Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

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

Andrew Hempel,[a]* Norman Camerman,[a] Zbigniew Dauter,[b] Donald Mastropaolo[c] and Arthur Camerman[c]

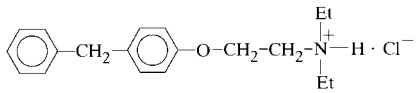
[a]Department of Biochemistry, University of Toronto, Medical Sciences Building, Toronto, Canada M5S 1A8, [b]National Cancer Institute, Frederick and Brookhaven National Laboratory, NSLS, Building 725A-X9, Upton, NY 11973, USA, and [c]Ardono Research, 8515C 35 Ave. NE, Seattle, WA 98115, USA
Correspondence e-mail: andrew.hempel@utoronto.ca

Received 27 September 1999
Accepted 22 December 1999

The crystal structure of the title compound, $C_{19}H_{26}NO^{+}\cdot Cl^{-}$ (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).



(I)

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

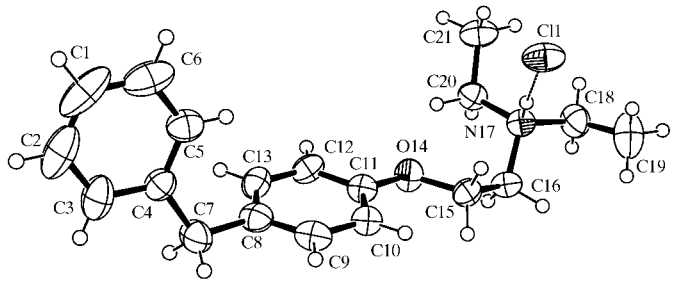


Figure 1
*ORTEP*3 (Farrugia, 1997) view of (I), showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

The only hydrogen bond in (I) is between N17 (*D*) and Cl1 (*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

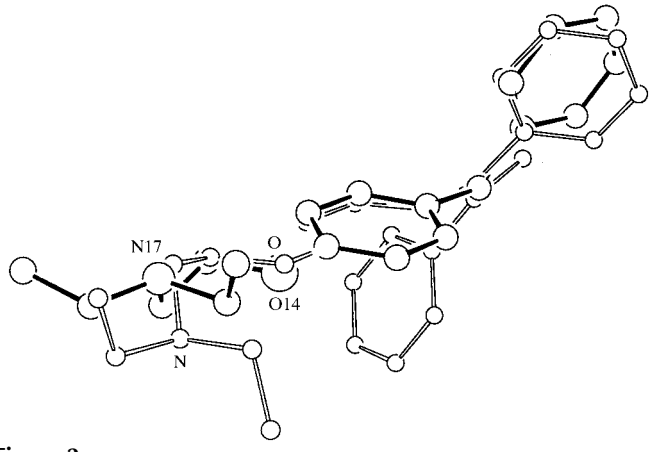


Figure 2
Superposition of the crystal structures of (I) (solid lines) and clomiphene (open lines).

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

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

Data collection

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

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.105
S = 1.002
2438 reflections
208 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0618P)^2 + 0.388P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}
Extinction correction: *SHELX*97 (Sheldrick, 1997)
Extinction coefficient: 0.0153 (18)
Absolute structure: Flack (1983)
Flack parameter = 0.58 (5)

The *SHELX*97 (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: *SHELX*97; program(s) used to refine structure: *SHELX*97; molecular graphics: *ORTEP*3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELX*97.

This work was supported by the National Cancer Institute of Canada with funds from the Canadian Cancer Society (NC), and by grant AI40392 from the National Institutes of Health (AC).

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.

References

Brandes, L. J. & Bracken, S. P. (1998). *Breast Cancer Res. Treatment*, **49**, 61–68.
Brandes, L. J., Bracken, S. P. & Ramsey, E. W. (1995). *J. Clin. Oncol.* **13**, 1398–1403.
Brandes, L. J., Simons, K. J., Bracken, S. P. & Warrington, R. C. (1994). *J. Clin. Oncol.* **12**, 1281–1290.
Camerman, N., Chan, L. Y. Y. & Camerman, A. (1980). *J. Med. Chem.* **23**, 941–945.
Ernst, S. & Hite, G. (1976). *Acta Cryst.* B**32**, 291–293.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Hiramatsu, H., Kikuchi, Y., Kudoh, K., Kita, T., Tode, T. & Nagata, I. (1997). *Jpn. J. Cancer Res.* **88**, 1003–1008.
Lavie, Y., Zhang, Z. C., Cao, H. T., Han, T. Y., Jones, R. C., Liu, Y. Y., Jarman, M., Hardcastle, I. R., Giulano, A. E. & Cabot, M. C. (1998). *Int. J. Cancer*, **77**, 928–932.
Otwinowski, Z. & Minor, W. (1997). *Methods Enzymol.* **276**, 307–326.
Precigoux, G., Courseille, C., Geoffre, S. & Hospital, M. (1979). *Acta Cryst.* B**35**, 3070–3972.
Sheldrick, G. M. (1997). *SHELX*97. University of Göttingen, Germany.