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D-Secoestrone derivatives. V[1]. 3-Methoxy-17-oxo-17-phenyl-16,17-secoestra-1,3,5(10)-triene-16-nitrile and 17-hydroxy-3-methoxy-17-phenyl-16,17-secoestra-1,3,5(10)-triene-16-nitrile

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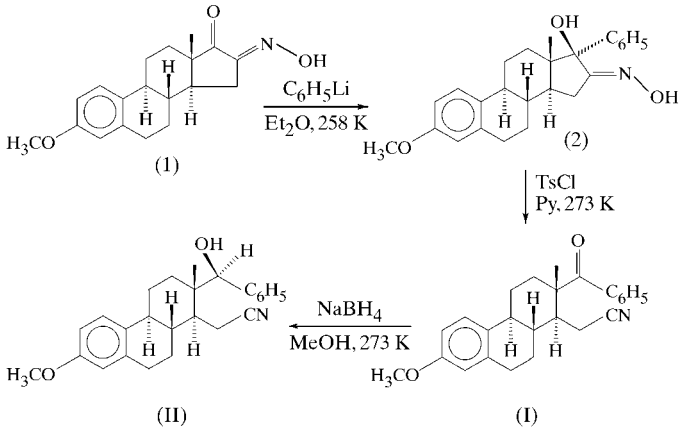
The two title 16,17-secoestrone derivatives, 3-methoxy-17-oxo-17-phenyl-16,17-secoestra-1,3,5(10)-triene-16-nitrile, $C_{25}H_{27}NO_2$, (I) (17-oxo substituent), and 17-hydroxy-3-methoxy-17-phenyl-16,17-secoestra-1,3,5(10)-triene-16-nitrile, $C_{25}H_{29}NO_2$, (II) (17-hydroxy substituent), have quite different conformations in the solid state. These conformational differences can be minimized by molecular mechanics calculations. Thus, the remarkable difference in the biological activity of the two compounds, *e.g.* the strong oestrogenic characteristics of (I) and the moderate antioestrogenic action of (II), must be caused by the difference in substitution at C17. In (II), the molecules are linked by O—H···N hydrogen bonds, forming spirals along the *b* direction.

Comment

Within the framework of a broader project aimed at obtaining potential antioestrogens, a series of new 16,17-secoestrone derivatives has been reported by Petrović *et al.* (1990). While studying the structure–activity relationships of these derivatives (Stanković, Petrović *et al.*, 1992; Stanković, Stefanović *et al.*, 1992; Stanković *et al.*, 1994), we observed that the substituent at C17 has a remarkable influence on the biological properties of the synthesized compounds. Thus, to a large extent, 3-methoxy-17-hydroxy-17-methyl-16,17-secoestra-1,3,5(10)-triene-16-nitrile retained oestrogenic characteristics, while the corresponding 17-benzyl derivative showed a complete loss of oestrogenic activity, exhibiting a moderate antioestrogenic action (Medić-Mijačević, 1992).

[1] Part IV: Stanković *et al.* (1998).

With the aim of further investigations into the influence of C17 substituents on biological activity, the two new title 16,17-secoestrone derivatives, (I) and (II), were prepared. Since the starting materials were synthesized from natural oestrone, the absolute stereochemistry of which is known (Fieser & Fieser, 1967), the X-ray structures of (I) and (II) are described for the appropriate enantiomer.



Perspective views of the molecules of (I) and (II) are shown in Figs. 1 and 2. During the anisotropic refinement, it became evident from the displacement parameters of compound (I) that the phenyl ring is disordered; the phenyl-ring atoms exibit large thermal displacements which are almost parallel with the plane containing them. The model that describes this disorder has at least two phenyl rings, denoted *A* and *B*. Since the phenyl-ring plane practically coincides with the plane containing the C13—C17 and C17—C20 bonds, as seen from the C13—C17—C20*A*/*B*—C25*A*/*B* torsion angles (Table 1), these thermal displacements cause deformation of the C13—C17—C20*A*/*B* angles (Table 1), which is significant for conformer *A*.

Molecular mechanics calculations (MMC) using *PC-MODEL* (Serena Software, 1989) were also performed to define the conformation of the molecules in terms of energy minima. It was found that the molecule of (I) with an unsplit

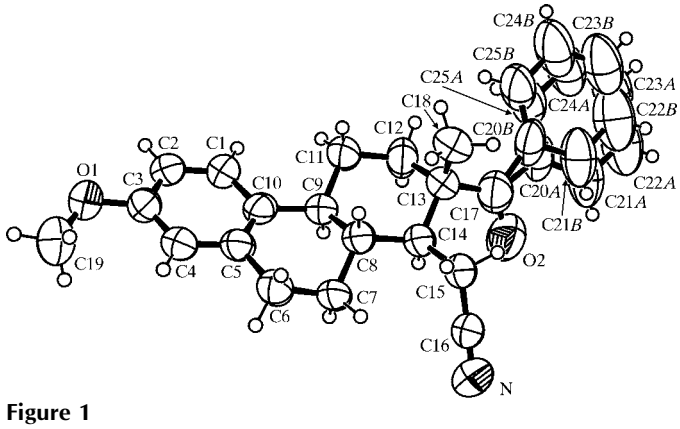


Figure 1
A perspective view of (I) with the atomic labelling scheme. Displacement ellipsoids are shown at the 30% probability level and H atoms are drawn as spheres of arbitrary radii. The disordered phenyl ring is represented by two subgroups, C20*A*–C25*A* and C20*B*–C25*B*. The site-occupancy factor of subgroup *A* is 0.287 (6) and that of subgroup *B* 0.713 (6).

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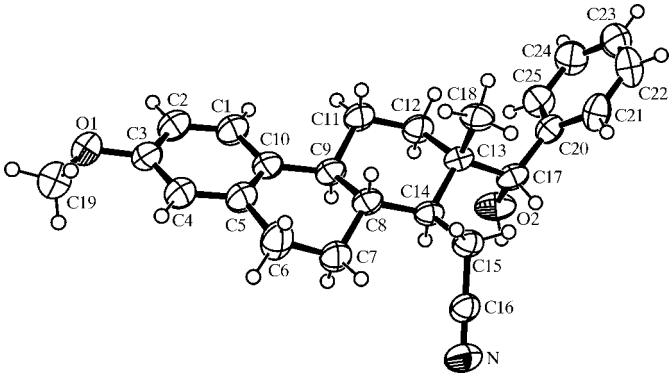

Figure 2
A perspective view of (II) with the atomic labelling scheme. Displacement ellipsoids are shown at the 30% probability level and H atoms are drawn as spheres of arbitrary radii.

phenyl ring has an energy minimum conformation with respect to the molecule with disordered phenyl rings, so this model was used for MMC in the ring-conformation and molecular-energy analysis.

Ring puckering parameters (Cremer & Pople, 1975) and asymmetry parameters (Duax *et al.*, 1976) define the ring conformations for both (I) and (II). Steroid ring *B* exhibits a 7α,8β-half chair conformation ($^3H_4$) in both molecules, which is slightly distorted towards a 7α-envelope (^3E) after MMC. Steroid ring *C* has an almost ideal 8β,12α-chair conformation in (I), but it is significantly distorted in (II). After MMC, the conformation of ring *C* in (I) also became significantly distorted and similar to (II). The orientation of the phenyl ring, defined by the C14—C13—C17—C20 and C13—C17—C20—C25 torsion angles, was also changed, by about 26 and −75°, respectively. Rotation of the phenyl ring about the C17—C20 bond in the rigid-rotor approximation confirmed that, in the crystalline state, molecule (I) is in a shallow minimum, significantly removed from the absolute minimum. The orientation of atom O2 was also changed by about 10°, going from synperiplanar to synclinal in relation to atom C14. Since the conformations of the molecules became similar after MMC (Fig. 3), the difference in biological activity can be interpreted as being due to the different substituents at C17, as well as the fact that, in (II), a new chiral centre has been introduced.

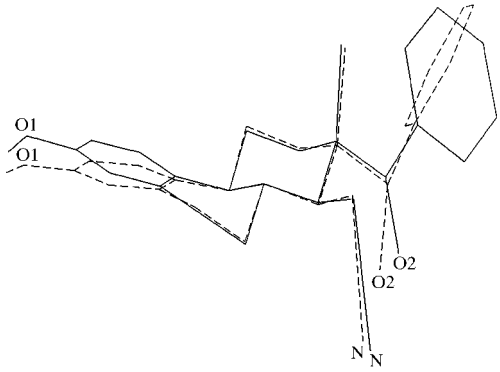

Figure 3
The superimposed fit for the energy minimized molecular structures of (I) (solid lines) and (II) (dashed lines).

In compound (II), there is a short intramolecular contact of 1.96 Å between H17 and H151, which is much shorter than the van der Waals sum of 2.4 Å. However, the corresponding value of 2.04 Å in the energy-minimized structure suggests that this shortness is simply a consequence of the minimum energy conformation of the molecule.

Also in compound (II), there is an O—H···N hydrogen bond (Table 3). In (I), there are only van der Waals separations between molecules. The non-bonded intramolecular O1···O2 distances, which could be responsible for biological activity, are shorter than the corresponding distance of 10.9 Å found in oestradiol (Fullerton, 1977; Duax *et al.*, 1977).

Experimental

The starting material was 3-methoxy-1,3,5(10)-triene-16,17-dione 16-oxime, (1), which was prepared from oestrone using the procedure of Miljković & Petrović (1977). Addition of phenyllithium to the C17 carbonyl function of (1) led to the formation of 3-methoxy-17α-phenyl-17β-hydroxyestra-1,3,5(10)-triene-16-one oxime, (2), in a 69.64% yield. The action of *p*-toluenesulfonyl chloride on (2) in dry pyridine resulted in a Beckmann fragmentation reaction and the formation of the 16,17-seco derivative, (I), in high yield. Finally, sodium borohydride reduction of (I) afforded (II) as the sole product.

Compound (I)

Crystal data

$C_{25}H_{27}NO_2$
M_r = 373.48
Monoclinic, $P2_1$
a = 8.1540 (10) Å
b = 8.602 (3) Å
c = 15.005 (4) Å
β = 102.47 (2)°
V = 1027.6 (5) Å^3
Z = 2
D_x = 1.207 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 10–20°
μ = 0.59 mm^{-1}
T = 293 (2) K
Prism, colourless
0.45 × 0.08 × 0.03 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω/θ scans
1616 measured reflections
1616 independent reflections
978 reflections with $I > 2\sigma(I)$
θ_{max} = 59.9°
$h = -9 \rightarrow 8$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 16$
3 standard reflections
frequency: 180 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.061
$wR(F^2)$ = 0.150
S = 1.18
1616 reflections
251 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0443P)^2 + 0.3945P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.007
$\Delta\rho_{max}$ = 0.11 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

Table 1
Selected interatomic distance (Å, °) for (I).

O1···O2	10.368 (1)		
C20*A*—C17—C13	137 (2)	C13—C17—C20B	118.4 (10)
C13—C17—C20*A*—C25*A*	−11 (3)	C13—C17—C20*B*—C25*B*	−8.6 (13)

Table 2
Selected interatomic distance (Å) for (II).

O1···O2	10.119 (2)

Table 3
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O2—H1O2···N^{i}	0.82	2.01	2.829 (3)	171

Symmetry code: (i) $-x, y-\frac{1}{2}, 2-z$.

Compound (II)

Crystal data

$C_{25}H_{29}NO_2$
M_r = 375.49
Monoclinic, $P2_1$
a = 9.8063 (5) Å
b = 6.697 (1) Å
c = 16.201 (1) Å
β = 101.455 (5)°
V = 1042.8 (2) Å^3
Z = 2
D_x = 1.196 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 22.0–30.5°
μ = 0.58 mm^{-1}
T = 293 (2) K
Prism, colourless
0.38 × 0.18 × 0.15 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω/θ scans
2305 measured reflections
2305 independent reflections
2134 reflections with $I > 2\sigma(I)$
θ_{max} = 74°
$h = -12 \rightarrow 11$
$k = 0 \rightarrow 8$
$l = 0 \rightarrow 20$
3 standard reflections
frequency: 120 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.100
S = 0.96
2305 reflections
257 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0520P)^2 + 0.2489P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.12 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

The crystals of (I) were very thin and their diffracting power very low, so the data collection was stopped at θ = 59.93°. For this reason, the calculated $\sin(\theta_{max})$/wavelength (0.561) is less than the required value of 0.575, and the required ratio of reflections to parameters of 8 has not been satisfied either (6.11). The H atoms were generated and refined as riding, with isotropic displacement parameters fixed at $1.2U_{eq}$ or $1.3U_{eq}$ of the parent atoms, or $1.5U_{eq}$ for the methyl-H atoms. Refinement of the Flack (1983) parameter was not successful for either compound.

For both compounds, data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *CAD*-4 *Software*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *CSU* (Vicković, 1988).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1086). Services for accessing these data are described at the back of the journal.

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