96, O—H 0.82 Å)
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0527P)^2 + 0.0545P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0488P)^2 + 0.2430P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0602P)^2 + 0.1629P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0677P)^2 + 0.0990P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0573P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.011	0.001	0.001	−0.020	0.001
$\Delta\rho_{max}$ (e Å^{-3})	0.098	0.161	0.171	0.139	0.137
$\Delta\rho_{min}$ (e Å^{-3})	−0.134	−0.111	−0.101	−0.184	−0.130
Extinction method	None	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)	None	*SHELXL*93 (Sheldrick, 1993)
Extinction coefficient	0	0.0047 (5)	0.0078 (8)	0	0.0015 (4)

Table 1 (continued)

	(10)	(11)	(12)	(13)	(14)
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Computer programs					
Data collection	Kuma KM-4	Kuma KM-4	Kuma KM-4	Kuma KM-4	Kuma KM-4
Cell refinement	Kuma KM-4	Kuma KM-4	Kuma KM-4	Kuma KM-4	Kuma KM-4
Data reduction	Kuma KM-4	Kuma KM-4	Kuma KM-4	Kuma KM-4	Kuma KM-4
Structure solution	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)
Structure refinement	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)
Preparation of material for publication	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)

(*b*)

	(15)	(22)
Crystal data		
Chemical formula	$C_{18}H_{26}O_4$	$0.72(C_{18}H_{24}O_4).0.28(C_{18}H_{24}O_4)$
Chemical formula weight	306.39	304.37
Cell setting	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
a (Å)	9.3361 (7)	6.2246 (7)
b (Å)	9.6261 (7)	12.014 (1)
c (Å)	17.764 (2)	10.915 (1)
β (°)	90	103.09 (1)
V (Å^3)	1596.5 (2)	795.04 (13)
Z	4	2
D_x (Mg m^{-3})	1.275	1.271
Radiation type	Cu $K\alpha$	Cu $K\alpha$
Wavelength (Å)	1.54178	1.54178
No. of reflections for cell parameters	56	58
θ range (°)	13–72	14.7–71.3
μ (mm^{-1})	0.714	0.717
Temperature (K)	293 (2)	293 (2)
Crystal form	Prism	Cubic
Crystal size (mm)	0.5 × 0.4 × 0.2	0.35 × 0.30 × 0.30
Crystal colour	White	Light brown
Melting point (K)	500–503	517–518
Data collection		
Diffractometer	KM-4	KM-4
Data collection method	ω–2θ scans	ω–2θ scans
Absorption correction	None	None
No. of measured reflections	1746	1651
No. of independent reflections	1746	1542
No. of observed reflections	1634	1497
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0000	0.0188
θ_{max} (°)	70.13	70.13
Range of h, k, l	$0 \rightarrow h \rightarrow 11$ $0 \rightarrow k \rightarrow 11$ $0 \rightarrow l \rightarrow 21$	$0 \rightarrow h \rightarrow 7$ $0 \rightarrow k \rightarrow 14$ $-13 \rightarrow l \rightarrow 12$
No. of standard reflections	2	2
Frequency of standard reflections	Every 100 reflections	Every 100 reflections
Refinement		
Refinement on	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0305	0.0321
$wR(F^2)$	0.0859	0.0880
S	1.059	1.039
No. of reflections used in refinement	1741	1542
No. of parameters used	234	202
H-atom treatment	Riding	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0538P)^2 + 0.2314P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0542P)^2 + 0.0888P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.042	0.000
$\Delta\rho_{max}$ (e Å^{-3})	0.174	0.134

Table 1 (continued)

	(15)	(22)
$\Delta\rho_{min}$ (e Å^{-3})	−0.106	−0.120
Extinction method	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)
Extinction coefficient	0.0007 (2)	0.0040 (8)
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Computer programs		
Data collection	Kuma KM-4	Kuma KM-4
Cell refinement	Kuma KM-4	Kuma KM-4
Data reduction	Kuma KM-4	Kuma KM-4
Structure solution	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1986)
Structure refinement	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)
Preparation of material for publication	*SHELXL*93 (Sheldrick, 1993)	*SHELXL*93 (Sheldrick, 1993)

molecule. There are four such screw-axis related layers stacked in one unit length along the *c* axis.

The crystal structures of 6-hydroxy lactone (13) and methylene lactone (10) belong to the monoclinic space group $P2_1$. In (13), C6—OH and C6β—H are bonded to the lactone carbonyl oxygen atom (O3) of distinct screw-axis related molecules, in effect forming a chain of O—H···O [1.90 (5) Å, 171 (3)°] and C—H···O (2.38 Å, 158°) hydrogen bonds along the *a* axis (Fig. 9*a*). The packing is further stabilized by a chain of C—H···O hydrogen bonds from C1 and C11 H atoms to O17. In the crystal structure of (10), the C6-methylene H atoms of screw-axis-related molecules are bonded to the lactone O3 in a bifurcated motif (2.38 Å, 154°; 2.67 Å, 157°; Fig. 9*b*), while the C1 and C11 H atoms are bonded to ketone O17. Thus, the C6α H atom in (10) behaves as a surrogate of the OH group in (13) such that the stronger of the two C6—H···O interactions (2.38 Å) in the former structure replaces the O—H···O bond in the latter (Anthony *et al.*, 1998). It may be noted that in both pairs of OH/H lactones, (15)/(12) and (13)/(10), C6—OH is replaced by an H atom. Although the

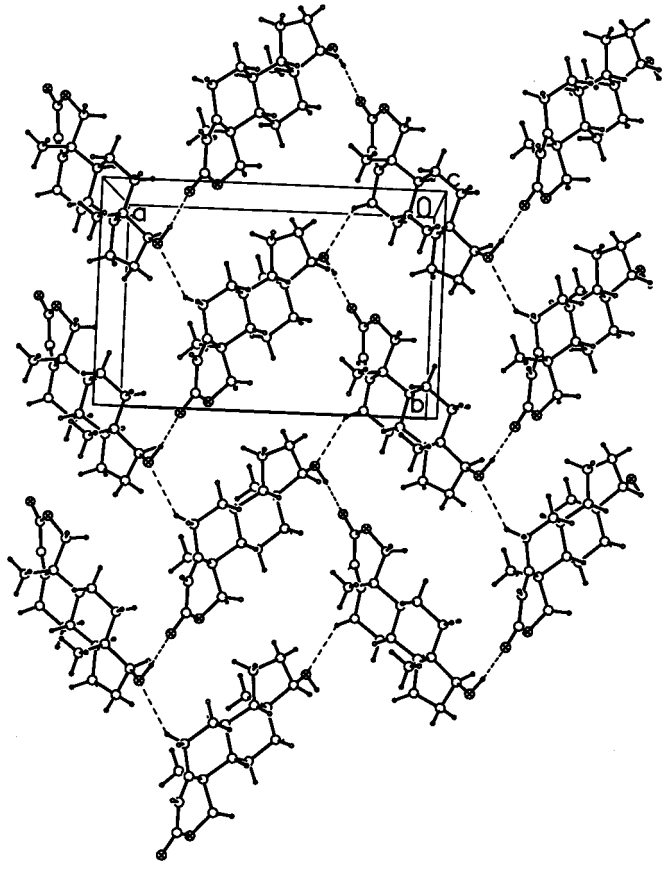


Figure 7
Crystal structure of 17-hydroxy lactone (12). Notice the zigzag chain of O—H···O hydrogen-bonded molecules along the *a* axis and the C—H···O interaction between the chains.

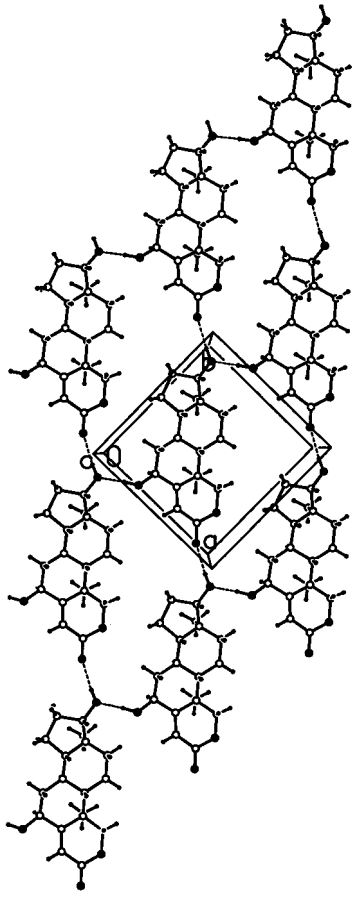


Figure 8
Crystal structure of 6,17-dihydroxy lactone (15). The O17—H···O3 hydrogen-bonded chains interlinked by O6—H···O17 hydrogen bonds form the (110) layer.

Table 2
Geometry of O—H···O and C—H···O hydrogen bonds.

All C—H distances are neutron-normalized to 1.083 Å.

Steroid	Interaction	H···O (Å)	O/C···O (Å)	O/C—H···O (°)	Symmetry
(10)	C1—H12···O17	2.54	3.295 (3)	126	$2-x,-\frac{1}{2}+y,-z$
	C4—H4···O3	2.90	3.734 (4)	134	$3-x,\frac{1}{2}+y,1-z$
	C6—H61···O3	2.38	3.387 (4)	154	$3-x,\frac{1}{2}+y,1-z$
	C6—H62···O3	2.67	3.691 (4)	157	$2-x,\frac{1}{2}+y,1-z$
	C11—H111···O17	2.81	3.566 (3)	127	$2-x,-\frac{1}{2}+y,-z$
	C11—H112···O17	2.58	3.409 (3)	133	$1-x,-\frac{1}{2}+y,-z$
	C15—H151···O2	2.77	3.545 (4)	129	$x,1+y,z$
	C16—H162···O2	2.63	3.446 (4)	132	$x,1+y,z$
(11)	C1—H11···O3	2.39	3.280 (2)	138	$-x,-\frac{1}{2}+y,\frac{3}{2}-z$
	C1—H12···O3	2.70	3.715 (2)	156	$-x,\frac{1}{2}+y,\frac{3}{2}-z$
	C4—H41···O3	2.82	3.519 (3)	122	$1-x,\frac{1}{2}+y,\frac{3}{2}-z$
	C6—H61···O3	2.67	3.579 (2)	142	$1-x,\frac{1}{2}+y,\frac{3}{2}-z$
	C15—H152···O17	2.63	3.624 (2)	153	$1+x,y,z$
	C16—H161···O17	2.80	3.634 (3)	134	$\frac{1}{2}+x,\frac{3}{2}-y,2-z$
	C19—H193···O17	2.50	3.349 (3)	135	$\frac{1}{2}+x,\frac{3}{2}-y,2-z$
(12)	O17—H17···O3	1.97 (3)	2.853 (3)	171(3)	$-\frac{1}{2}+x,-\frac{1}{2}-y,1-z$
	C6—H62···O17	2.55	3.354 (3)	131	$\frac{1}{2}+x,\frac{1}{2}-y,1-z$
	C11—H112···O17	2.60	3.565 (3)	149	$-x,-\frac{1}{2}+y,\frac{3}{2}-z$
	C12—H122···O3	2.77	3.604 (3)	134	$-\frac{1}{2}+x,-\frac{1}{2}-y,1-z$
	C15—H152···O2	2.77	3.454 (3)	121	$x,1+y,z$
	C18—H181···O17	2.73	3.804 (3)	174	$-x,-\frac{1}{2}+y,\frac{3}{2}-z$
	C18—H182···O3	2.86	3.561 (3)	123	$\frac{1}{2}-x,-1-y,\frac{1}{2}+z$
(13)	O6—H6···O3	1.90 (5)	2.831 (4)	171 (3)	$-x,-\frac{1}{2}+y,1-z$
	C1—H12···O17	2.31	3.376 (4)	168	$-x,\frac{1}{2}+y,-z$
	C6—H61···O3	2.38	3.409 (4)	158	$1-x,-\frac{1}{2}+y,1-z$
	C8—H8···O3	2.87	3.752 (4)	139	$1-x,-\frac{1}{2}+y,1-z$
	C9—H9···O17	2.79	3.706 (3)	142	$-x,\frac{1}{2}+y,-z$
	C11—H112···O17	2.62	3.339 (4)	123	$1-x,\frac{1}{2}+y,-z$
	C15—H151···O6	2.83	3.797 (4)	148	$1-x,-\frac{1}{2}+y,1-z$
	C15—H152···O6	2.76	3.686 (4)	144	$-x,-\frac{1}{2}+y,1-z$
	C16—H161···O2	2.71	3.625 (4)	142	$x,-1+y,z$
	C18—H183···O6	2.69	3.757 (4)	167	$1-x,-\frac{1}{2}+y,1-z$
	C19—H191···O3	2.63	3.693 (4)	168	$1-x,-\frac{1}{2}+y,1-z$
	C19—H193···O17	2.55	3.607 (4)	165	$1-x,\frac{1}{2}+y,-z$
(14)	O6—H6···O3	1.99 (7)	2.883 (5)	172 (6)	$-1+x,y,z$
	C1—H11···O6	2.37	3.196 (5)	132	$1-x,-\frac{1}{2}+y,\frac{1}{2}-z$
	C7—H71···O3	2.55	3.538 (6)	151	$-x,\frac{1}{2}+y,\frac{1}{2}-z$
	C9—H91···O2	2.60	3.032 (5)	103	x,y,z
	C16—H161···O17	2.37	3.303 (6)	144	$-\frac{1}{2}+x,\frac{3}{2}-y,-z$
(15)	O6—H60···O17	1.70 (5)	2.760 (2)	166 (3)	$x,-1+y,z$
	O17—H17···O3	1.91 (3)	2.794 (2)	167 (3)	$1+x,1+y,z$
	C1—H12···O6	2.67	3.698 (3)	157	$1-x,\frac{1}{2}+y,\frac{3}{2}-z$
	C14—H141···O3	2.72	3.687 (3)	149	$1-x,\frac{1}{2}+y,\frac{3}{2}-z$
	C19—H192···O17	2.64	3.631 (3)	152	$-\frac{1}{2}+x,\frac{5}{2}-y,2-z$
	C19—H193···O2	2.58	3.508 (3)	143	$\frac{1}{2}+x,\frac{3}{2}-y,2-z$

latter pair of crystals shows some similarity in hydrogen-bonded chains, the former pair is quite different. The similarity in hydrogen-bond patterns and the mimicry of H/OH groups in (10) and (13) will be elaborated later.

In the crystal structure of 5α-lactone (11) ($P2_12_12_1$), the molecules pack in a head-to-head and tail-to-tail fashion (Fig. 10). In the head portion, both the C1—H donors are bonded to the O3 atom (2.39 Å, 138°; 2.70 Å, 156°) of distinct screw-axis-related molecules, forming C—H···O hydrogen-bonded zigzag tapes along [010]. At the tail end, 2_1-related molecules are connected by C—H···O hydrogen bonds to O17 along [100].

The 5β-lactone (14) ($P2_12_12_1$) has a bent shape because of the *cis* stereochemistry at the *A*/*B* ring junction compared with the *A*-ring unsaturated and *trans* *A*/*B* ring junction lactones which are flat. Crystal packing in this structure is determined by the O6—H···O3 [1.99 (7) Å, 172 (6)°] hydrogen bond between translation-related molecules along [001] to generate close-packed columns of S-shaped molecules. Adjacent screw-axis-related columns are connected in the tail portion by a right-handed (*P*) helix of C16—H···O17 (2.37 Å, 144°) hydrogen bonds (Fig. 11).

The hydrogen bonds and packing motifs in the 2-oxa-steroid crystal structures are summarized. When the O17-hydroxy group is present, the commonly observed head-to-tail O—H···O chain with O3 is formed, similar to the natural steroids. Even in the presence of a C6-hydroxy group, O17—H leads in hydrogen bonding because it is on the periphery of the tetracyclic skeleton, while O6—H···O17 bonds cross-link chains of molecules. However, when O6 is a hydroxy group and O17 a ketone, the O—H···O hydrogen bond is formed with lactone O3 rather than with ketone O17, perhaps because the former is more basic (Steiner, 1998). The preference of different C—H donors to participate in C—H···O hydrogen bonds in 2-oxa-steroid structures is similar to the trend in the CSD study on the parent steroids discussed in Fig. 6. Inspection of the metrics of C—H···O hydrogen bonds in Table 2 shows some interesting trends:

(i) The H atoms at C1, C6 and C16 generally form shorter contacts compared with other C—H donors, a possible reason for this preference being that these donor atoms are activated because C1 is adjacent to an electronegative atom, C6 is allylic and C16 is proximal to a carbonyl group. In this respect, the non-participation of sp^2 hybridized and activated (Steiner & Desiraju, 1998) C4—H is quite surprising. The C—H···O

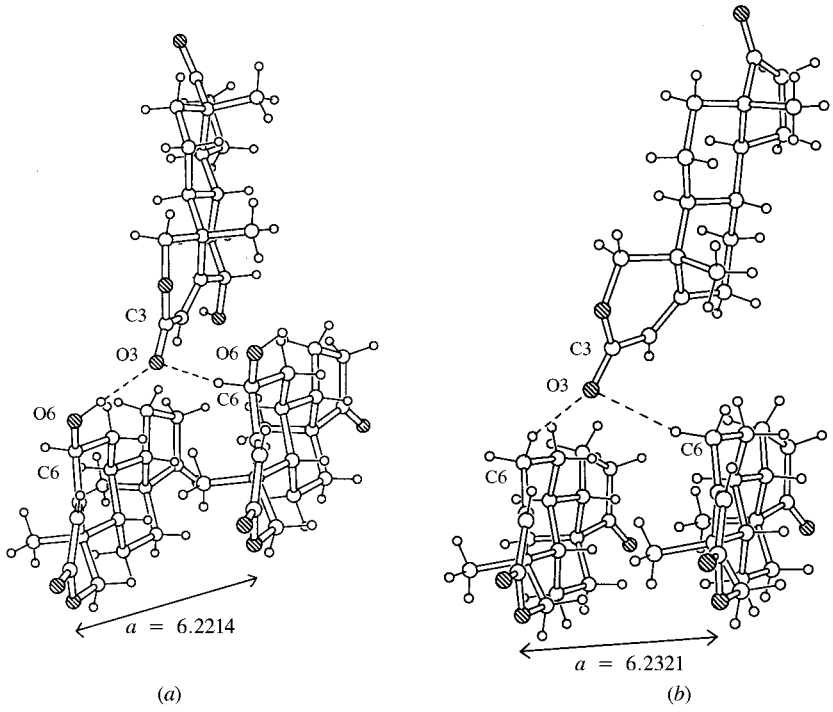


Figure 9
Hydrogen-bonded chains along the *a* axis in (*a*) 6-hydroxy lactone (13) and (*b*) methylene lactone (10). The lactone carbonyl O3 is bonded to distinct screw-axis related molecules in a bifurcated motif. Notice the near identity of the *a* axis in the two structures.

hydrogen-bonding ability of C18- and C19-methyl H atoms on the convex face is better ascribed to their geometric accessibility than to acidity effects.

(ii) Out of the four acceptor atoms, O2, O3, O6 and O17, O3 and O17 form more intermolecular contacts compared with O2 and O6, perhaps because they are on the periphery of the molecule and also more basic.

3.3. Conformation

The binding of steroid biomolecules to the receptor protein is strongly influenced by their conformation (Duax *et al.*, 1994; Wallimann *et al.*, 1997), with the flexible *A*-ring playing an important role in steroid–receptor interactions. Of the three possible *A*-ring conformations, 1α,2β half-chair, 1α sofa and inverted 1β,2α half-chair, the 1α,2β half-chair conformation is the most commonly observed (Duax & Norton, 1975).

Selected bond lengths, bond angles and torsion angles in the *A* ring of lactone steroids (10)–(15) are listed in Table 3. Comparison of the distances and angles in the C1—O2—C3—O3—C4 moiety suggests that canonical form (17*b*) contributes to the geometry of the *A* ring (Fig. 12). The four unsaturated 2-oxa-4-ene-3-one steroids (10), (12), (13) and (15) adopt the normal 1α,2β half-chair conformation, while the saturated 2-oxa-5α analogue (11) has the 1α sofa conformation. In the 2-oxa-5β steroid (14), the *A* ring has a bowing angle of 81.7° with respect to the mean plane

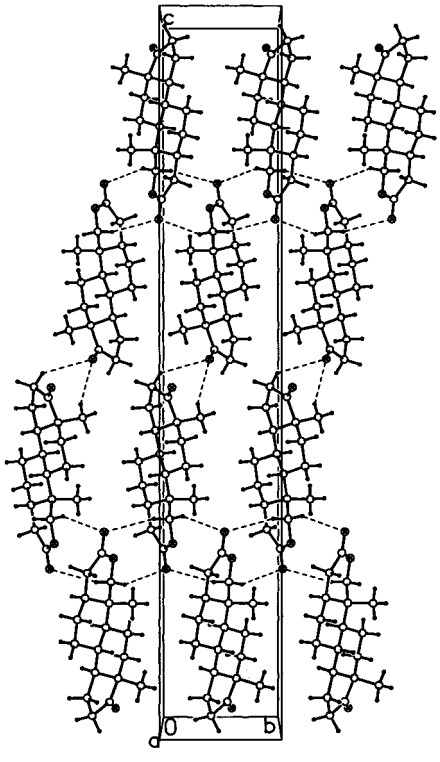


Figure 10
Head-to-head and tail-to-tail packing of molecules in the crystal structure of 5α-lactone (11). The C—H···O hydrogen-bonded zigzag tape along the *b* axis is constructed from methylene C1 H atoms and lactone O3.

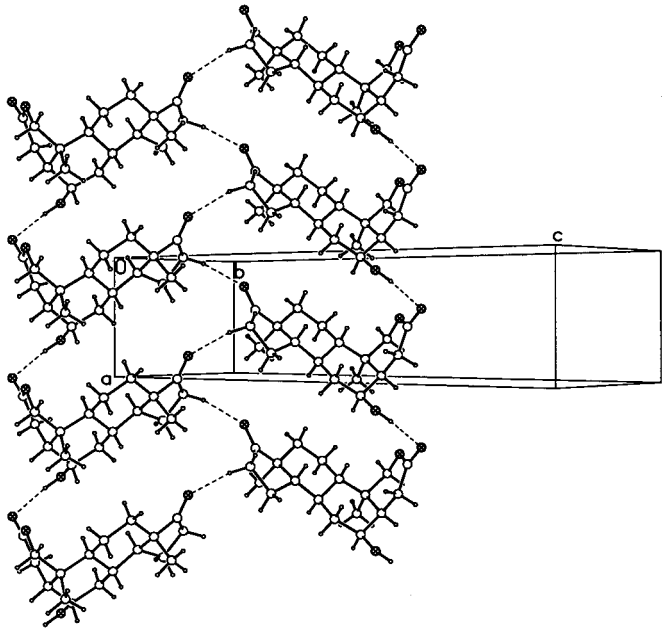
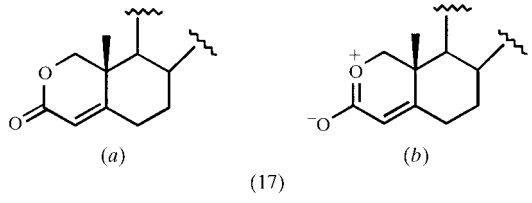


Figure 11
Packing of S-shaped molecules of 5β-lactone (14). The molecule is tethered at the two ends by O—H···O and C—H···O hydrogen bonds.

Table 3
Bond lengths, bond angles and torsion angles of *A* rings in lactones (10)–(15).

	(10)	(11)	(12)	(13)	(14)	(15)
C1—O2	1.441 (3)	1.452 (2)	1.447 (2)	1.446 (4)	1.438 (5)	1.453 (2)
C1—C10	1.515 (3)	1.520 (2)	1.523 (2)	1.519 (4)	1.517 (5)	1.521 (3)
O2—C3	1.351 (4)	1.337 (3)	1.332 (3)	1.342 (4)	1.343 (5)	1.338 (3)
C3—O3	1.209 (3)	1.206 (2)	1.220 (3)	1.215 (3)	1.211 (5)	1.213 (3)
C3—C4	1.442 (4)	1.496 (3)	1.443 (3)	1.454 (4)	1.477 (6)	1.460 (3)
C4—C5	1.333 (4)	1.529 (2)	1.335 (3)	1.328 (4)	1.532 (5)	1.334 (3)
C5—C10	1.517 (3)	1.531 (2)	1.503 (3)	1.517 (3)	1.541 (5)	1.518 (2)
C5—C6	1.488 (4)	1.515 (2)	1.495 (3)	1.503 (3)	1.529 (5)	1.497 (3)
C6—O6				1.417 (3)	1.429 (4)	1.415 (2)
O2—C1—C10	113.6 (2)	112.9 (2)	114.0 (2)	114.2 (2)	115.5 (3)	113.7 (2)
C3—O2—C1	116.2 (2)	121.10 (15)	117.0 (2)	116.8 (2)	118.9 (3)	117.2 (2)
O3—C3—O2	117.4 (3)	117.8 (2)	117.9 (2)	118.5 (3)	116.2 (5)	118.7 (2)
O3—C3—C4	124.6 (3)	122.1 (2)	123.4 (2)	123.5 (3)	122.9 (4)	123.0 (2)
O2—C3—C4	117.8 (2)	120.1 (2)	118.4 (2)	117.8 (2)	120.8 (4)	118.2 (2)
C5—C4—C3	123.1 (3)	116.8 (2)	122.4 (2)	122.6 (2)	118.8 (3)	122.3 (2)
C4—C5—C10	119.0 (3)	109.88 (14)	120.4 (2)	120.7 (2)	112.0 (3)	120.0 (2)
C10—C1—O2—C3	−49.5 (3)	−35.0 (2)	−48.3 (3)	−49.7 (4)	41.8 (5)	−47.7 (3)
C1—O2—C3—O3	169.7 (2)	177.9 (2)	166.4 (2)	165.6 (3)	171.6 (3)	168.7 (2)
C1—O2—C3—C4	14.2 (3)	4.1 (3)	19.0 (3)	19.4 (4)	12.1 (5)	14.2 (3)
O3—C3—C4—C5	−160.1 (3)	177.7 (2)	−163.6 (2)	−164.2 (3)	−178.7 (4)	−163.6 (2)
O2—C3—C4—C5	15.7 (4)	−4.4 (3)	10.7 (3)	10.5 (4)	5.2 (5)	13.3 (3)
C3—C4—C5—C10	−8.4 (3)	34.6 (2)	−9.6 (3)	−9.1 (4)	−26.3 (5)	−5.6 (3)



(17)

Figure 12
Canonical forms of the lactone *A* ring in 2-oxa-steroids.

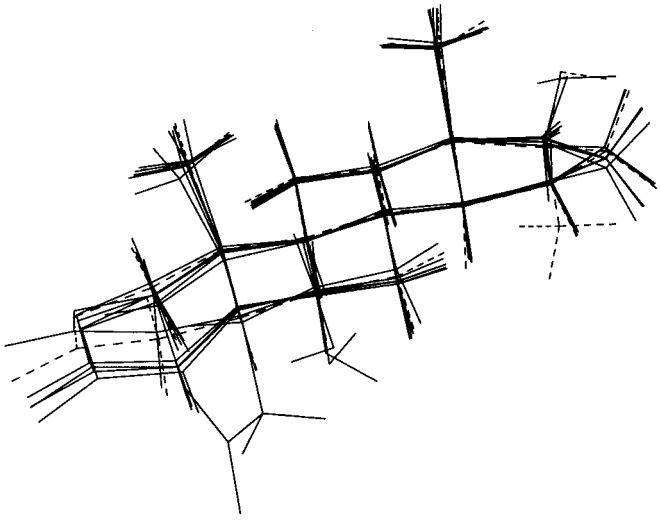


Figure 13
Overlay plot of 2-oxa-steroids (10)–(15) (solid line) and Anavar® (3) (dashed line). Notice that the *A*-ring unsaturated and *trans* *A*/*B*-ring junction oxa-steroids form a closely bunched population, while the *cis* *A*/*B*-ring junction oxa-steroid (14) projects out of the cluster.

of *B*/*C*/*D* rings, a value comparable to other 5β steroids reported recently (Andrade *et al.*, 1997; Ramos Silva *et al.*, 1996). The *D* ring in 2-oxa-steroids has an envelope conformation with the weighted average torsion angle, τ_{av}[3] having a value of 27 (3) and 30 (2)° for the C17-ketone and C17-hydroxy molecules, respectively. The *B* and *C* rings are rigid and adopt slightly flattened chair conformations with τ_{av} of 53 (2) and 55 (2)°, values similar to those found in some natural steroids reported recently (Paixão *et al.*, 1998).[4]

The overlay plot of the seven 2-oxa-steroids (six in this study and Anavar®) is displayed in Fig. 13. The unsaturated 4-ene-3-one and the saturated 5α oxa-steroids are tightly bunched while the 5β lactone is not part of this cluster. Further, the overlay plot of 2-oxa-4-androstene-3,17-dione (10) with 4-androstene-3,17-dione (18) (ANDSEO) has a modest overall r.m.s. deviation of 0.1003 Å for the common tetracyclic *A*/*B*/*C*/*D* ring system. The overlay is far superior when only the *B*/*C*/*D* rings are considered (0.0485 Å), indicating that the main difference between the 2-oxa analogues and the natural substrates lies in the *A*-ring geometry. This is also the region that is responsible for differences in their crystal structures. The C2—H atom is involved in hydrogen bonding with O17 (2.51 Å, 171°) in the crystal structure of (18), which is not possible in the 2-oxa analogue (10). The conformation and crystal packing in oxa-steroids (11) and (12) are quite different from androstanedione (19) (ANDION) and testosterone (1) (TESTON10; Fig. 14), because of reasons that are similar to those ascribed for the pair of molecules (10) and (18).

3.4. Isostructurality

Isostructurality in steroid crystal structures has been recently reviewed by Kálmán & Párkányi (1997). The extent of isostructurality, or likeness, between two crystal structures may be calculated from the *unit-cell similarity index*, Π, and the *isostructurality index*, $I_i(n)$. For a pair of isostructural crystals, $\Pi \simeq 0$ and $I_i(n) > 95\%$.

$$\Pi = \left| \frac{a+b+c}{a'+b'+c'} - 1 \right| \simeq 0$$

$$I_i(n) = \left[1 - (\Sigma \Delta R_i^2/n)^{1/2}\right] \times 100.$$

[3] τ_{av} is the average of the torsion angles in a ring, *e.g.* the *D* ring comprises atoms C13–C17, *B*-ring atoms C5–C10 and *A*-ring atoms C1–C5, C10.
[4] The τ_{av} values for *B* and *C* rings in these steroids are 55.5 (8), 54.7 (7), 55 (3)° and 56 (3), 55 (2), 56 (2)°.

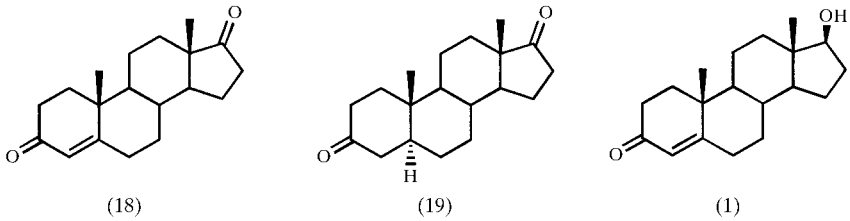


Figure 14
Androgenic steroids and their Refcodes.

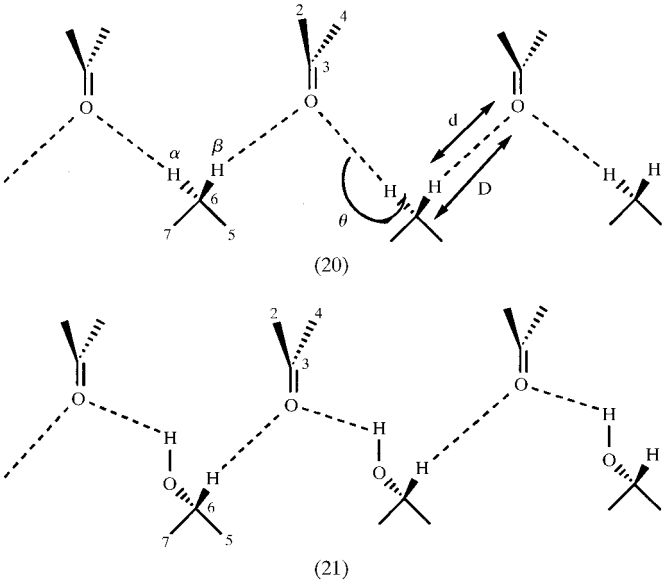


Figure 15
Supramolecular synthons (20) and (21) in the crystal structures of (10) and (13) to show the O—H···O/C—H···O interaction mimicry.

The unit cell similarity index (Π) for the pair of structures (10) and (13), is 0.002, but the isostructurality index, $I_i(17)$ is only 75%. This indicates that although the sums of cell dimensions in the two crystals are fortuitously identical ($a + b + c \simeq a' + b' + c'$), the conformation and arrangement of molecules within the lattice are quite different. Such relaxed forms of isostructurality were termed as homeostructural relationships (Kálmán *et al.*, 1993). The two molecules crystallize in the monoclinic space group $P2_1$ with very similar *a* axis (6.232 and 6.221 Å), while *b*, *c* and β are quite different (Table 1). The hydrogen bonds may be analysed along [100]. A chain of alternating strong and weak hydrogen bonds with the bifurcated lactone carbonyl group, C6—O—H···O3···H—C6β, is found in the crystal structure of hydroxy lactone (13). In methylene lactone (10), a similar chain occurs constructed solely with weak hydrogen bonds, C6α—H···O3···H—C6β (Fig. 9). Thus, a strong C—O—H···O hydrogen bond is replaced by a weak C—H···O interaction along the *a*-axis in the two crystals. Although structural mimicry between N—H···O and C—H···O hydrogen bonds (Berkovitch-Yellin & Leiserowitz, 1984; Shimon *et al.*, 1990; Steiner *et al.*, 1995) and between O—H···Cl and C—H···Cl interactions (Davies *et al.*, 1996; James *et al.*, 1996) in crystals has been reported, a C—H···O interaction behaving as a surrogate of an O—H···O hydrogen bond is a novel occurrence (Anthony *et al.*, 1998). The significance of supramolecular synthons (Desiraju, 1995) (20) and (21) (Fig. 15) in the two structures was assessed by the formation of a binary solid solution (22).

Recrystallization of a 1:1 mixture of (13) and (10) from a solution of EtOAc–MeOH afforded crystals of (22) in space group $P2_1$ with cell dimensions very close to that of hydroxy lactone (13). Structure solution and refinement with a partial positional occupancy of O6 yielded a converged model with s.o.f. = 0.720 (6) for O6 and 0.28 for C6—H, that is binary solid solution (22) of (13) and (10) (Table 1). The presence of these two components in the binary crystals was established by IR and their ratio determined to be in the range 7:3–6:4 by ^{1}H NMR integration on individual crystals. The preponderance of hydroxy lactone (13) compared with methylene lactone (10) in solid solution (22) is the result of two concerted effects: the larger size of the O—H group compared with the H atom (Kitaigorodskii, 1973) and the greater strength of O—H···O compared with the C—H···O hydrogen bond (Jeffrey & Saenger, 1991). Solid solution formation is the most stringent criterion for isostructurality and occurs here because the structure-determining domains, the supramolecular synthons (20) and (21), are similar in the two crystals. Such an equivalence in crystals has been termed 'one-dimensional isostructurality' (Anthony *et al.*, 1998).

The above example of one-dimensional isostructurality *and* binary solid-solution formation is significant. While mimicry between strong and weak hydrogen bonds (N—H···O/C—H···O and O—H···Cl/C—H···Cl) has been noted earlier, no solid solution crystals are reported for these cases. On the other hand, steroid binary crystals are well known, but the mimicry of intermolecular interactions in such pairs of structures has not been examined. The present case of oxa-steroids (13) and (10) is unprecedented in that not only do these structures exhibit O—H···O/C—H···O interaction mimicry, but furthermore they form binary crystals (22). The basis for solid-solution formation between two not so similar crystal structures is the invariant, topologically equivalent hydrogen-bond chain in synthons (20) and (21). This shows that isostructurality parameters Π and $I_i(n)$, together with the concept of supramolecular synthons, may be used to compare less similar crystal structures, thereby expanding the scope and application of these terms.[5]

[5] Traditionally, isostructurality and solid solutions have been examined for structures with very close unit-cell parameters and in such cases binary crystals are formed over a continuous range of stoichiometry (Kitaigorodskii, 1984). The present system is different in that the solid solution occurs even though the cell axes and structures of the components are ony approximately similar. Instead of introducing a new term, existing definitions of isostructurality and solid solution have been adapted to describe this related phenomenon.

Analysis of steroids in the CSD furnished two pregnanes, (23) (HMERPG) and (24) (HPRGDP; Fig. 16), which also exhibit similarity in their hydrogen-bonding pattern in one dimension. The hydrogen-bonded chains in (23) and (24) are parallel to the *c* axis and it is of note that the metrics of *c* axes in these structures (6.450 and 6.162 Å) are close to the *a* axes in (10) and (13). In the pregnane pair of crystals, a CH_3 group behaves as a surrogate of the OH group and this represents another example of O—H···O/C—H···O interaction mimicry.

The interesting results on one-dimensional isostructurality prompted us to search for related examples of two-dimensional and three-dimensional isostructurality. Although the C6-hydroxy oxa-steroid (15) was found to be different from its methylene analogue (12), the structure of (15) is similar to Anavar® (3) in the (110) layer. In both these structures the molecules pack in a head-to-tail fashion connected through O17—H···O3 hydrogen bonds. In (15) the chains are interlinked through a O6—H···O17 hydrogen bond, while in (3) an equivalent C6—H···O17 interaction is present (Fig. 17). The steroid sapogenin hydrate polymorphs reported recently (Fábián *et al.*, 1999) have identical symmetry-independent hydrogen-bond layers and exhibit the phenomenon of two-dimensional isostructurality. Androst-4-ene-3,17-dione (18) (ANDSEO) is a natural substrate for aromatase (Cole & Robinson, 1990) and androst-4-ene-3,6,17-trione (25) is a potent inhibitor of the same enzyme (Numazawa & Tachibana, 1994). Both these steroids compete for the receptor active site and so their crystal structures were compared (Anthony *et al.*, 1999). The conformation of the two steroids are similar with an r.m.s. deviation of 0.090 Å, unit-cell similarity index Π of 0.0015 and isostructurality index $I_i(17)$ of 93.2%. The intermolecular interactions in the two structures are identical and the additional C6-carbonyl in androstenetrione does not change the arrangement of molecules and the hydrogen bonding in the crystal. The hydrogen bonds formed by O3 and O17 acceptor atoms extend in three dimensions (Fig. 18). A possible reason for the similarity in the two structures could be that O6 is buried in the central portion of the molecule and is unable to perturb the crystal structure.

In summary, isostructurality in steroids has been analysed at increasing levels of detail. Two pairs of steroids show one-dimensional isostructurality and O—H···O/C—H···O interaction mimicry, while different pairs of steroids exhibit two-dimensional and three-dimensional isostructurality. In these examples, the value of $I_i(n)$ increases as the dimensionality of isostructurality increases. It may be noted that although similarities between nearly equivalent crystal structures have been studied (Kálmán & Párkányi, 1997), comparisons between not so closely related structures can be accomplished in limited domains of chains and layers by the identification of robust supramolecular synthons (Nangia & Desiraju, 1998).

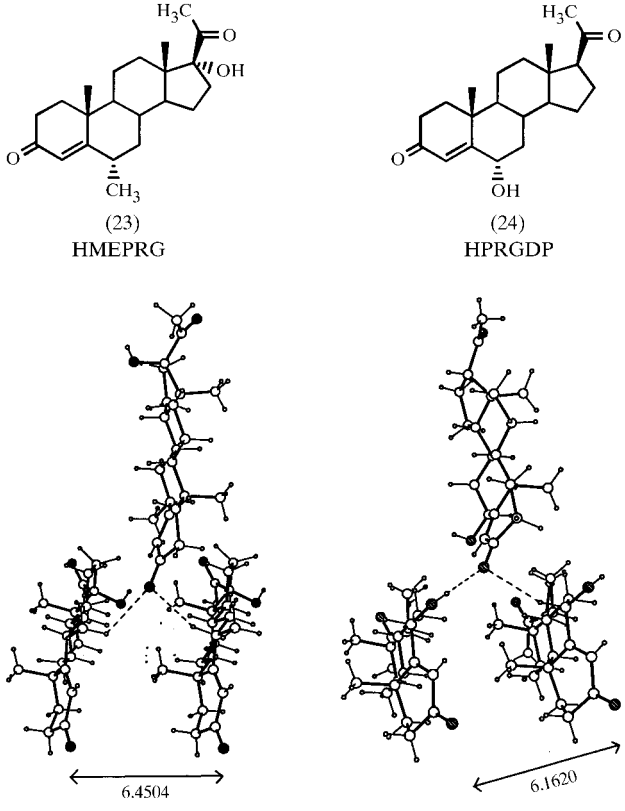


Figure 16
Pregnanes retrieved from the CSD that exhibit one-dimensional isostructurality by the replacement of C6—OH with the CH_3 group.

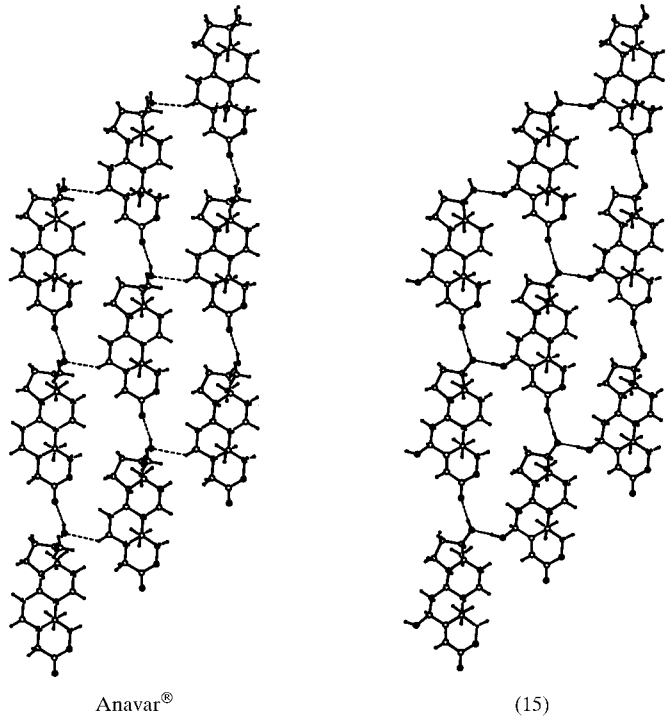


Figure 17
Similarity in the (110) layer structure of Anavar® (3) and oxa-steroid (15). Notice the common O17—H···O3 hydrogen bond in the two structures and the mimicry between O6—H···O17 and C6—H···O17 interactions.

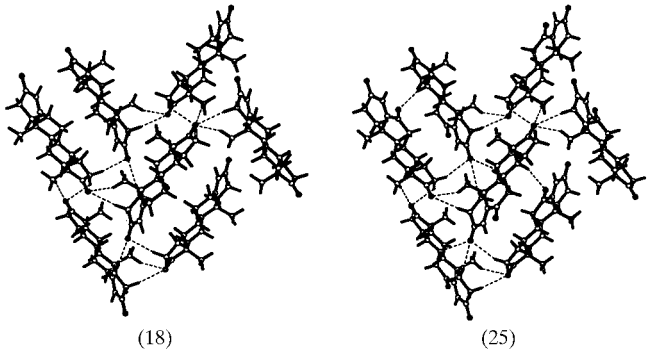


Figure 18
Three-dimensional isostructurality in the crystal structures of the substrate (18) and inhibitor (25) of aromatase.

4. Conclusions

Some selected 2-oxa-steroids have been synthesized and their packing characteristics examined. The analysis of hydrogen bonding and conformations in the crystal structures of six lactone steroid analogues is a significant advancement compared with the sole example, Anavar®, reported in the literature at the beginning of this study. A common motif observed in steroid crystal structures is the head-to-tail arrangement of molecules mediated through O—H···O hydrogen bonds, and this is also found in the 2-oxa-steroids. In the absence of strong donors, however, the weak C—H···O hydrogen bonds take the lead in stabilizing the oxa-steroid crystal structures. The replacement of the C2-methylene group by an O-atom changes the *A*-ring conformation and the hydrogen-bond donor/acceptor ratio and preferences, leading to differences in crystal packing in the oxa-analogues compared with the natural steroids. The analysis of intermolecular interactions in these structures shows that the robust supramolecular synthons are similar, as exemplified by the pairs of lactones that exhibit one- and two-dimensional isostructurality.

The approach geometries of hydrogen-bonding donor and acceptor groups in crystal structures parallel those found in ligand–receptor macromolecular complexes (Klebe, 1994). Therefore, this study on the conformation and hydrogen bonding in 2-oxa-steroids and the striking example of three-dimensional isostructurality should be meaningful inputs for structure-based drug design.

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