Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

6β-Azido-7α-hydroxy-17-oxo-5α-androstan-3β-yl acetate

J. I. F. Paixão,[a] J. A. R. Salvador,[b] J. A. Paixão,[c]* A. Matos Beja,[c] M. Ramos Silva[c] and A. M. d'A. Rocha Gonsalves[a]

[a]Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, P-3004-535 Coimbra, Portugal, [b]Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, P-3000-295 Coimbra, Portugal, and [c]CEMDRX, Departamento de Física, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, P-3004-516 Coimbra, Portugal
Correspondence e-mail: jap@pollux.fis.uc.pt

Received 10 May 2004
Accepted 17 May 2004
Online 11 August 2004

In the title compound, $C_{21}H_{31}N_3O_4$, a potential inhibitor of aromatase, all rings are fused *trans*. Rings *A*, *B* and *C* have chair conformations which are slightly flattened. Ring *D* has a 14α-envelope conformation. The steroid nucleus has a small twist, as shown by the C19—C10···C13—C18 torsion angle of 6.6 (2)°. *Ab initio* calculations of the equilibrium geometry of the molecule reproduce this small twist, which appears to be due to the steric effect of the 6β-azide substituent rather than to packing effects.

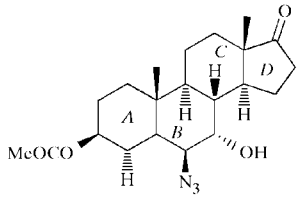
Comment

In the western world, breast cancer is the most common malignancy in women. About one third of tumours require a source of oestrogens for growth and until recently treatment was based mainly on chemotherapy, which blocks the uptake of oestrogens by the tumour cells (Miller & Ingle, 2002). Nowadays, an alternative strategy has emerged which involves the use of inhibitors of the biosynthesis of oestrogen, *i.e.* inhibitors of the aromatase enzyme. Aromatase is a cytochrome P-450 enzyme complex which catalyses the conversion of androgens into oestrogens (Thompson & Siiteri, 1974; Njar *et al.*, 1993).

The therapeutic potential of aromatase inhibitors in the treatment of oestrogen-dependent diseases has raised much interest in this area. The results of the research of many different investigators has led to the synthesis and evaluation of various steroids (Brodie & Njar, 2000). Two of these, namely formestane (Lentaron) and, more recently, exemestane (Aromasin), have already been approved for breast cancer treatment (Brueggemeier, 2002; Buzdar, 2003).

Most of the steroids which have been studied as aromatase inhibitors are analogues of androstenedione, with substituents at C4, C6, C7 and C19 (Numazawa *et al.*, 2002). Several 6- and 7-substituted analogues of androstenedione are powerful inhibitors of human placental aromatase (Njar *et al.*, 1995).

The title compound, (I), a potential aromatase inhibitor, is a very promising molecule as it combines the steric requirements that are important for the inhibition of the enzyme with the presence of three N atoms, which are thought to coordinate to the haem Fe atom of the enzyme, leading to the formation of a type II competitive inhibitor (Cole & Robinson, 1990).



(I)

A view of the molecule of (I), with the atomic numbering scheme, is shown in Fig. 1. Bond lengths and angles are within the expected ranges (Allen *et al.*, 1987), with average bond lengths (Å) $Csp^3—Csp^3$ = 1.54 (3), $Csp^3—Csp^2$ = 1.52 (2), $O—Csp^3$ = 1.449 (18), $O—Csp^2$ = 1.325 (3) and $O{=}Csp^2$ = 1.194 (10). The C15—C16 bond [1.585 (5) Å] in ring *D* is exceptionally long and a pronounced asymmetry is observed between the two $Csp^3—Csp^2$ bonds in ring *D* [C13—C17 = 1.509 (2) Å and C16—C17 = 1.554 (6) Å], and as a result this ring is considerably strained. However, the displacement tensor of atom C16 is significantly more anisotropic than those of its neighbours, and the C15—C16 and C16—C17 bond distances both fail the Hirshfeld rigid-bond test at the 5.6 and 7.2 s.u. levels, respectively. Therefore, some caution is recommended in attaching chemical significance to the deviation of these bond lengths from their average values.

All ring junctions are *trans*. Rings *A*, *B* and *C* have average torsion angles of 57.2 (7), 54.3 (3) and 56.7 (12)°, respectively, and slightly flattened chair conformations, as shown by the Cremer & Pople (1975) puckering parameters [for ring *A* (C1–C5/C10): Q = 0.587 (3) Å, θ = 1.9 (3)° and φ = 177 (8)°; for ring *B* (C5–C10): Q = 0.557 (2) Å, θ = 0.0 (2)° and φ = 257 (8)°; for

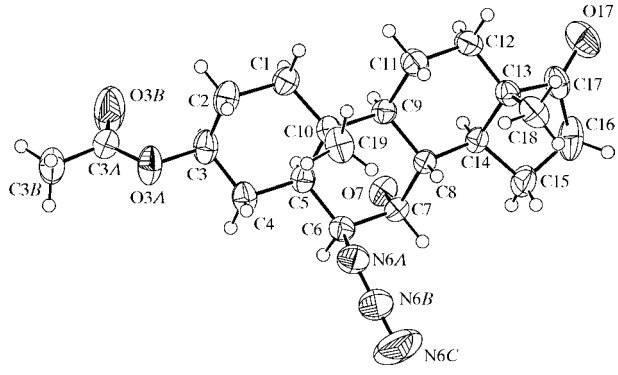


Figure 1
The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

  DOI: 10.1107/S0108270104011989

ring *C* (C8/C9/C11–C14): $Q = 0.579$ (2) Å, $\theta = 3.3$ (2)° and $\varphi = 287$ (4)°].

The five-membered ring *D* has a 14α-envelope conformation, with an average torsion angle of 32 (6)°. The puckering parameters calculated using the atom sequence C13–C17 are $q_2 = 0.439$ (3) Å and $\varphi_2 = 211.3$ (4)° [pseudorotation (Altona *et al.*, 1968) and asymmetry parameters $\Delta = 24.4$ (4), $\varphi_m = 45.0$ (1) and $\Delta C_s(14) = 5.6$ (4)°].

The acetyl substituent is 3β-equatorial to ring *A* and is (+)-anticlinal to the C2—C3 bond. The acetyl group is planar, with an average deviation of the non-H atoms from the least-squares plane of 0.005 (3) Å. The angle between this plane and the least-squares plane of ring *A* is 65.31 (15)°. The 6β-azide group is oriented axially to ring *B* and is (+)-antiperiplanar to the C5—C6 bond. It features a small but significant asymmetry between the two N⋯N bonds [1.215 (4) and 1.132 (5) Å].

The distance between the terminal atoms O17⋯C3*B* is 13.124 (4) Å and the pseudo-torsion angle C19—C10⋯C13—C18 is 6.6 (2)°, showing that the molecule is slightly twisted. For *trans*-fused saturated rings, this torsion angle rarely exceeds 4°, except when bulky sustituents, *e.g.* attached to ring *D* at C17, induce larger deviations due to steric effects (Andrade *et al.*, 2001).

In order to investigate whether this twist is indeed due to a steric effect of the azide group that would be present in the isolated molecule or is rather due to packing effects, we have performed an *ab initio* molecular orbital Roothaan Hartree–Fock (MO–RHF) calculation of the equilibrium molecular geometry using the computer program *GAMESS* (Schmidt *et al.*, 1993). An extended 6-31G(*d*,*p*) basis set was used and tight conditions were applied for convergence of the self-consistent field (SCF) cycles and location of the equilibrium geometry. The final electron-density variation at the end of the SCF cycles and the maximum energy gradient at the end of the geometry optimization were less than 10^{-5} atomic units. The code was run in parallel on a cluster of 12 Compac XP1000 workstations (Alpha EV67 processors, 667 MHz) running Linux.

The conformation of the steroid nucleus as determined from the X-ray data is well reproduced by the MO–RHF calculations, the mean deviations of the bond lengths and angles being 0.011 Å and 0.64°, respectively. However, the calculation does not reproduce the exceptionally long C15—C16 bond [calculated 1.543 Å, observed 1.585 (5) Å] and also predicts a longer O3*A*—C3 bond (calculated 1.467 Å, observed 1.430 Å). The small asymmetry between the two N⋯N bonds is well reproduced in the calculations (calculated 1.103 and 1.226 Å).

The conformations of the acetyl and azide susbtituents, which have some rotational freedom around the O3*A*—C3 and C6—N6*A* single bonds, are similar in the isolated molecule and in the crystal. The calculated values of the C3*A*—O3*A*—C3—C2 and C5—C6—N6*A*—N6*B* torsion angles for the isolated molecule are 84.2 and 145.7°, respectively, compared with the measured values of 94.2 (3) and 168.1 (3)°.

It was found that the equilibrium geometry of the isolated molecule also features a sizable twist of the steroid nucleus, as measured by the pseudo-torsion angle C19—C10⋯C13—C18 of 6.1° [experimental value of 6.6 (2)°]. Therefore, we can conclude that this twist is most probably due to a steric interaction between the C19-methyl and azide groups, rather than to packing effects in the crystal structure.

The molecules of (I) are joined together in chains parallel to the *b* axis *via* strong hydrogen bonds between the hydroxyl group and carbonyl atom O17. In addition, an inspection of the short contact distances shows that a weak intermolecular interaction appears to exist between the terminal N atom of the azide group and one methylenic H atom of a neighbouring molecule.

Experimental

6,7α-Epoxy-17-oxo-5α-androstan-3β-yl acetate, prepared according to procedures to be described elsewhere, was treated with activated sodium azide and sulfuric acid in dimethyl sulfoxide to afford compound (I). Crystals of (I) (m.p. 501 K) were obtained by crystallization from ethyl acetate–*n*-hexane (1:2). Spectroscopic analysis, IR (ν, cm^{-1}): 1257, 1728, 2098, 2924, 3508; ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 0.89 (*s*, 18-H3), 1.00 (*s*, 19-H3), 3.50 (*m*, 6α-H), 3.90 (*m*, 7β-H), 4.75 (*m*, 3α-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 67.82 (C6), 68.62 (C7), 73.46 (C3), 170.98 (CH_3CO), 221.14 (C17).

Crystal data

$C_{21}H_{31}N_3O_4$
$M_r = 389.49$
Monoclinic, $P2_1$
$a = 6.1997$ (6) Å
$b = 10.6324$ (12) Å
$c = 15.8948$ (14) Å
$\beta = 97.145$ (7)°
$V = 1039.61$ (18) Å^3
$Z = 2$
$D_x = 1.244$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 8.1$–16.8°
$\mu = 0.09$ mm^{-1}
$T = 293$ (2) K
Block, colourless
0.28 × 0.25 × 0.20 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Profile data from $\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.941$, $T_{max} = 0.988$
9496 measured reflections
3178 independent reflections
2431 reflections with $I > 2\sigma(I)$
$R_{int} = 0.031$
$\theta_{max} = 30.0°$
$h = -8 \rightarrow 8$
$k = -13 \rightarrow 14$
$l = -22 \rightarrow 22$
3 standard reflections
frequency: 180 min
intensity decay: 1.9%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.047$
$wR(F^2) = 0.148$
$S = 1.02$
3178 reflections
257 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0957P)^2 + 0.1023P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.47$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}

Table 1
Selected interatomic distances (Å).

O3*A*—C3	1.467 (3)	C13—C17	1.509 (3)
N6*A*—N6*B*	1.215 (4)	C15—C16	1.581 (5)
N6*A*—C6	1.488 (3)	C16—C17	1.554 (6)
N6*B*—N6*C*	1.132 (5)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O7—H7A···O17^{i}	0.82	2.02	2.825 (3)	166
C3B—H3B3···N6C^{ii}	0.96	2.56	3.405 (6)	147

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

All H atoms were refined as riding on their parent atoms, with C—H distances in the range 0.93–0.98 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl groups and $1.2U_{eq}(C)$ for the other H atoms, except for the H atom of the hydroxyl group, for which the torsion angle was refined using the *SHELXL*97 AFIX 147 instruction. The absolute configuration was not determined from the X-ray data as the Flack (1983) parameter of −0.5 (16) was inconclusive, but the absolute configuration was known from the synthesis route. Due to the lack of any significant anomalous scattering at the Mo $K\alpha$ wavelength, Friedel pairs were merged before refinement.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

The authors gratefully acknowledge computing time provided by the Computational Physics Centre of the FCTUC at the Centopeia parallel cluster, and Dr Fernando Nogueira for his help in setting up the parallel version of *GAMESS*. This work was supported by Fundação para a Ciência e Tecnologia.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1730). Services for accessing these data are described at the back of the journal.

References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.
Altona, C., Geise, H. J. & Romers, C. (1968). *Tetrahedron*, **24**, 13–32.
Andrade, L. C. R., Paixão, J. A., de Almeida, M. J. M., Martins, R. M. L. M., Soares, H. I. M., Morais, G. J. R., Moreno, M. J. S. M., Sá e Melo, M. L. & Campos Neves, A. S. (2001). *Acta Cryst.* C**57**, 587–589.
Brodie, A. M. H. & Njar, V. C. O. (2000). *Steroids*, **65**, 171–179.
Brueggemeier, R. W. (2002). *Breast Cancer Res. Treat.* **74**, 177–185.
Buzdar, A. U. (2003). *Clin. Cancer. Res.* **9**, 4360–4368.
Cole, P. A. & Robinson, C. H. (1990). *J. Med. Chem.* **33**, 2933–2942.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Enraf–Nonius (1989). *CAD*-4 *Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Miller, W. R. & Ingle, J. N. (2002). Editors. *Endocrine Therapy in Breast Cancer*. New York: Marcel Dekker Inc.
Njar, V. C. O., Hartmann, R. W. & Robinson, C. H. (1995). *J. Chem. Soc. Perkin Trans.* 1, pp. 985–991.
Njar, V. C. O., Safi, E., Silverton, J. V. & Robinson, C. H. (1993). *J. Chem. Soc. Perkin Trans.* 1, pp. 1161–1168.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Numazawa, M., Yamada, K., Watari, Y. & Ando, M. (2002). *Chem. Pharm. Bull.* **50**, 703–705.
Schmidt, M. W., Baldrige, K. K., Boatz, J. A., Elbert, S. T., Gordon, M. S., Jensen, J. J., Koseki, S., Matsunaga, N., Nguyen, K. A., Su, S., Windus, T. L., Dupuis, M. & Montgomery, J. A. (1993). *J. Comput. Chem.* **14**, 1347–1363.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (1997). *HELENA*. University of Utrecht, The Netherlands.
Thompson, E. A. Jr & Siiteri, P. K. (1974). *J. Biol. Chem.* **249**, 5373–5378.