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D-Secoestrone Derivatives. III. 17-Fluoro-3-methoxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile

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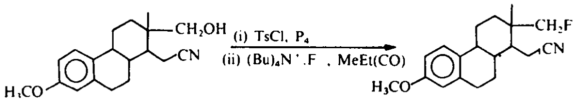
Abstract

The asymmetric unit of the title compound, $C_{19}H_{24}FNO$, contains two molecules which differ in the orientation of the 16-cyano moieties. A discussion and comparison of the structure–activity relationships among the different halogeno derivatives of the title compound is given.

Comment

As a part of a broader project dealing with the synthesis and testing of novel potential antiestrogenic agents, we have previously reported a series of new 17-halogeno-16,17-secoestrone derivatives (Petrović, Pejanović, Miljković & Hranisavljević, 1990). By testing the residual estrogenic and antiestrogenic effect of these derivatives it was found that most of the compounds examined had lost their hormone activity completely, but at the same time expressed a considerable antagonistic effect, which was most pronounced in the case of the 17-bromo derivative. The 17-fluoro-16,17-secoestrone derivative (I) proved to be an exception as it retained about 34% of the original hormonal activity and, furthermore, was found to act as a synergist in combination with estradiol.



(I)

Keeping these facts in mind, we undertook the X-ray structure analysis of a number of 17-substituted seco compounds. On comparing the structural features of the 17-chloro, bromo and iodo derivatives (Stanković, Petrović, Miljković, Pejanović, Kovačević, Stefanović & Bruvo, 1992) and the 17-toluenesulfonyloxy compound (Stanković, Stefanović, Bruvo & Altomare, 1992) with those of the 17-fluoro derivative desribed here a high degree of similarity was noticed. Selected geometric parameters for the two independent molecules of the title compound found in the unit cell, together with the corresponding mean values for the chloro, bromo, and iodo derivatives and the mean values for the two independent molecules found in the unit cell of the toluenesulfonyloxy (Ts) derivative are given in Table 2. The most significant difference appears in the orientations of the F atoms in molecules 1 and 2 of the title compound compared to the rest of the halogeno derivatives. Taking C(13)—C(14)—C(15) as a reference plane, the C(18) methyl group and the C(16) nitrile function are in an *anti* orientation in molecule 1 (Fig. 2*a*) and in a *syn* orientation in molecule 2 (Fig. 2*b*). The *syn* orientation is observed in the 17-chloro, bromo and iodo derivatives (Stanković, Petrović, Miljković, Pejanović, Kovačević, Stefanović & Bruvo, 1992). The orientation of the 3-methoxy group, which is the same in

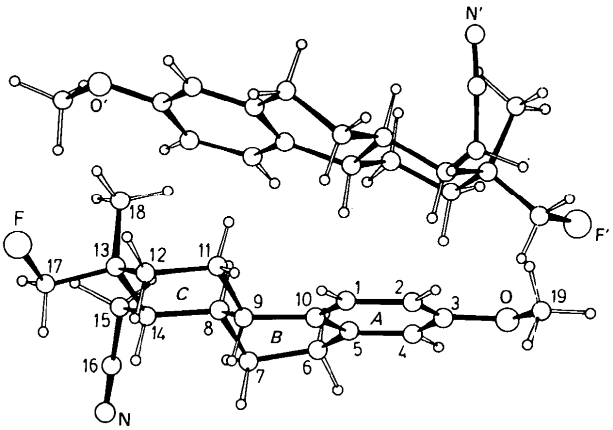


Fig. 1. A perspective view of the two symmetry independent molecules 1 and 2. The numbers correspond with C-atom labelling.

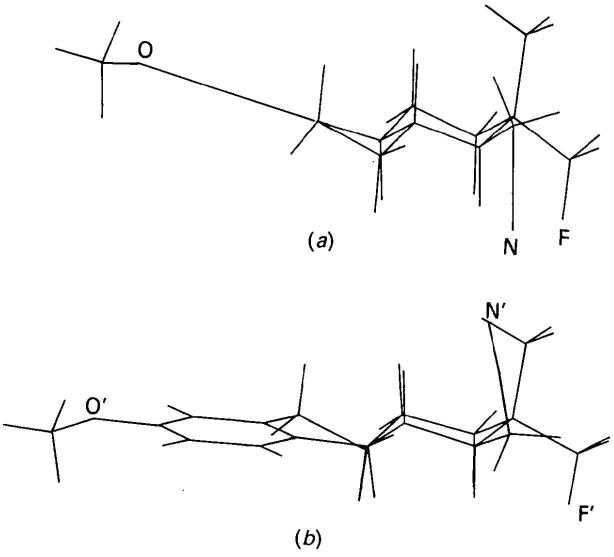


Fig. 2. The conformational differences in (*a*) molecule 1 and (*b*) molecule 2.

both molecules of the fluoro derivative, differs slightly from that found in the other halageno compounds.

Comparing the whole series of 17-halogeno seco steroids, one can conclude that only the 17-fluoro compound shows a pronounced estrogenic activity. This might be a consequence of the ability of the F atom (unique among the halogeno series) to form hydrogen bonds, as well as the greater conformational flexibility of the system.

Ring-puckering coordinates (Cremer & Pople, 1975) and asymmetry parameters (Duax, Weeks & Rohrer, 1976), listed in Table 3, define the usual ring conformation which is $7\alpha,8\beta$-half-chair for the *B* ring and chair for the *C* ring. The values of the C(1)—C(10)···C(13)—C(18) non-bonded torsion angles [−86.1 (4) and −98.7 (5)° in molecules 1 and 2, respectively] show that there is no twist along the principal axis of either molecule.

The molecules are connected only by van der Waals contacts and lie along the *b* axis.

Experimental

Crystal data

$C_{19}H_{24}FNO$
$M_r = 301.405$
Monoclinic
$P2_1$
$a = 8.981\ (6)$ Å
$b = 25.310\ (6)$ Å
$c = 7.545\ (3)$ Å
$\beta = 109.11\ (3)°$
$V = 1620.6\ (1)$ Å^3
$Z = 4$
$D_x = 1.235$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.71069$ Å
Cell parameters from 18 reflections
$\theta = 6.4–7.3°$
$\mu = 0.078$ mm^{-1}
$T = 293$ K
Prism
0.51 × 0.46 × 0.16 mm
Colourless

Data collection

Philips PW1100 diffractometer
ω scans
Absorption correction: none
2419 measured reflections
2260 independent reflections
2127 observed reflections [$F > 6\sigma(F)$]

$\theta_{\max} = 28°$
$h = -11 \rightarrow 10$
$k = 0 \rightarrow 31$
$l = 0 \rightarrow 9$
3 standard reflections
frequency: 120 min
intensity variation: none

Refinement

Refinement on F
$R = 0.051$
$wR = 0.055$
$S = 0.349$
2124 reflections
459 parameters
H atoms riding

$w = 0.7465/[\sigma^2(F) + 0.003592F^2]$
$(\Delta/\sigma)_{\max} = 0.585$
$\Delta\rho_{\max} = 0.28$ e Å^{-3}
$\Delta\rho_{\min} = -0.21$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *SHELX76* (Sheldrick, 1976)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
Molecule 1				
F	−0.8512 (5)	0.2113 (1)	−1.1453 (5)	0.089 (1)
O	−0.7717 (4)	0.6160 (1)	−0.7218 (5)	0.066 (1)
N	−0.5075 (8)	0.2509 (3)	−0.2997 (7)	0.109 (2)
C(1)	−0.7660 (6)	0.4907	−0.9664 (6)	0.049 (1)
C(2)	−0.7790 (6)	0.5448 (2)	−0.9408 (6)	0.052 (1)
C(3)	−0.7625 (5)	0.5629 (2)	−0.7632 (6)	0.047 (1)
C(4)	−0.7308 (5)	0.5290 (2)	−0.6155 (6)	0.041 (1)
C(5)	−0.7200 (5)	0.4744 (2)	−0.6429 (5)	0.038 (1)
C(6)	−0.6885 (6)	0.4382 (2)	−0.4746 (6)	0.046 (1)
C(7)	−0.6435 (5)	0.3823 (2)	−0.5116 (6)	0.046 (1)
C(8)	−0.7508 (5)	0.3623 (2)	−0.7031 (5)	0.037 (1)
C(9)	−0.7222 (5)	0.3960 (2)	−0.8557 (5)	0.040 (1)
C(10)	−0.7379 (5)	0.4548 (2)	−0.8212 (5)	0.037 (1)
C(11)	−0.8296 (7)	0.3784 (2)	−1.0490 (6)	0.053 (1)
C(12)	−0.7992 (6)	0.3205 (2)	−1.0784 (6)	0.053 (1)
C(13)	−0.8263 (5)	0.2834 (2)	−0.9336 (6)	0.047 (1)
C(14)	−0.7264 (5)	0.3033 (2)	−0.7327 (6)	0.044 (1)
C(15)	−0.7614 (7)	0.2690 (2)	−0.5782 (7)	0.062 (1)
C(16)	−0.6177 (9)	0.2585 (2)	−0.4195 (8)	0.074 (2)
C(17)	−0.7670 (7)	0.2290 (2)	−0.9625 (8)	0.063 (1)
C(18)	−1.0018 (6)	0.2805 (2)	−0.9545 (8)	0.066 (1)
C(19)	−0.7836 (9)	0.6530 (2)	−0.8668 (9)	0.078 (2)
Molecule 2				
F′	−1.0878 (5)	0.6383 (1)	−0.3375 (5)	0.085 (1)
O′	−1.3429 (5)	0.2364 (1)	−0.7778 (5)	0.070 (1)
N′	−1.4948 (8)	0.5783 (3)	−1.1307 (7)	0.105 (2)
C(1′)	−1.1968 (6)	0.3579 (2)	−0.5132 (6)	0.056 (1)
C(2′)	−1.2339 (6)	0.3050 (2)	−0.5452 (7)	0.058 (1)
C(3′)	−1.3018 (5)	0.2878 (2)	−0.7270 (6)	0.049 (1)
C(4′)	−1.3317 (5)	0.3228 (2)	−0.8736 (6)	0.048 (1)
C(5′)	−1.2923 (5)	0.3764 (2)	−0.8407 (6)	0.042 (1)
C(6′)	−1.3221 (6)	0.4129 (2)	−1.0065 (6)	0.053 (1)
C(7′)	−1.2206 (6)	0.4628 (2)	−0.9590 (6)	0.051 (1)
C(8′)	−1.2418 (5)	0.4890 (2)	−0.7854 (5)	0.037 (1)
C(9′)	−1.1763 (5)	0.4522 (2)	−0.6162 (5)	0.040 (1)
C(10′)	−1.2251 (5)	0.3943 (2)	−0.6590 (6)	0.042 (1)
C(11′)	−1.2150 (7)	0.4754 (2)	−0.4490 (6)	0.062 (1)
C(12′)	−1.1421 (7)	0.5298 (2)	−0.4027 (6)	0.061 (1)
C(13′)	−1.1899 (5)	0.5697 (2)	−0.5651 (6)	0.045 (1)
C(14′)	−1.1624 (5)	0.5435 (2)	−0.7387 (6)	0.042 (1)
C(15′)	−1.2045 (7)	0.5796 (2)	−0.9130 (6)	0.059 (1)

C(16′)	−1.3669 (9)	0.5804 (2)	−1.0315 (8)	0.073 (2)
C(17′)	−1.0815 (6)	0.6170 (2)	−0.5072 (7)	0.060 (1)
C(18′)	−1.3607 (6)	0.5878 (2)	−0.6037 (8)	0.066 (1)
C(19′)	−1.3044 (9)	0.1972 (2)	−0.6353 (9)	0.082 (2)

Table 2. *Selected geometric parameters* (Å, °)

	Molecule 1	Molecule 2	Cl, Br and I derivatives	Ts derivative
Bond distances				
C(17)—F	1.411 (6)	1.407 (7)	–	–
C(17)—C(13)	1.518 (7)	1.514 (7)	1.523	1.528
C(13)—C(14)	1.570 (6)	1.558 (7)	1.558	1.564
C(14)—C(15)	1.566 (8)	1.543 (7)	1.563	1.552
C(15)—C(16)	1.469 (8)	1.440 (9)	1.456	1.462
C(16)—N	1.117 (8)	1.149 (9)	1.134	1.147
C(3)—O	1.388 (6)	1.372 (6)	1.376	1.376
C(19)—O	1.417 (7)	1.420 (7)	1.417	1.437
Bond angles				
C(13)—C(17)—F	109.1 (4)	110.6 (4)	115.9	109.0
C(12)—C(13)—C(17)	108.1 (4)	107.7 (4)	108.8	108.1
C(14)—C(13)—C(17)	108.3 (4)	108.4 (4)	112.7	111.2
C(13)—C(14)—C(15)	110.5 (4)	113.7 (4)	113.7	113.1
C(14)—C(15)—C(16)	111.7 (5)	117.0 (5)	115.0	113.9
C(15)—C(16)—N	179.2 (7)	176.0 (7)	178.2	178.3
C(2)—C(3)—O	123.1 (4)	124.7 (4)	116.3	124.1
C(4)—C(3)—O	116.0 (4)	115.0 (4)	124.2	116.8
Torsion angles				
C(12)—C(13)—C(17)—F	−60.1 (5)	−56.1 (5)	62.6	58.7
C(14)—C(13)—C(17)—F	−177.7 (4)	−172.9 (4)	−57.6	−61.0
C(17)—C(13)—C(14)—C(15)	−67.5 (5)	−63.0 (5)	−54.8	−59.7
C(13)—C(14)—C(15)—C(16)	140.5 (5)	−84.8 (6)	−74.7	−82.9
C(8)—C(14)—C(15)—C(16)	−93.6 (5)	44.0 (6)	53.6	45.1
C(2)—C(3)—O—C(19)	−6.2 (7)	−4.2 (7)	1.8	179.5

Table 3. *Ring-puckering coordinates and asymmetry parameters* (Å, °)

	Q	φ	θ	C_s	C_2
Ring *B*, molecule 1	0.520 (5)	340.1 (7)	130.7 (6)	–	9.2 [C(7)—C(8)]
Ring *B*, molecule 2	0.528 (5)	322.3 (7)	129.9 (6)	–	7.9 [C(7)—C(8)]
Ring *C*, molecule 1	0.569 (6)	274 (7)	175.5 (6)	5.8 [C(8)] 3.8 [C(9)] 2.6 [C(11)]	6.9 [C(8)—C(9)] 1.4 [C(9)—C(11)] 5.7 [C(11)—C(12)]
Ring *C*, molecule 2	0.589 (6)	217 (5)	173.1 (6)	5.3 [C(8)] 2.1 [C(9)] 7.4 [C(11)]	3.0 [C(8)—C(9)] 4.6 [C(9)—C(11)] 5.3 [C(11)—C(12)]

H atoms were generated and refined as riding groups (overall isotropic displacement parameters were refined for different CH types). Program used to solve structure: *SIR*88 (Burla, Camalli, Cascarano, Giacovazzo, Polidori, Spagna & Viterbo, 1989). Program used to refine structure: *SHELX*76 (Sheldrick, 1976). Software used to prepare material for publication: *CSU* (Vicković, 1988).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: KA1034). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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5-Acetyl[2.2]paracyclophane

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Abstract

The title compound 5-acetyltricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene, $C_{18}H_{18}O$, is the first example of a mono-π-substituted [2.2]paracyclophane to be structurally characterized. The average bending angles are $\alpha = 13.2$ and $\beta = 9.9°$. The distance between the 'bottoms' of the practically parallel boat-like benzene nuclei is 3.098 (2) Å. The π conjugation between the acetyl group and the substituted benzene cycle is negligible (rotation angle *ca* 45°) because of steric hindrance.

Comment

In order to study the influence of substituents on the degree of steric strain in [2.2]paracyclophanes (Linde-

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