organic papers

17-Bromo-16-formyl-3-methoxyestra-1,3,5(10),16-tetraene

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Key indicators

Single-crystal X-ray study
T = 123 K
Mean σ(C–C) = 0.003 Å
R factor = 0.023
wR factor = 0.061
Data-to-parameter ratio = 15.2

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

In the title estrane derivative, $C_{20}H_{23}BrO_2$, the five-membered ring adopts a conformation that is intermediate between twist and envelope. The C atom of the formyl group and the bromo function are in close proximity. Close intermolecular Br$\cdots$Br and Br$\cdots$C contacts are observed in the crystal structure.

Comment

The title compound, (I), was synthesized by Thiemann *et al.* (1997) as an important precursor for steroidal bromo-butadiene systems and *E*-ring annelated estranes (Thiemann *et al.*, 2001). The chloro analog of (I) is known to have a cholesterol-lowering effect (Kaneko & Yamato, 1969). We have used (I) in numerous metal-catalyzed cross-coupling processes, such as in Suzuki and Sonogashira reactions, with varying degrees of success (Watanabe *et al.*, 2005).

(I)
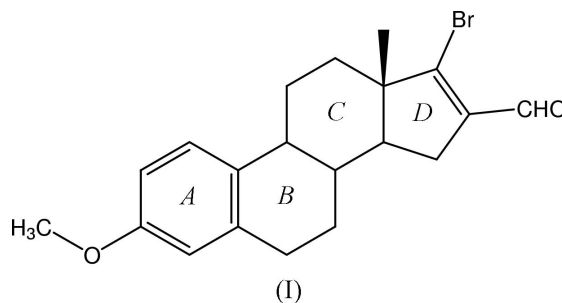
Steric restrictions in the transition state seem to have an influence on the success of the reactions. In order to understand the steric characteristics of (I), particularly the effects of the substituents on the five-membered ring (Fig. 1), a single-crystal X-ray diffraction study of (I) was carried out.
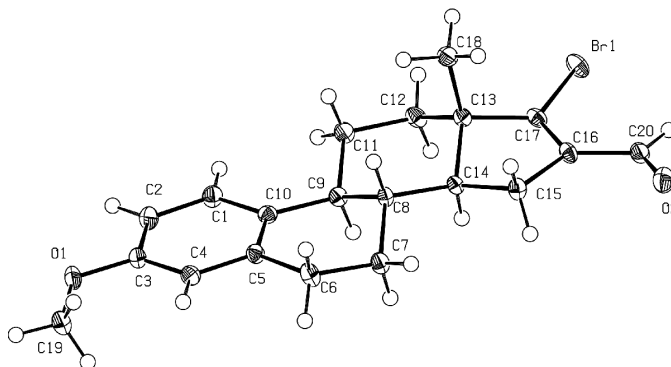

Figure 1
A view of the molecule of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level; H atoms are shown as small spheres of arbitrary radii.
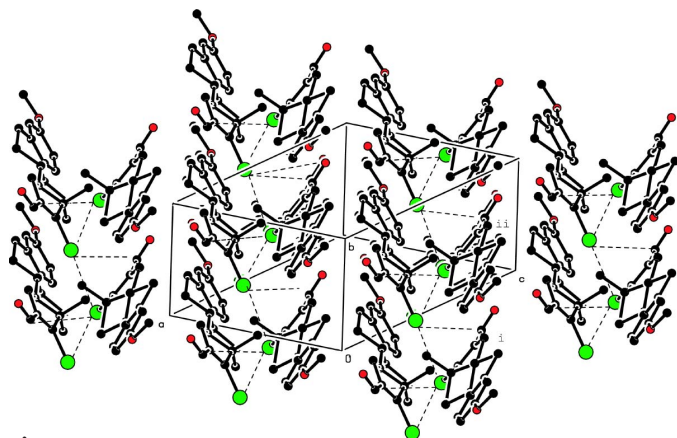
Figure 2
A view of the unit cell of (I) down the [212] direction. The intermolecular Br$\cdots$Br and Br$\cdots$C contacts are shown as dashed lines. [Symmetry codes: (i) $-x$, $y - \frac{1}{2}$, $1 - z$; (ii) $-x$, $\frac{1}{2} + y$, $1 - z$.]

There is one independent molecule of (I) in the asymmetric unit. Ring A shows little distortion from planarity, as is usual in other estrones and estradiols. The ring conformations in the molecule of (I) were analyzed using the Cremer & Pople (1975) puckering parameters. Ring B has a half-chair conformation [the Cremer & Pople puckering parameters are Q = 0.496 (3) Å, θ = 4.61 (3)° and φ = 165.6 (3)°]. This conformation is also in accordance with the endocyclic torsion angles within ring B (see Boeyens, 1978). Ring C, with a *trans*-fusion to rings B and D, has a chair conformation [Q = 0.590 (2) Å, θ = 6.7 (2)° and φ = 297 (2)°]. Ring D has a conformation between half-chair (twist) and envelope [Q = 0.383 (3) Å and φ = 206.8 (4)°, 51% half-chair (twist) character and 49% envelope character (Evans & Boeyens, 1989) with a pseudo-rotation angle P = 7.1 (2)°, and an upper limit of the endocyclic torsion angle τ_m = 38.5 (1)° (Altona & Sundaralingam, 1972; Rao *et al.*, 1981) for the atom sequence C13–C17].

The intramolecular distance from Br1 to C20 is 3.349 (2) Å, which is smaller than the sum of the van der Waals radii of C (1.70 Å) and Br (1.85 Å) [3.55 Å, according to Bondi (1964)]. These steric constraints are reflected in the poor results of certain transformations, such as the replacement of a bromo- by an iodo-functionality at C17 of (I) using a nickel catalyst (Takagi *et al.*, 1978). Classical Pd-catalyzed C—C bond-forming reactions (de Meijere & Diederich, 2004) of (I), such as Suzuki cross-coupling, Sonogashira, and Heck reactions, work quite well (Watanabe *et al.*, 2005). It can be deduced from the close proximity of Br1 and C20 that, after oxidative insertion of the palladium species into C17—Br1, with concomitant rotation about the C16—C20 bond, the geometry favors a stabilization of the Pd^{II} complex of (I) by the carbonyl O atom.

In the crystal structure, (I) packs in chains, each consisting of two rows of molecules, where parallel chains are arranged in a stepwise fashion. The dihedral angle between the mean plane of the steroidal frameworks of one row and the mean plane of the molecules in the second row is 73.90 (4)°. Between molecules of the two rows making up one chain, there exist halogen–carbon and halogen–halogen interactions

(Fig. 2), where the intermolecular Br1$\cdots$C20^i and Br1$\cdots$Br1^i distances are 3.508 (2) and 3.6165 (6) Å, respectively [symmetry code: (i) $-x$, $y - \frac{1}{2}$, $1 - z$]. The Br1$^i\cdots$Br1$\cdots$C20^i angle is 56.06 (4)°. Many C—halogen$\cdots\pi$ intermolecular interactions have been reported and have been studied primarily because of their importance in drug-protein interactions (Prasanna & Row, 2000). The Br1$\cdots$C20^i distance [3.508 (2) Å] in (I) is shorter than the mean value for the Br$\cdots$C(intermolecular) distances reported in the Cambridge Structural Database (2004 Release; Allen, 2002) and the Bookhaven Protein Data Bank according to the study performed by Prasanna & Row (2000) [3.625 (9) Å for Br$\cdots$C(intermolecular) for 387 such short contacts reported before 2000]. The distance Br1$\cdots$Br1^i in (I) is in the typical range of halogen–halogen interactions (3.2–4.0 Å for Cl and Br; Saruma & Desiraju, 1986, Moorthy *et al.*, 2002).

Experimental

Compound (1) was prepared from 3-methoxyestra-1,3,5(10)-trien-17-one (3-*O*-methylestrone) by an Arnold Vilsmeier reaction with PBr$_3$–DMF reagent (*i.e.* bromoiminium salt) according to the method described by Thiemann *et al.* (1997).

Crystal data

$C_{20}H_{23}BrO_2$	D_x = 1.467 Mg m^{-3}
M_r = 375.30	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 3041
a = 9.702 (3) Å	reflections
b = 6.093 (2) Å	θ = 3.6–27.5°
c = 14.640 (5) Å	μ = 2.43 mm^{-1}
β = 100.914 (1)°	T = 123.1 K
V = 849.7 (4) Å^3	Platelet, colorless
Z = 2	0.20 × 0.18 × 0.06 mm

Data collection

Rigaku Saturn diffractometer	3354 reflections with $I > 2\sigma(I)$
ω scans	R_{int} = 0.025
Absorption correction: multi-scan	θ_{max} = 27.5°
(Jacobson, 1998)	h = −11 → 12
T_{min} = 0.711, T_{max} = 0.864	k = −7 → 7
6860 measured reflections	l = −19 → 18
3534 independent reflections	

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max} < 0.001$
$R[F^2 > 2\sigma(F^2)]$ = 0.023	$\Delta\rho_{max}$ = 0.56 e Å^{-3}
$wR(F^2)$ = 0.061	$\Delta\rho_{min}$ = −0.65 e Å^{-3}
S = 1.01	Extinction correction: none
3534 reflections	Absolute structure: (Flack, 1983),
232 parameters	1422 Friedel pairs
H-atom parameters constrained	Flack parameter: 0.000 (7)
$w = 1/[0.0001F_o^2 + \sigma(F_o^2) + 1.7]/$	
$(4F_o^2)$	

All H atoms were included in the refinement as riding on their parent atoms with U_{iso}(H) values set to 1.2U_{eq} of the parent C atoms (C—H = 0.95 Å).

Data collection: *CrystalClear* (Rigaku Corporation, 1999); cell refinement: *CrystalClear*; data reduction: *CrystalStructure* (Rigaku/MSC, 2004); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *CrystalStructure*.

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