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D-Secoestrone derivatives. VI. 17β-Benzyl-17α-hydroxy-3-methoxyestra-1,3,5(10)-trien-16-one

Slobodanka Stanković,[a]* Dušan Lazar,[a] Ljubica Medić-Mijačević,[b] Katarina Penov-Gaši,[a] Marija Sakač,[a] Silvana Andrić[a] and Bruvo Milenko[c]

[a]Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradoviá 4, 21000 Novi Sad, Yugoslavia, [b]ICN–Galenika Yugoslavia, 29. Novembar 111, 11000 Beograd, Yugoslavia, and [c]Laboratory of General and Inorganic Chemistry, Faculty of Sciences, Ul. kralja Zvonimira 8, 10000 Zagreb, Croatia
Correspondence e-mail: cica@uns.ns.ac.yu

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The title molecule, $C_{26}H_{30}O_3$, shows a novel chemical rearrangement of the substituents at position 17, *i.e.* an α-orientation of the hydroxy group and a β-orientation of the bulky benzyl moiety. The packing arrangement consists of coils formed by O2···O3 hydrogen bonds along the *c* axis. The compound shows complete loss of oestrogenic activity, and neither does it exhibit an antagonistic effect.

Comment

In earlier reports (Miljković *et al.*, 1973, 1978; Miljković & Petrović, 1977; Miljković & Gaši, 1981), we established that *D*-ring fragmentation occurs in selected 16-oximino-17β-hydroxy steroid derivatives, under Beckmann reaction conditions, affording the corresponding 16,17-seco-16-cyano-17-oxo derivatives in reasonable yields. While continuing our study of the Beckmann fragmentation reaction, we have now unexpectedly discovered a novel rearrangement reaction.

By the action of acidic aqueous $TiCl_3$ (a reagent which caused fragmentation in all earlier cases) on 16-oximino-17α-benzyl-17β-hydroxy derivatives in the androstane and oestrane series, 16-oxo-17β-benzyl-17α-hydroxy derivatives with the inverse configuration at C17 were obtained (Miljković *et al.*, 1997). Thus, acidic aqueous $TiCl_3$ mainly caused the hydrolysis of the 16-oximino group to the corresponding 16-keto group, with simultaneous rearrangement of the benzyl substituent from the 17α to the 17β position. The same rearrangement reaction was observed in the case of α-oxyimino alcohol (I) (Stanković *et al.*, 1996), which afforded compound (II) as the main reaction product under analogous reaction conditions. The intended and expected fragmentation product, (III), was isolated only as a minor product in 10% yield.

The crude structure of (II) was deduced on the basis of spectroscopic evidence. Subsequently, X-ray diffraction analysis revealed the detailed structure, indicating a novel chemical rearrangement, described recently by Miljković *et al.* (1997), *i.e.* the migration of the benzyl substituent from the 17α-position in (I) to the 17β-position in (II).

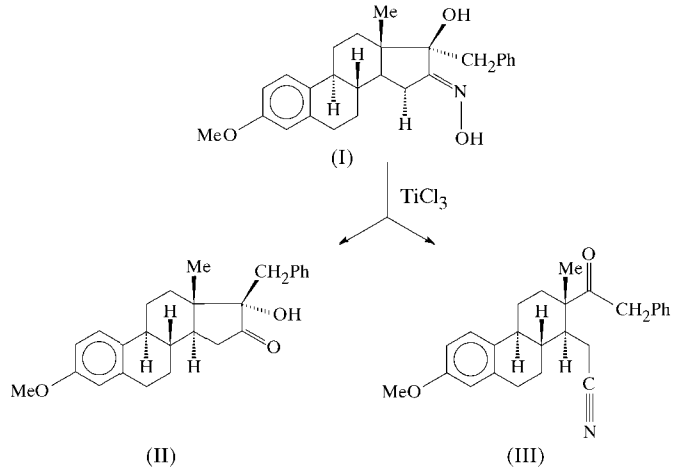

Fig. 1 shows a perspective view of the molecule of (II). Since the starting materials were synthesized from natural oestrone, the absolute stereochemistry of which is known (Fieser & Fieser, 1967), the X-ray structure of (II) is described for the appropriate enantiomer. The puckering (Cremer & Pople, 1975) and asymmetry parameters (Duax *et al.*, 1976) reveal the usual ring conformations: ring *B* is a 7α,8β-half-chair, ring *C* has a chair conformation, and ring *D* exhibits a transitional form between a 13β-envelope and a 13β,14α-half-chair conformation.

The C1—C10···C13—C18 non-bonded torsion angle of 88.1 (3)° shows that there is no significant twist along the principal axis of the molecule. The conformation of the steroidal skeleton of (II) compared with its precursor, (I), shows no significant difference (Fig. 2). Even so, the orientations of the two substituents at C17 are reversed. Biological screening demonstrated that (II) showed a complete loss of oestrogenic activity, which was considerable in (I) (a dose of 25 mg kg^{-1} in experimental animals showed 74.98% agonistic activity), as

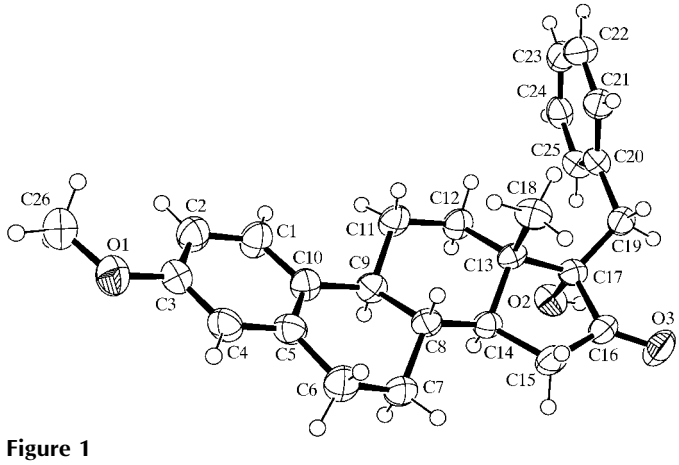

Figure 1
A perspective view of the molecule of (II) with the atomic labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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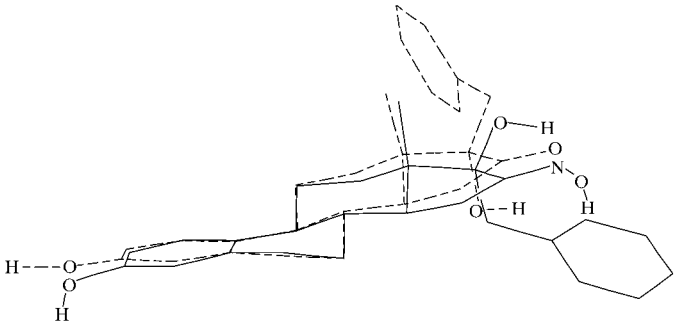

Figure 2
The superimposed fit for the molecules of (I) (dashed lines) and (II) (solid lines).

well as an absence of antagonistic effect. The unexpected β-orientation of the bulky substituent is thought to be the main reason for this significant change of biological activity (Duax *et al.*, 1976).

In the crystal packing of (II), molecules related by the screw axis are linked by O2···O3 hydrogen bonds (Table 2), forming coils along the *c* axis.

Experimental

The action of acidic aqueous $TiCl_3$ on 16-oximino-17α-benzyl-17β-hydroxy-16-hydroxyimino-3-methoxyestra-1,3,5(10)-triene, (I), at room temperature afforded the title compound, (II), as the main reaction product (78% yield; m.p. 385–387 K, from methanol). The expected fragmentation product, (III), was isolated only as a minor product in 10% yield.

Crystal data

$C_{26}H_{30}O_3$
M_r = 390.50
Orthorhombic, $P2_12_12_1$
a = 36.426 (9) Å
b = 9.1410 (10) Å
c = 6.281 (2) Å
V = 2091.4 (9) Å^3
Z = 4
D_x = 1.240 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 20 reflections
θ = 6.6–12.8°
μ = 0.63 mm^{-1}
T = 293 (2) K
Prism, colourless
0.47 × 0.07 × 0.03 mm

Table 1
Selected interatomic distances (Å).

O1—C3	1.372 (4)	O2—C17	1.446 (4)
O1—C26	1.410 (5)	C16—O3	1.218 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—HO2···O3^{i}	0.82	2.25	3.063 (4)	168

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

Data collection

Philips *PW*1100 diffractometer
$\omega/2\theta$ scans
3923 measured reflections
2222 independent reflections
1827 reflections with $I > 2\sigma(I)$
R_{int} = 0.066
θ_{max} = 70°
$h = -43 \rightarrow 44$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 7$
3 standard reflections
frequency: 120 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.125
S = 1.02
2222 reflections
263 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0461P)^2 + 0.2999]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

H atoms were generated and refined as riding with C—H distancies in the range 0.93–0.98 Å and U_{iso}(H) values of $1.2U_{eq}$(carrier atom) or $1.5U_{eq}$(methyl C).

Data collection: *PW*1100/20 *Software* (Philips, 1978); cell refinement: *PW*1100/20 *Software*; data reduction: *PW*1100/20 *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: SK1521). Services for accessing these data are described at the back of the journal.

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