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2′-Amino-3-methoxypyrimidino-[5′,4′:16,17]estra-1,3,5(10),16-tetraene

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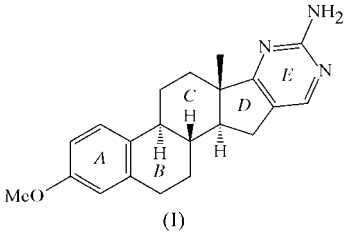
In the title compound, $C_{21}H_{25}N_3O$, the six-membered ring that is fused to two other six-membered rings in the estrane moiety adopts an envelope conformation. The compound shows intermolecular hydrogen bonding of the amine group to an N atom of the pyrimidine moiety, as well as weak intermolecular interactions involving H atoms in the hydrophobic residue of the molecule.

Comment

Over the years, several steroidal derivatives with an additional ring (*E*) fused at either the C2,3 or the C16,17 positions have been prepared (Siddiqui *et al.*, 1995; Camoutsis, 1996; Singh & Singh, 1999). These compounds exhibit a variety of biological properties, such as steroidal receptor antagonistic activity and/or anti-inflammatory activity. The title compound, (I), was synthesized in order to study the influence of ring annelation of aminopyrimidine to the estrane framework on the binding affinity to the estrogen receptor (ERα). Furthermore, a number of tripeptides have been linked to the amine group as potential ligands for 99*m*-technetium or 186-rhenium and 188-rhenium radionuclides (Matsumoto *et al.*, 2003). These compounds are to be assayed as potential radiodiagnostics, *e.g.* for minimal estrogen positive breast cancer.



(I)

In order to investigate the conformation of (I) as the steroid component of these estrane–tripeptide hybrids, an X-ray structural analysis was carried out. There is one independent molecule per asymmetric unit (Fig. 1). Ring *A* shows little distortion from planarity, as is evident in other estrones and estradiols for which X-ray crystal structural analyses have been carried out. Ring *C*, with *trans* fusion to rings *B* and *D*, has a chair conformation. As a cyclohexene, ring *B* in estranes is usually conformationally more flexible (Bucourt & Hainault, 1967; Yamamoto *et al.*, 2004). In (I), ring *B* has an envelope conformation, as characterized by the Cremer & Pople (1975) puckering parameters Q = 0.533 (2) Å, θ = 52.0 (3)° and φ = 172.1 (3)° [for a perfect envelope conformation, θ = 54.7° and $\varphi = k \times 60°$; for a perfect half-chair conformation (the next closest conformation), θ = 50.8° and $\varphi = k \times 60° + 30°$ (Boeyens, 1978)]. This configuration is also in accordance with the relative signs of the endocyclic torsion angles within ring *B* (see Boeyens, 1978).

Ring *D* has an envelope conformation [Q = 0.378 (2) Å and φ = 211.0 (3)°], with atom C14 as the flap, a pseudorotation angle Δ = 12.8 (2)° and a maximum torsion angle φ_m = 38.2 (1)° (Rao *et al.*, 1981) for the atom sequence C13–C17. The aminopyrimidine ring shows a minor distortion from planarity [C16—C19—N1···N3 = 4.7 (4)°], which may be due to the hydrogen bonding involving atom N1 and one of the H atoms on N3 (see below). While the C19—N1 [1.335 (3) Å] and C17—N2 [1.326 (3) Å] bond distances, as well as the N1—C20 [1.350 (3) Å] and N2—C20 [1.358 (3) Å] bond distances, are similar to one another and to the corresponding bond lengths found in the parent compound 2-aminopyrimidine

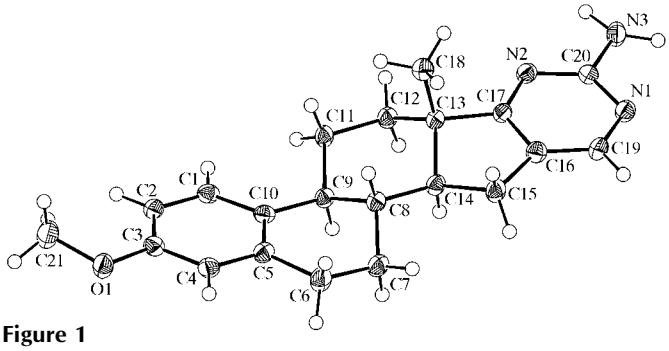


Figure 1
A view of the molecule of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

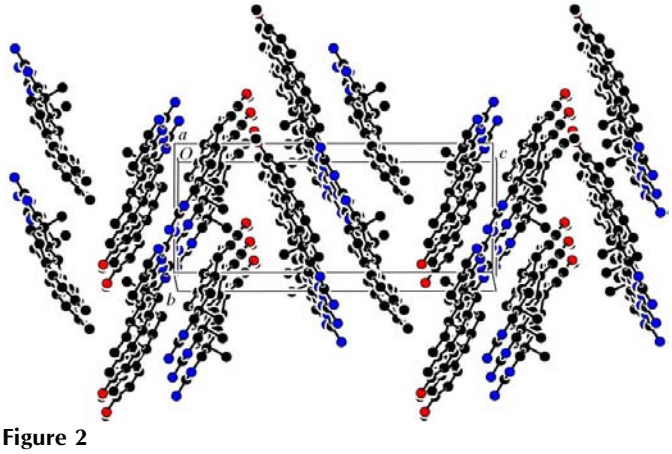


Figure 2
The unit cell of (I), viewed down the *a* axis.

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(Furberg *et al.*, 1979), the C16—C17 bond length [1.404 (3) Å] is longer than both the corresponding bond length in 2-aminopyrimidine (Furberg *et al.*, 1979) and the corresponding typical bond lengths found in 16,17-unsaturated steroids, *e.g.* in 5α-androst-16-en-3-one (1.302 Å; Cox & Turner, 1984) and in 17-(3-oxazolin-4-yl)androsta-4,16-dien-3-one (1.342 Å; Meetsma *et al.*, 1993). These differences may be rationalized by taking into account that a hydrogen bond to N1 as donor favours the iminodiazacyclohexadiene ring having a single bond at C16—C17 over other resonance forms for the aminopyrimidine unit.

In the crystal structure (Fig. 2), molecules of (I) pack in chains of two rows of molecules, where parallel chains are arranged in a stepwise fashion. Another arrangement of parallel chains, tilted by 81.02 (7)°, is also ordered in a stepwise fashion. The governing factor is the hydrogen bond formed by the amine group of the aminopyrimidine moiety with one of the pyrimidine N atoms of a neighbouring molecule. It is clear from the X-ray data that only one H atom of the amine group bound to atom C20 forms a strong hydrogen bond with one adjacent atom, namely N1 (Table 1). The N3—H25···N2^{ii} interaction is weaker, with an H25···N2 distance of 2.48 Å (Table 1).

From an AM1 calculation of the pyrimidine fragment of (I), it is evident that the electrostatic potential at atom N1 (−0.310) is higher than that at the other N atoms, especially at atom N2 (−0.273 for N2 and −0.235 for the NH_2 N atom). This result strongly suggests that any protic interaction will take place predominantly at atom N1. This fact is not only important in evaluating the crystal structure of (I), but can also be used to argue the possible conformations of (I)–tripeptide hybrids.

Experimental

Compound (I) was prepared by condensation of 3-methoxy-16-(*N*-methyl-*N*-phenylaminomethylidene)estra-1,3,5(10)-trien-17-one with guanidine hydrochoride (Matsumoto *et al.*, 2003). The crystal used for X-ray structure analysis was obtained by recrystallization of (I) from dichloromethane–ether–hexane (1:1:1). Analysis found: C 75.13, H 7.48, N 12.45%; calculated for $C_{21}H_{25}N_3O$: C 75.19, H 7.51, N 12.53%.

Crystal data

$C_{21}H_{25}N_3O$
M_r = 335.45
Orthorhombic, $P2_12_12_1$
a = 8.198 (2) Å
b = 9.303 (2) Å
c = 22.644 (5) Å
V = 1727.0 (6) Å^3
Z = 4
D_x = 1.290 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4940 reflections
θ = 3.1–27.5°
μ = 0.08 mm^{-1}
T = 123.1 K
Prism, colourless
0.12 × 0.10 × 0.08 mm

Data collection

Rigaku Saturn area-detector diffractometer
ω scans
Absorption correction: multi-scan (Jacobson, 1998)
T_{min} = 0.919, T_{max} = 0.994
14 004 measured reflections
3850 independent reflections
2690 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.038
θ_{max} = 27.5°
$h = -10 \rightarrow 8$
$k = -11 \rightarrow 10$
$l = -29 \rightarrow 29$

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H24···N1^{i}	1.00	2.05	3.019 (3)	164
N3—H25···N2^{ii}	0.94	2.48	3.409 (3)	169

Symmetry codes: (i) $x-\frac{1}{2}, \frac{3}{2}-y, -z$; (ii) $\frac{1}{2}+x, \frac{3}{2}-y, -z$.

Refinement

Refinement on F^2
$R(F)$ = 0.041
$wR(F^2)$ = 0.112
S = 1.01
3850 reflections
253 parameters
H-atom parameters constrained
$w = 1/[0.0007F_o^2 + 0.5\sigma(F_o^2)]/(4F_o^2)$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.64 e Å^{-3}
$\Delta\rho_{min}$ = −0.58 e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 107.2 (39)

All H atoms were refined as riding on their parent atoms, with U_{iso}(H) values set at 1.2U_{eq} of the parent O and C atoms. The final difference-map peak is 1.69 Å from atom H3. The absolute configuration could not be determined from the X-ray data but was known from the synthetic route.

Data collection: *CrystalClear* (Rigaku, 1999); cell refinement: *CrystalClear*; data reduction: *CrystalStructure* (Rigaku/MSC, 2004); 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: *PLATON* (Spek, 2003); software used to prepare material for publication: *CrystalStructure*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA1051). Services for accessing these data are described at the back of the journal.

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