Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Steroid 19,*B*-dinor-8,10-iso-analogues

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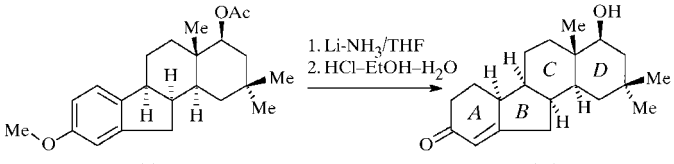
Received 19 November 2001
Accepted 17 January 2002
Online 20 February 2002

The Birch reduction of 3-methoxy-*B*-nor-8-isoestra-1,3,5(10)-trienes followed by acid hydrolysis produces steroid androgen 19,*B*-dinor-8,10-iso-analogues. By means of X-ray analysis and correlation NMR spectroscopy of 16,16-dimethyl-*D*-homo-19,*B*-dinor-8-isotestosterone, $C_{20}H_{30}O_2$, it is demonstrated that the main conformations in the crystal and in solution for two 19,*B*-dinor-8,10-iso-analogues are, in general, the same.

Comment

Steroid estrogen *B*-nor-8-iso-analogues are known to have more favourable biological properties than the natural hormones (Georgian & Pfeiffer, 1970). Similar androgen steroids have remained practically uninvestigated. The Birch reduction of 17β-hydroxy-18-methyl-3-methoxy-*B*-nor-8-isoestra-1,3,5(10)-triene and subsequent acid hydrolysis were reported to give only 16,16-dimethyl-*D*-homo-19,*B*-dinor-8-isotestosterone, (II), whose structure has been reported previously by Rao *et al.* (1977), but which has not been strictly established. The object of the present investigation is the determination of the configuration at C10, since this is critical for revealing structure–activity relationships.



(I) (II)

We decided to carry out the Birch reduction (see *Scheme* above) of 17aβ-acetoxy-16,16-dimethyl-3-methoxy-*D*-homo-*B*-nor-8-isoestra-1,3,5(10)-triene, (I), because, according to our data, it does not have any uterotropic activity at doses up to 100 mg kg^{-1} of body weight per day. The oestrogen- and androgen-receptor hormone-binding domains being similar (Ekena *et al.*, 1998), we expect that the final androgen analogue, (II), will not have hormonal activity, and it will be possible to evaluate the convenience of such compounds for the realisation of non-genomic mechanisms of action.

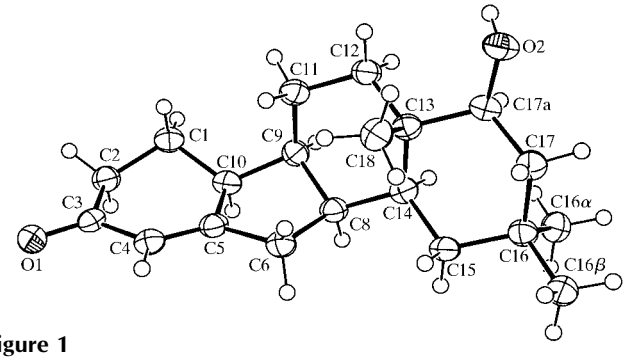


Figure 1
The all-*S* enantiomer of (II) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

The synthesis of (II) has been described previously by Egorov *et al.* (2001). By means of the present X-ray analysis, the conformation and relative stereochemistry in racemic (II) have been determined (Fig. 1).

Ring *B* is a 9β-envelope, and the angle between the C5/C6/C8/C10 and C8/C9/C10 planes is 39.7°. Ring *A* is a half-chair, and the angle between the C2/C3/C4/C5/C10 and C1/C2/C10 planes is 48.4°. Atoms H1β and H2α are pseudo-axial. All chiral centres in the selected asymmetric unit have an *S* configuration (Fig. 1), and in the enantiomeric form, all have an *R* configuration. Rings *B* and *C* possess a *cis*-junction which causes the rings to be folded; this is usual for 8 iso-analogue molecules. The angle between the planes containing rings *A* and *B* (the angle between planes C2/C3/C4/C5/C10 and C5/C6/C8/C10 is 0.8°), and *C* and *D* (the angle between planes C9/C11/C13/C14 and C13/C14/C16/C17 is 7.7°) is 91.1°.

In the crystal structure of (II), two molecules are joined by O2—HO2···O1 hydrogen bonds, with O1···O2 = 2.829 Å, HO2···O1 = 2.030 Å and O2—HO2···O1 = 164.58°. Positional parameters, bond lengths, bond angles and torsion angles have been deposited in the Cambridge Structural Database (No. 164256; Allen & Kennard, 1993). Using correlation NMR spectroscopy, we also found that (II) in chloroform solution has the same structure as that reported by Egorov *et al.* (2001).

Atom H10 has an α orientation, contrary to the assumption of Rao *et al.* (1977), who synthesized a similar 19,*B*-dinor-analogue with a five-membered *D* ring and a methyl group at C18. We reproduced their synthesis and proved by correlation NMR spectroscopy that the orientation of H10 was α (Egorov *et al*. 2001). Our results are in agreement with data published by Banerjee *et al.* (1969) concerning an analogous synthesis and X-ray structure determination of a six-membered *B*-ring analogue of (II).

In the light of these results, we can conclude that the Birch reduction of 3-methoxy-*B*-nor-8-isoestra-1,3,5(10)-trienes followed by acid hydrolysis produces steroid androgen 19,*B*-dinor-8,10-iso-analogues, irrespective of the size and substitutions of ring *D*.

Experimental

Compound (II) was synthesized according to the method described by Egorov *et al.* (2001). Colourless crystals of (II) suitable for

  DOI: 10.1107/S0108270102001002

diffraction analysis were obtained from hexane–ethyl acetate solution by slow evaporation at room temperature.

Crystal data

$C_{20}H_{30}O_2$
M_r = 302.44
Monoclinic, $P2_1/n$
a = 6.957 (2) Å
b = 12.035 (3) Å
c = 19.950 (6) Å
β = 90.100 (6)°
V = 1670.4 (8) Å^3
Z = 4
D_x = 1.203 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 612 reflections
θ = 2.5–23.1°
μ = 0.08 mm^{-1}
T = 293 (2) K
Plate, colourless
0.4 × 0.3 × 0.1 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
φ and ω scans
7713 measured reflections
2925 independent reflections
1587 reflections with $I > 2\sigma(I)$
R_{int} = 0.047
θ_{max} = 25°
$h = -8 \rightarrow 7$
$k = -13 \rightarrow 14$
$l = -23 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.061
$wR(F^2)$ = 0.164
S = 0.91
2925 reflections
199 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0886P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

H atoms were treated as riding, with O—H = 0.82 Å and C—H = 0.93–0.98 Å, and with $U_{iso}(H) = 1.5U_{eq}$ of the parent atom.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SHELXTL* (Bruker, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1099). Services for accessing these data are described at the back of the journal.

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