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5α-Androst-3-en-17-one oxime

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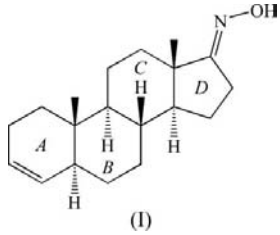
The title compound, $C_{19}H_{29}NO$, is a C17-oxime derivative of a potent aromatase inhibitor, which surprisingly has been found to have no inhibitory power. It crystallizes with two independent molecules in the asymmetric unit. C═N—O—H···N hydrogen bonds link pairs of molecules to form dimers almost parallel to the *bc* plane. Cohesion of the structure is also due to another three C—H···O hydrogen bonds directed along the *a* axis. This hydrogen-bonding scheme can be correlated to the almost complete loss of inhibitory power of the title compound.

Comment

Following on from our previous work focused on the structure–activity relationships (SAR) of new steroidal aromatase inhibitors (Cepa *et al.*, 2005), several *D*-ring derivatives of the potent aromatase inhibitor 5α-androst-3-en-17-one [structural studies by Paixão *et al.* (2001)] have been recently prepared and evaluated.

The title compound, (I) (Fig. 1), a C17-oxime derivative, has almost zero inhibitory activity. Hence, it was important, from the point of view of SAR studies, to understand this change of behaviour. X-ray studies indicate that this compound crystallizes with two independent molecules which have almost identical geometry. The internal degree of structural similarity



(I)

between the two molecules (Kálmán *et al.*, 1991) can be inferred from the values $I_D^{(24)}$ (distances) = 99.0% and $I_D^{(23)}$ (valency angles) = 99.7%. Ring bond lengths and angles are within expected values (Allen *et al.*, 1987).

Due to the C═C double bond, ring *A* adopts a conformation intermediate between 10β-sofa and 1,10-half-chair [asymmetry parameters (Duax & Norton, 1975): $\Delta C_s(3)$ = 10.9 (6) and 12.1 (5)°, $\Delta C_2(3,4)$ = 14.3 (7) and 12.4 (7)°, and $\Delta C_2(1,2)$ = 51.2 (7) and 50.2 (7)°, respectively, for molecules 1 and 2; puckering parameters (Cremer & Pople, 1975), calculated using the atom sequence from C1 through to C10: q_2 = 0.387 (5) and 0.380 (5) Å, and φ_2 = 313.1 (7) and 315.2 (8)°, respectively, for molecules 1 and 2]. Rings *B* and *C* have slightly flattened chair conformations. The five-membered ring *D* adopts a 14α-envelope conformation, slightly distorted towards 13β,14α-half-chair [pseudorotation (Altona *et al.*, 1968) and asymmetry parameters (Duax & Norton, 1975): Δ = −22.0 (5) and −23.5 (6)°, φ_m = 43.6 (2) and 43.0 (2)°, $\Delta C_s(14)$ = 6.2 (4) and 5.5 (4)°, and $\Delta C_2(13,14)$ = 13.2 (4) and 13.8 (4)°, respectively, for molecules 1 and 2]. Due to the existence of only *trans* ring junctions, both molecules in the asymmetric unit have an almost planar distribution of the ring atoms (r.m.s. deviations = 0.2466 and 0.2506, respectively, for molecules 1 and 2), with an angle between the ring planes of 44.90 (3)°.

The oxime group of both molecules lies on the plane of the *D*-ring 14α-envelope, as evidenced by the r.m.s. deviation of atoms C13–C15–C17/O1/N1 of 0.0430 and 0.0383 Å for molecules 1 and 2, respectively. Two strong O—H···N hydrogen bonds lead to a crystal packing built up of dimers, with a six-

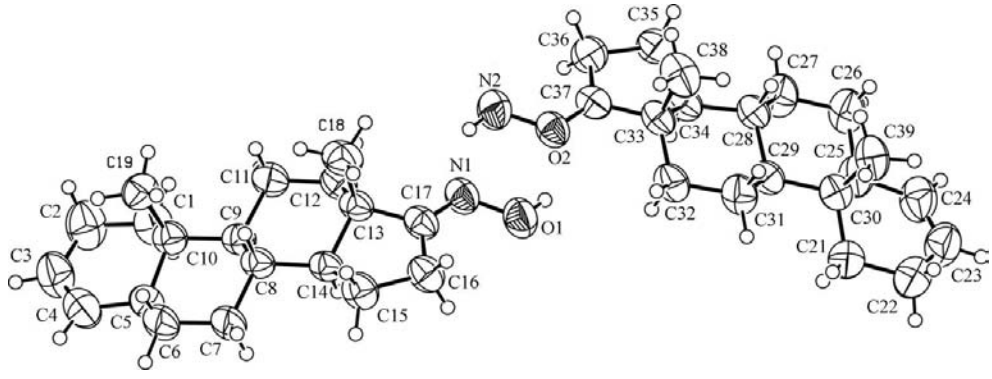


Figure 1
ORTEPII (Johnson, 1976) plot of the two molecules of the title compound. Displacement ellipsoids are drawn at the 50% probability level.

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membered O1—H1···N2—O2—H2···N1 ring (Fig. 2). These hydrogen bonds, in which the O atom acts as a donor, are almost parallel to the *c* axis. There are three additional C—H···O hydrogen bonds linking molecules along the *a* axis (Fig. 3), in which the same O atoms act as acceptors. The oxime C—N and N—O bond lengths are slightly smaller and significantly larger, respectively, than the values reported by Allen *et al.* (1987). These differences may be due to the special features of oxime groups and their involvement in hydrogen bonds. In fact, the values determined fit well with the work of Jerslev (1983), who studied the correlations between these bond lengths in several oximes.

According to his work, the values obtained in the present study imply a certain degree of conjugation between the oxime group and the *D*-ring electronic distribution. Following Bertolasi *et al.* (1982), the large values obtained for the N—O bonds can be further related to the multiple hydrogen bonds in which the oxime group participates. The hydrogen-bonding scheme determined in this study is, eventually, responsible for the almost total loss of aromatase inhibition behaviour. In fact, by replacing the C17-ketone with the C17-oxime group, the dual acceptor/donor hydrogen-bonding ability of this group can probably destabilize the structure of the receptor by hydrogen bonding to specific residues (Cepa *et al.*, 2008).

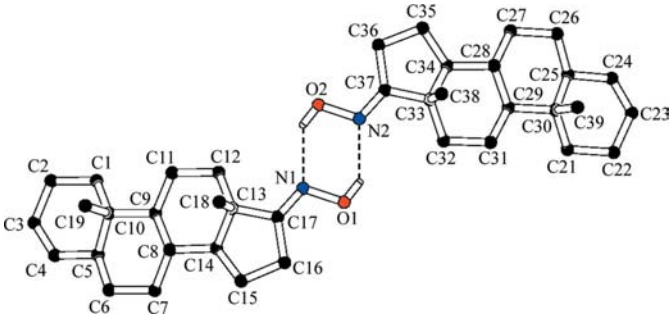

Figure 2
View of the unit cell parallel to the *bc* plane, showing the dimers and the six-membered O1—H1···N2—O2—H2···N1 hydrogen-bonded ring.

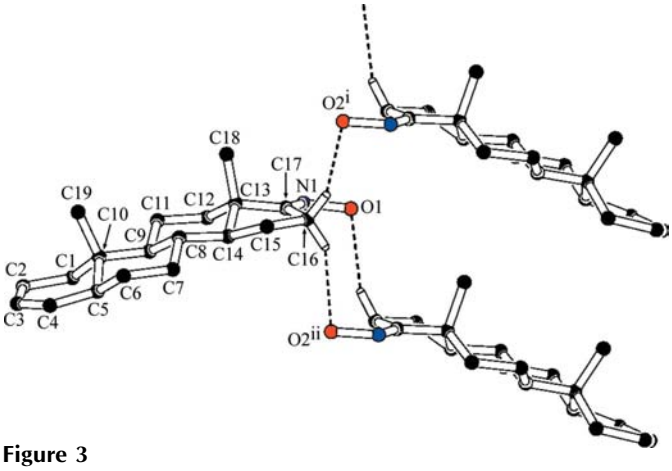

Figure 3
View of the unit cell along the *a* axis, showing the three C—H···O hydrogen bonds linking molecules. [Symmetry codes: (i) $x, y, z-1$, (iii) $x-1, y, z-1$.]

Experimental

To a solution of 5α-androst-3-en-17-one (150 mg, 0.55 mmol) in methanol (7.0 ml), hydroxylamine hydrochloride (49.2 mg, 0.7 mmol) and sodium acetate trihydrate (90 mg, 0.66 mmol) were added. The reaction was stirred at 313 K for 5 h until all the starting material had been consumed. After addition of water (50 ml), the methanol was evaporated and the aqueous phase was extracted with methylene chloride (100 ml). The organic layer was then washed with $NaHCO_3$ (10%, 2 × 50 ml), water (3 × 100 ml), dried over $MgSO_4$, filtered and evaporated to dryness, yielding 133.7 mg (84%) of the title oxime (m.p. 432–434 K). IR ν_{max}(KBr) cm^{-1}: 3281 (O—H), 3013 (C—H); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.75 (3H, *s*, 19-H$_3$), 0.82 (3H, *s*, 18-H$_3$), 5.27 (1H, *ddd*, $J_{4,3}$ = 9.5, $J_{4,5\alpha}$ = 4.5, $J_{4,2\alpha}$ = 2.5 Hz, 4-H), 5.54 (1H, *ddd*, $J_{3,4}$ = 9.5, $J_{3,2\beta}$ = 6.1, $J_{3,2\alpha}$ = 3.1 Hz, 3-H), 10.04 (1H, *s*, NOH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 11.7 (C19), 17.3 (C18), 20.2, 22.7, 23.0, 24.7, 26.8, 31.0, 33.5, 34.3, 34.5, 34.6, 43.3, 45.3 (C5), 52.9, 53.5, 125.3 (C3), 131.0 (C4), 167.9 (C17); ESI *m*/*z*: 288.2 (*M* + H, 100%).

Crystal data

$C_{19}H_{29}NO$
M_r = 287.43
Monoclinic, $P2_1$
a = 6.3510 (12) Å
b = 42.306 (6) Å
c = 7.1764 (6) Å
β = 115.651 (13)°
V = 1738.2 (5) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 0.51 mm^{-1}
T = 293 (2) K
0.48 × 0.24 × 0.24 mm

Data collection

Enraf–Nonius MACH-3 diffractometer
3820 measured reflections
3472 independent reflections
2868 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
3 standard reflections
frequency: 240 min
intensity decay: 4.8%

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.133
S = 1.08
3472 reflections
386 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.13 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N2	0.82	2.11	2.805 (4)	142
O2—H2···N1	0.82	2.13	2.815 (3)	142
C16—H16A···O2^{i}	0.97	2.55	3.458 (4)	155
C16—H16B···O2^{ii}	0.97	2.60	3.449 (5)	147
C36—H36A···O1^{iii}	0.97	2.55	3.465 (5)	158

Symmetry codes: (i) $x, y, z-1$; (ii) $x-1, y, z-1$; (iii) $x+1, y, z+1$.

All H atoms were refined as riding on their parent atoms using *SHELXL97* (Sheldrick, 2008). The absolute configuration was not determined from the X-ray data but was known from the synthesis route. Friedel pairs were merged before refinement. The structure contains small solvent-accessible voids of 35 Å^3 (Spek, 2003). No residual density was found in these voids.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989); cell refinement: *CAD-4 Software*; data reduction: *PLATON*/*HELENA* (Spek, 2003); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97*

(Sheldrick, 2008); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3256). Services for accessing these data are described at the back of the journal.

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