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6-[3-Hydroxy-17-oxoestra-1,3,5(10)-trien-7β-yl]hexanenitrile

Chishou Yamamoto,[a] Taisuke Matsumoto,[b] Masataka Watanabe,[a] Eckhard M. S. Hitzer,[c] Shuntaro Mataka[b] and Thies Thiemann[b]*

[a]Interdisciplinary Graduate School of Engineering, Kyushu University, 6-1 Kasuga-koh-en, Kasuga-shi, Fukuoka 816-8580, Japan, [b]Institute of Materials Chemistry and Engineering, Kyushu University, 6-1 Kasuga-koh-en, Kasuga-shi, Fukuoka 816-8580, Japan, and [c]Department of Mechanical Engineering, Fukui University, 3-9-1 Bunkyo, Fukui-shi, Fukui 910-8507, Japan
Correspondence e-mail: thies@cm.kyushu-u.ac.jp

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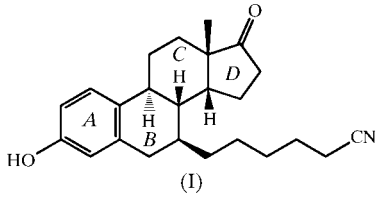
In the title compound, $C_{24}H_{31}NO_2$, ring *B* adopts a conformation between the boat and twisted-boat forms. This conformation best accommodates adverse intramolecular H$\cdots$H interactions between the H atoms of the 7β-substituent and the two nearest ring H atoms. The tilt angle between rings *A* and *D* is 28.6 (1)°.

Comment

Recently, synthetic steroids have been proposed as radiodiagnostic compounds (Katzenellenbogen, 1995; Melo e Silva *et al.*, 2001; Wang *et al.*, 2003), as well as potential drug delivery systems targeting oestrogen receptor positive breast cancer and other diseases associated with the oestrogen receptor ERα. Mandatory for the success of these compounds is a good binding affinity to the receptor. It has been determined that a C7 substituent carrying a long chain with a polar terminus often influences the binding affinity, where the commonly synthesized 7α-substituted estrane-derived steroids have a much better binding affinity than the corresponding 7β-epimers. The authors have studied the binding affinity to the oestrogen receptor of C7-substituted estra-1,3,5(10),6-tetraenes, *i.e.* compounds analogous to those described above, but



(I)

with the C7 substituent branching off from an sp^2-hybridized C atom (Inohae *et al.*, 1999; Thiemann *et al.*, 2002). It was deemed advantageous to prepare the 7β-substituted compounds in order to compare the binding affinity and *in vivo* biodistribution of a series of 7α- and 7β-substituted oestranes and of the corresponding 7-substituted estra-1,3,5(10),6-tetraenes. The measurement of the X-ray crystal structure of the title compound, (I), was carried out in order to better model the complex of a 7β-substituted steroidal ligand and the binding domain of the nuclear receptor, the X-ray crystal structure of which is known.

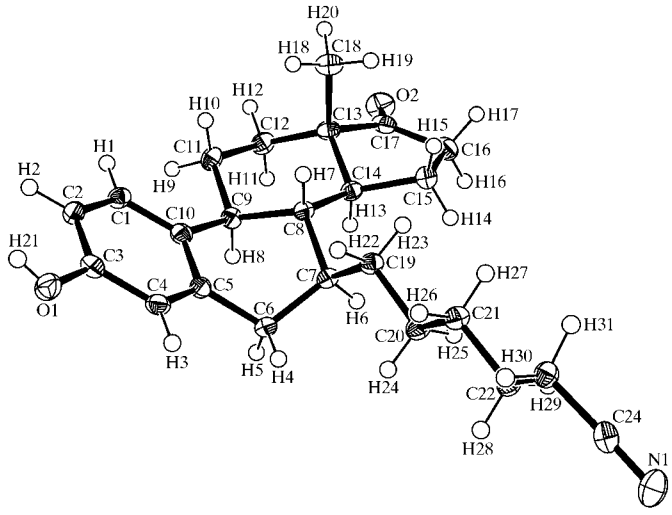


Figure 1
A view of the molecule of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

The molecule of (I), with the atomic numbering scheme, is depicted in Fig. 1. Ring *A* shows a little distortion from planarity [average mean plane deviation = 0.012 (2) Å], as is also evident in other estrones and estradiols for which X-ray structural analyses have been carried out. Ring *C*, with *trans* fusion to rings *B* and *D*, is fixed in a chair conformation. In estra-1,3,5(10)-trienes, ring *B*, as a cyclohexene, is known to be less rigid (Bucourt & Hainault, 1967). This is found in the three known polymorphs of estrone [estra-1,3,5(10)-trien-3-ol-17-one], where all three exhibit a slightly different conformation of ring *B*, although the α-H atom at C7 in each adopts an axial position (Busetta *et al.*, 1973, and references therein). This situation holds true for derivatives of oestrone that are unsubstituted in ring *B* and for estradiol [estra-1,3,5(10)-triene-3,17β-diol], where both X-ray crystal structure analyses and calculations (Sebag *et al.*, 2000) show that, again, the α-H atom at C7 (H6) takes an axial position.

The determining effect on the conformation of ring *B* in (I) is the 7β substituent, where potential interactions of the substituent with the C15α H atom (H14) and minor ones with the C5α and C5β H atoms (H5 and H4, respectively) force atom C7 and the C7β substituent upward, with a concomitant change in the C6—C7—C8—C9 torsion angle to −18.2 (2)°. This compares with the range of −60.9 to −70.6° measured for different estrane analogues of (I), such as for the polymorphs of estrone, epiestradiol and estradiol, and as calculated for these molecules (Kubli-Garfias, 1998). Similarly, the C5—C6—C7—C8 torsion angle here is −35.8 (2)°, compared with the range of 32.1–49.0° measured for the same estrane analogues

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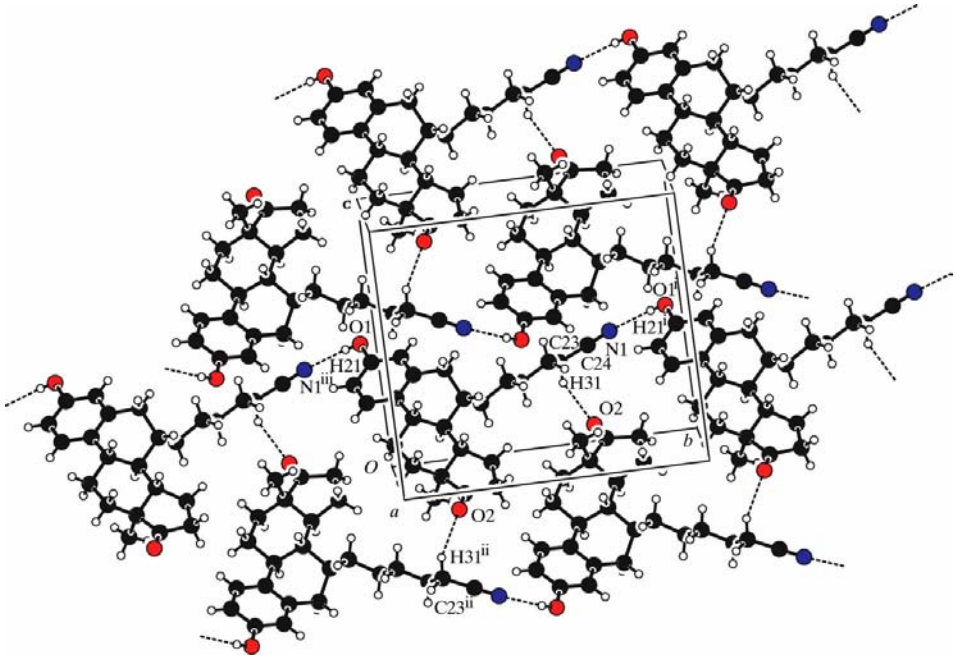

Figure 2
A view of the unit cell of (I) down the *a* axis, showing the intermolecular contacts. [Symmetry codes: (i) $x, 1+y, z$; (ii) $1-x, -\frac{1}{2}+y, -z$; (iii) $x, -1+y, z$.]

and as calculated (Kubli-Garfias, 1998). The C5—C6—C7—C19 torsion angle is 88.8 (2)°; the equivalent C5—C6—C7—H7β torsion angle in estrone is 156.9 and 166.1° for the two crystal forms, respectively (Busetta *et al.*, 1973). The intramolecular 1:4 contact distances H5···H6 (2.20 Å) and H4···H24 (2.17 Å) are short.

The conformation of ring *B* is intermediate between a boat and a twisted-boat conformation, as characterized by the Cremer & Pople (1975) puckering parameters, Q = 0.717 (3) Å, θ = 84.51 (21)° and φ = 227.8 (2)° [for a perfect boat conformation, θ = 90° and $\varphi = k \times 60°$; for a perfect twisted-boat conformation, θ = 90° and $\varphi = k \times 60° + 30°$ (Boeyens, 1978)]. This is also in accordance with the relative signs of the endocyclic torsion angles within ring *B* [see Boeyens (1978)]. In contrast with most other estrane derivatives, neither the α-H atom at C7 (H6) nor the β-H atom at C5 (H4) adopts an axial position. Importantly, this different conformation of ring *B* leads to a much larger tilt angle between ring *D* and the phenolic ring *A* than is known for estra-1,3,5(10)-trienes; for (I), the angle between the two mean planes defined by the C atoms of rings *A* and *D* is 28.6 (1)°.

The C5—C6, C7—C8 and C8—C9 bond lengths in (I) (Table 1) are significantly longer than those reported for non-substituted estrones (Busetta *et al.*, 1973; Hejaz *et al.*, 1999). The C5—C6 and C9—C10 bond lengths have comparable values or are a little shorter. In the crystal structure of (I), the C7 substituent lies above the mean plane defined by the steroidal skeleton (rings *A*, *B*, *C* and *D*, averaged over all 17 atoms of the framework), with a calculated distance from the plane of 3.862 Å for atom C24 and 3.798 Å for atom N1. The chiral centres at C7, C8, C9, C13 and C14 are *S*, *R*, *S*, *S* and *S*, respectively.

In the crystal, compound (I) packs as molecular chains along the *b* axis, bound by a strong O1—H21···N1^{i} hydrogen bond [O1···N1^{i} = 2.894 (3) Å, H21···N1^{i} = 2.07 Å, O1—H21···N1^{i} = 177°; symmetry code: (i) $x, y-1, z$] and a weaker C23—H31···O2^{ii} interaction [C23···O2^{ii} = 3.165 (3) Å, H31···O2^{ii} = 2.39 Å, C23—H31···O2^{ii} = 138 Å; symmetry code: (ii) $-x, \frac{1}{2}+y, -z$], as shown in Fig. 2.

Experimental

Compound (I) was prepared by hydrogenolysis of 3-*o*-benzyl-7-(5′-cyanopentyl)estra-1,3,5(10),6-tetraen-3-ol-17-one (Pd/C, H_2, MeOH; Thiemann *et al.*, 2004). 3-*o*-Benzyl-7α-(5′-cyanopentyl)estra-1,3,5(10),6-tetraen-3-ol-17-one was prepared from 3-*o*-benzylestra-1,3,5(10),6-trien-3-ol-6,17-dione 17,17-[2″-(5″,5″-dimethyl-1″,3″-dioxane)] by a procedure analogous to that described for 3-*o*-methylestra-1,3,5(10),6-trien-3-ol-6,17-dione 17,17-[2″-(5″,5″-dimethyl-1″,3″-dioxane)] (Inohae *et al.*, 1999; Thiemann *et al.*, 2002). The crystal used for the present X-ray structure analysis was obtained by recrystallization of (I) from dichloromethane–hexane (1:1).

Crystal data

$C_{24}H_{31}NO_2$
M_r = 365.51
Monoclinic, $P2_1$
a = 6.639 (3) Å
b = 13.530 (6) Å
c = 11.910 (5) Å
β = 107.25 (3)°
V = 1021.7 (7) Å^3
Z = 2
D_x = 1.188 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 9657 reflections
θ = 3.0–27.5°
μ = 0.07 mm^{-1}
T = 293.1 K
Needle, colourless
0.50 × 0.20 × 0.12 mm

Data collection

Rigaku R-AXIS RAPID diffractometer	2458 independent reflections
ω scans	2082 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (*ABSCOR*; Higashi, 1995)	$R_{int} = 0.034$
$T_{min} = 0.982$, $T_{max} = 0.991$	$\theta_{max} = 27.5^\circ$
20 270 measured reflections	$h = -8 \rightarrow 8$
	$k = -17 \rightarrow 17$
	$l = -15 \rightarrow 15$

Refinement

Refinement on F^2	$w = 1/[0.0003F_o^2 + \sigma(F_o^2)]/(4F_o^2)$
$R(F) = 0.035$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.082$	$\Delta\rho_{max} = 0.29$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.25$ e Å^{-3}
2441 reflections	Extinction correction: equation 22 in Larson (1970)
276 parameters	Extinction coefficient: 8.9 (5) $\times 10^2$
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

O1—C3	1.371 (3)	C7—C8	1.557 (3)
O2—C17	1.209 (3)	C7—C19	1.530 (3)
N1—C24	1.141 (3)	C8—C9	1.562 (3)
C6—C7	1.543 (3)		
C2—C1—C10	121.0 (2)	C9—C8—C7	111.6 (2)
C8—C7—C6	112.0 (2)	C11—C9—C8	113.1 (2)
C4—C5—C6—C7	−129.7 (2)	C6—C7—C8—C14	−140.4 (2)
C10—C5—C6—C7	51.6 (2)	C7—C8—C9—C10	60.3 (2)
C6—C7—C8—C9	−18.2 (2)	C14—C8—C9—C10	−175.9 (2)

The structure was solved by direct methods (Altomare *et al.*, 1999) and expanded using Fourier techniques (Beurskens *et al.*, 1999). The positional parameters of the H atoms were calculated geometrically (C—H = 0.95 Å and O—H = 0.82 Å) and refined using a riding model, with U_{iso}(H) set at 1.2U_{eq}(O, C). For geometric calculations, the program *DIHED* (Hitzer, 2003) was used. The ring-puckering analysis was carried out using *PLATON* (Spek, 2003).

Data collection: *PROCESS-AUTO* (Rigaku, 1998); cell refinement: *PROCESS-AUTO*; data reduction: *CrystalStructure* (Rigaku/MSC, 2003); program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*, 1996); molecular graphics: *ORTEP*-3 (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *CrystalStructure*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA1026). Services for accessing these data are described at the back of the journal.

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