

The antiestrogen [2-(4-benzylphenoxy)ethyl]diethylammonium chloride

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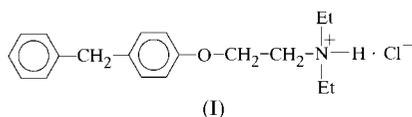
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The crystal structure of the title compound, C₁₉H₂₆NO⁺·Cl⁻ (common name: *N,N*-diethyl-2-[(4-phenylmethyl)phenoxy]ethanamine hydrochloride), contains one molecule in the asymmetric unit. The planes through the two phenyl rings are roughly perpendicular. Protonation occurs at the N atom, to which the Cl⁻ ion is linked *via* an N—H···Cl hydrogen bond. The molecule adopts an eclipsed rather than extended conformation.

Comment

[2-(4-Benzylphenoxy)ethyl]diethylammonium chloride, (I), is a diphenylmethane analogue of the antiestrogen tamoxifen which antagonizes the binding of histamine to intracellular growth-regulatory sites associated with antiestrogen-binding sites in microsomes and nuclei. It has been found that (I) increases the therapeutic index of some chemotherapy drugs, with the added benefit of lower toxicity to normal tissue like bone marrow, gut and hair, and the compound has been studied as a treatment for metastatic prostate cancer (Brandes *et al.*, 1994, 1995). A chemopotentiating effect of the drug in patients with early metastatic breast cancer has also been observed (Brandes & Bracken, 1998), and growth-inhibitory effects on human ovarian cancer cells when combined with cisplatin have been reported by Hiramatsu *et al.* (1997). Since knowledge of the stereochemistry is useful in the rational design of drugs with enhanced chemotherapeutic effects and lower toxicities, we now report on the three-dimensional structure of (I).



The molecular conformation in the crystal (Fig. 1) consists of two phenyl rings and an *N,N*-diethyl side chain in an

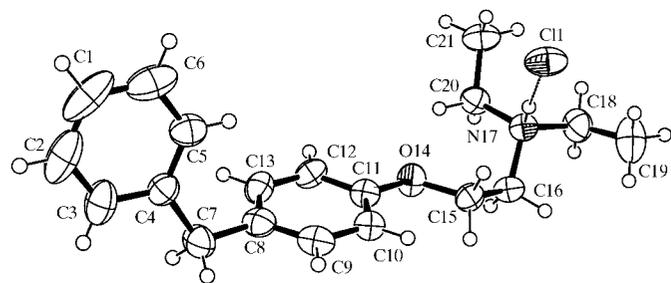


Figure 1

ORTEP3 (Farrugia, 1997) view of (I), showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

eclipsed conformation. The best planes through the phenyl rings intersect at an angle of 79.12 (12)°. In the closely related compounds clomiphene hydrochloride (Ernst & Hite, 1976), and tamoxifen (Precigoux *et al.*, 1979), the angles are 78 and 87° respectively. Protonation occurs in (I) at atom N17, as the reduction of the values of the angles at N17 [110.4 (2), 111.0 (2), 110.5 (2) and 108.3°] confirm.

The only hydrogen bond in (I) is between N17 (*D*) and C11 (*A*): H···*A* 2.208 (4) and *D*···*A* 3.116 (2) Å, and *D*—H···*A* 174.9 (2)°. The molecular bond distances and angles are consistent with the normal values. The C12—C11—O14—C15, C11—O14—C15—C16, O14—C15—C16—N17 and C15—C16—N17—C20 torsion angles are 178.2 (3), 169.7 (2), 73.9 (3) and -80.3 (3)°, respectively. Similar values were found in clomiphene (Ernst & Hite, 1976). In the crystal structure of (I) the molecules lie virtually parallel to the *b* axis, with only van der Waals contacts between them.

Fig. 2 shows the crystal structure conformation of (I) superimposed with that of clomiphene. The corresponding parts of the two molecules overlap closely; only small rotations about single bonds would be required for total overlap. The same situation holds for (I) and tamoxifen, as tamoxifen and clomiphene have been shown to share conformational and stereochemical features (Camerman *et al.*, 1980). It may be that this part of the molecular structure is responsible for the

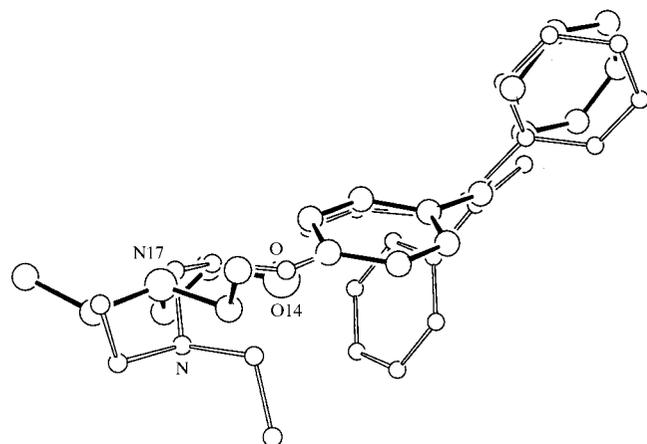


Figure 2

Superposition of the crystal structures of (I) (solid lines) and clomiphene (open lines).

common antiestrogen properties of these molecules and the third phenyl ring, absent in (I), may be involved in other antiproliferative actions of three-ring antiestrogens on cancer cells (Lavie *et al.*, 1998) independent of estrogen receptors.

Experimental

Crystals of (I) were obtained as very small needles by solvent evaporation from an ethanol/ethyl acetate mixture. Due to the small size of the available crystals, data were collected on the synchrotron at NSLS (Brookhaven).

Crystal data

$C_{19}H_{26}NO^+ \cdot Cl^-$	Synchrotron radiation
$M_r = 319.86$	$\lambda = 0.9200$ (1) Å
Orthorhombic, $Pca2_1$	Cell parameters from all reflections
$a = 16.427$ (2) Å	$\theta = 2.4\text{--}30.7^\circ$
$b = 15.195$ (2) Å	$\mu = 0.44$ mm $^{-1}$
$c = 7.194$ (1) Å	$T = 293$ (2) K
$V = 1795.7$ (5) Å 3	Needle, colourless
$Z = 4$	$0.130 \times 0.010 \times 0.008$ mm
$D_x = 1.183$ Mg m $^{-3}$	

Data collection

ADSC Quantum-4 CCD detector diffractometer	$R_{int} = 0.051$
Single axis rotation scans	$\theta_{max} = 30.72^\circ$
7875 measured reflections	$h = -18 \rightarrow 18$
1405 independent reflections plus 1033 Friedel-related reflections	$k = -16 \rightarrow 16$
2237 reflections with $I > 2\sigma(I)$	$l = -7 \rightarrow 7$
	Intensity decay: <1%

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max} < 0.001$
$R[F^2 > 2\sigma(F^2)] = 0.036$	$\Delta\rho_{max} = 0.14$ e Å $^{-3}$
$wR(F^2) = 0.105$	$\Delta\rho_{min} = -0.19$ e Å $^{-3}$
$S = 1.002$	Extinction correction: <i>SHELX97</i> (Sheldrick, 1997)
2438 reflections	Extinction coefficient: 0.0153 (18)
208 parameters	Absolute structure: Flack (1983)
H-atom parameters constrained	Flack parameter = 0.58 (5)
$w = 1/[\sigma^2(F_o^2) + (0.0618P)^2 + 0.388P]$	
where $P = (F_o^2 + 2F_c^2)/3$	

The *SHELX97* (Sheldrick, 1997) instructions *TWIN* and *BASF* were included; the Flack parameter is the volume fraction of one of the individuals of the racemic twin.

Data collection: *DENZO-SMN* (Otwinowski & Minor, 1997); cell refinement: *DENZO-SMN*; data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELX97*; program(s) used to refine structure: *SHELX97*; molecular graphics: *ORTEP3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELX97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1510). Services for accessing these data are described at the back of the journal.

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