

**(E)-1-[p-(Diethylaminoethoxy)phenyl]-1,2-diphenyl-2-chloroethylene Hydrochloride
(Clomiphene Hydrochloride)**

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Abstract. *B* isomer of clomiphene HCl, C₂₆H₂₉NOCl₂, (IB).HCl: space group *P*2₁/*c*, *a* = 15.564 (1), *b* = 9.229 (1), *c* = 18.285 (2) Å; β = 116.40 (1)°, *Z* = 4, *D*_x = 1.24, *D*_m = 1.25 g cm⁻³. The structure was solved by direct methods. The positional and thermal parameters were refined by the full-matrix procedure, converging at *R* = 0.053. The unsubstituted aromatic rings are *trans* (torsion angle = 174.4°), not *cis* as previously reported.

Introduction. A crystal (0.14 × 0.17 × 0.20 mm) of (IB).HCl (m.p. 150–151°, from pentanone) mounted on a Nonius CAD-IV automatic diffractometer (graphite-monochromated Cu *K*α radiation, λ = 1.5418 Å) was used to obtain intensity data in the θ/2θ mode to a limit of 52° in θ beyond which Weissenberg photographs showed few observable reflections. Other than systematic absences (*h*0*l*, 0*k*0; *l*, *k* odd) 2576 independent reflections (*hkl*, *hk* \bar{l}) were measured. Only those (1905) satisfying the relationship |*F*_o| > 3σ(*F*) were considered reliably observed. An absorption correction was not applied. Scattering factors and anomalous dis-

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Table 1. Atomic positional and thermal parameters

The estimated standard deviations are shown in parentheses and refer to the last digit of the respective values. The positional parameters are fractions of the lattice translations. The numbering system is shown in Fig. 1. The anisotropic temperature factor expression used is $\exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})]$.

(a) Non-hydrogen atoms (× 10⁴)

	<i>x</i>	<i>y</i>	<i>z</i>	β ₁₁	β ₂₂	β ₃₂	β ₁₂	β ₁₃	β ₂₃
C(1)	8399 (4)	2145 (7)	5931 (3)	44 (4)	112 (9)	29 (2)	10 (5)	11 (2)	8 (4)
C(2)	8667 (4)	3489 (7)	5954 (3)	45 (4)	118 (9)	31 (3)	3 (5)	15 (3)	19 (4)
C(3)	7153 (4)	-211 (7)	8697 (4)	58 (4)	163 (9)	33 (3)	-26 (5)	28 (3)	-12 (4)
C(4)	6698 (4)	-1363 (7)	9007 (3)	39 (4)	158 (9)	32 (3)	-2 (5)	15 (3)	5 (4)
C(5)	5035 (4)	-1667 (7)	7887 (3)	49 (4)	166 (9)	31 (3)	-7 (5)	17 (3)	-1 (4)
C(6)	4046 (5)	-1007 (8)	7523 (4)	55 (4)	185 (9)	59 (4)	-11 (6)	17 (3)	-17 (6)
C(7)	5335 (4)	-1791 (7)	9349 (4)	59 (4)	145 (9)	35 (3)	-11 (5)	26 (2)	15 (4)
C(8)	5641 (6)	-3325 (9)	9569 (5)	84 (6)	200 (9)	74 (4)	1 (7)	40 (4)	49 (6)
C(9)	7928 (4)	1650 (6)	6455 (3)	50 (4)	90 (8)	34 (3)	7 (5)	22 (3)	17 (4)
C(10)	7091 (4)	847 (6)	6108 (3)	52 (4)	104 (8)	35 (3)	-11 (5)	21 (3)	6 (4)
C(11)	6705 (4)	223 (6)	6584 (3)	51 (4)	110 (9)	29 (3)	-13 (5)	13 (3)	-5 (4)
C(12)	7170 (4)	415 (6)	7426 (3)	49 (4)	91 (8)	34 (3)	-4 (5)	24 (3)	-4 (4)
C(13)	7980 (4)	1252 (6)	7794 (3)	45 (4)	114 (9)	30 (2)	-3 (5)	18 (3)	-9 (4)
C(14)	8362 (4)	1872 (6)	7305 (3)	38 (3)	107 (9)	38 (3)	3 (4)	18 (3)	4 (4)
C(15)	8554 (4)	983 (6)	5436 (3)	52 (4)	94 (8)	31 (3)	4 (5)	21 (3)	-5 (4)
C(16)	8233 (5)	1126 (7)	4593 (4)	81 (5)	104 (9)	41 (3)	16 (5)	32 (3)	0 (4)
C(17)	8367 (5)	28 (8)	4145 (4)	77 (5)	172 (9)	41 (3)	26 (6)	32 (3)	-2 (5)
C(18)	8815 (5)	-1222 (8)	4503 (4)	66 (5)	162 (9)	51 (4)	3 (6)	27 (3)	-24 (5)
C(19)	9113 (6)	-1417 (7)	5330 (5)	93 (6)	106 (9)	61 (4)	20 (6)	33 (4)	-2 (5)
C(20)	8975 (5)	-319 (7)	5792 (4)	74 (5)	124 (9)	38 (3)	12 (6)	22 (3)	5 (5)
C(21)	8452 (4)	4714 (6)	6387 (3)	52 (4)	67 (7)	35 (3)	2 (4)	17 (3)	5 (4)
C(22)	7506 (4)	5039 (7)	6205 (4)	52 (4)	112 (9)	40 (3)	16 (5)	20 (3)	19 (4)
C(23)	7304 (5)	6171 (8)	6601 (4)	68 (5)	169 (9)	47 (3)	39 (6)	28 (4)	27 (5)
C(24)	8056 (6)	6968 (8)	7180 (4)	107 (7)	134 (9)	40 (3)	39 (7)	30 (4)	-3 (5)
C(25)	8994 (6)	6667 (8)	7358 (4)	78 (5)	121 (9)	45 (3)	17 (6)	14 (3)	1 (4)
C(26)	9198 (4)	5547 (7)	6958 (4)	53 (4)	102 (9)	43 (3)	-12 (5)	19 (3)	-8 (4)
N(1) ⁺	5644 (3)	-1129 (5)	8744 (3)	58 (3)	128 (7)	30 (2)	-9 (4)	22 (2)	0 (3)
O(1)	6744 (3)	-334 (5)	7834 (2)	69 (3)	181 (7)	32 (2)	-38 (4)	27 (2)	-9 (3)
Cl	9382 (1)	4022 (2)	5474 (1)	70 (1)	119 (2)	53 (1)	-6 (1)	41 (1)	10 (1)
Cl ⁻	5484 (1)	2028 (2)	9103 (1)	86 (1)	125 (2)	48 (1)	1 (1)	38 (1)	0 (1)

Table 1 (cont.)

(b) Hydrogen atoms (coordinates* $\times 10^4$, $B \times 10^2$)The isotropic temperature factor expression used is $\exp[-B(\sin \theta/\lambda)^2]$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
H(N)	5542	-52	8740	348 Å ²
H(3 1)	6990	844	8864	415
H(3 2)	7908	-326	8969	415
H(4 1)	7065	-1412	9658	404
H(4 2)	6791	-2395	8775	404
H(5 1)	4970	-2820	7895	428
H(5 2)	5381	-1405	7512	428
H(6 1)	4098	0	7566	584
H(6 2)	3548	-1347	7774	584
H(6 3)	3747	-1392	6969	584
H(7 1)	4566	-1740	9097	422
H(7 2)	5623	-1153	9896	422
H(8 1)	5455	-3850	9046	618
H(8 2)	5337	-3571	9836	618
H(8 3)	6214	-3571	9878	618
H(10)	6742	684	5455	399
H(11)	6061	-414	6308	388
H(13)	8318	1407	8444	360
H(14)	9005	2516	7582	358
H(16)	7884	2129	4298	463
H(17)	8136	165	3497	513
H(18)	8910	-2055	4146	509
H(19)	9455	-2415	5613	538
H(20)	9205	-458	6433	505
H(22)	6929	4402	5761	385
H(23)	6563	6407	6463	514
H(24)	7890	7835	7485	558
H(25)	9568	7307	7803	542
H(26)	9932	5297	7093	436

* Hydrogen atoms fixed by geometrical considerations were placed in idealized positions with C-H bond lengths of 1.07 Å. Thus, no e.s.d.'s are included here.

position factors were taken from *International Tables for X-ray Crystallography* (1968).

The structure was solved by direct methods. Following block-diagonal refinement of positional atomic and isotropic thermal parameters, a difference map revealed the positions of all H atoms. These were assigned isotropic temperature factors equal to those of the heavier atoms to which they were attached. Full-matrix refinement converged at $R=0.053$. A final difference Fourier map revealed no peaks greater than $0.2 \text{ e } \text{Å}^{-3}$. The average shift in a parameter was 0.2σ . The final positional and thermal parameters are listed in Table 1.* All calculations were performed on the University of Pittsburgh PDP-10 computer using programs of Shiono (1963-1973) and the X-RAY 72 system of programs (Stewart, 1972; Ernst & Poppleton, 1974).

Discussion. The *cis* stereochemistry was assigned to (IB) since it exhibited ultraviolet absorption at higher wavelength than (IA) (Palopoli, Feil, Allen, Holtkamp & Richardson, 1967).

- $p\text{-R}_1\text{O-C}_6\text{H}_4$; $\text{C}_6\text{H}_5(\text{C}=\text{C})\text{C}_6\text{H}_5$; R_2
 (II) $\text{R}_1 = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{R}_2 = \text{CH}_2\text{CH}_3$
 (III) $\text{R}_1 = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$, $\text{R}_2 = \text{Br}$
 (IV) $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{Br}$
 (V) $\text{R}_1 = \text{CH}_3$, $\text{R}_2 = \text{Br}$.

A similar rationalization for (II) results in a stereochemical assignment now known from X-ray diffraction studies to be incorrect (Kilbourn & Owston, 1970). Yet dipole moment studies appeared to be consistent with the geometric assignments made for isomers of (I) and (II) (Richardson & Benson, 1967; Bedford & Richardson, 1966; Kilbourn & Owston, 1970). In addition, the chemical transformations, (III) \leftarrow (IV) \rightarrow (V), and comparison of the ultraviolet and n.m.r. data for (IA) with that for (III) (m.p. 51.5-53°) and (V) (117.5-119°), both of which were prepared from (IV) (m.p. 145-147°), established that these have the same stereochemistry (Richardson & Benson, 1967) and supported the original assignment of *trans* stereochemistry to (IA) on the basis of the admittedly tenuous *trans* stereochemical assignment for (V) (Koelsch, 1932; Curtin, Harris & Meislich, 1952; Richardson & Benson, 1967; Longfellow & Jackson, 1947, 1948). For these reasons, the n.m.r. spectral data of (I) and (II) appeared to be open to different interpretations (Richardson & Benson, 1967; Bedford & Richardson, 1966; Kilbourn & Owston, 1970) although the rationalization provided for the n.m.r. data of (II) is more convincing on both stereochemical and theoretical grounds. Finally, the *trans* isomer of (II) is the antiestrogenic isomer, while (IB), which had been assigned the *cis* geometry, is the antiestrogenic isomer (Harper & Walpole, 1966; Self, Holtkamp & Kuhn, 1967). These inconsistencies and uncertainties provided the impetus for the determination of the stereochemistry of isomers of (I) by single-crystal X-ray diffraction analysis.

The bond distances and angles (Fig. 1) are not significantly different from those found in (II) (Kilbourn & Owston, 1970). The e.s.d.'s for (IB) are about half those cited for (II). The dihedral angles between least-squares planes of the aromatic rings and the central vinyl group (Table 2*) describe a propeller-like arrangement of the rings with respect to the vinyl plane - a feature paralleling that found in (II). The C(11)-C(12)-O(1)-C(3), C(12)-O(1)-C(3)-C(4), O(1)-C(3)-C(4)-N(1) and C(3)-C(4)-N(1)-C(5) torsion angles are -179.6, -168.1, -66.1 and 81.3°, respectively. The O(1)-to-C(6) and Cl-to-H(N) interatomic distances are 2.97 and 2.05 Å, respectively. All these conformational details are shown in Fig. 2.* The *gauche* (-synclinal) N⁺-C-C-O conformation and the short O(1)-to-C(6) distance are consistent though not invariable features of such systems (Kilbourn & Owston, 1970; Sundaralingam, 1968; Chothia & Pauling, 1968; Hite & Craven, 1973) in the solid state and in solution. Other close contacts involving Cl⁻ are: 3.57 Å [C(5)]; 3.57, 2.59 Å [C(7)]; 3.70 Å [C(4)]; and 3.65 Å [C(3)]. There are no additional in-

* The table of $|F_o|$ and $|F_c|$, Table 2 and Fig. 2 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31315 (18 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

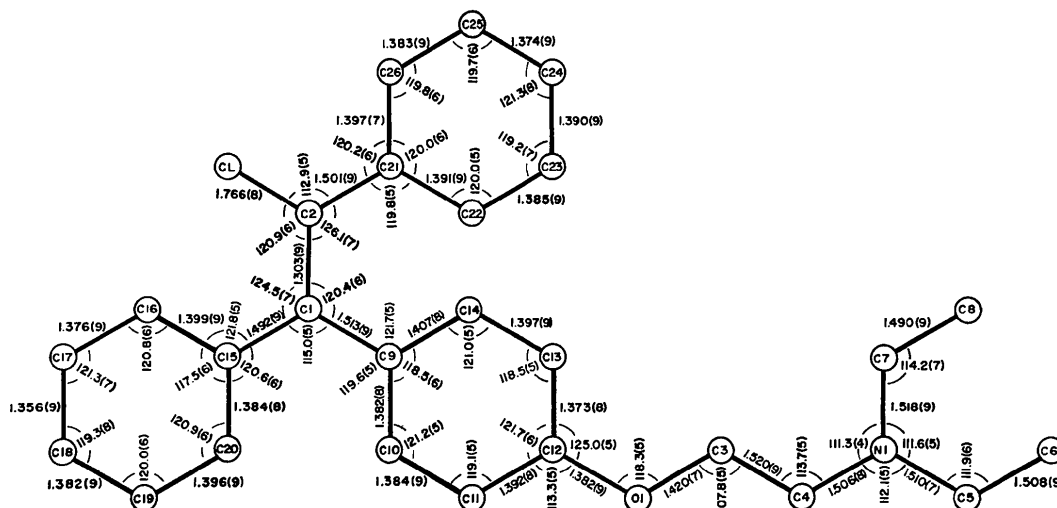


Fig. 1. Bond distances and angles of (*E*)-1-[*p*-(diethylaminoethoxy)phenyl]-1,2-diphenyl-2-chloroethylene hydrochloride, (*IB*·HCl). The numbers in parentheses are the estimated standard deviations in the last digit of the respective value.

terionic contacts significantly shorter than the sum of van der Waals radii.

The C(15)–C(1)–C(2)–C(21) torsion angle of 174.4° establishes the *trans* stereochemistry for (*IB*), the ovulation inducing, antiestrogenic (Leavitt & Meisner, 1968; Self, Holtkamp & Kuhn, 1967) isomer of clomiphene (*I*) and the *cis* stereochemistry for (*III*)–(*V*). These assignments are the opposite of those originally reported. The correlation of structure with both physical properties and biological action (the *trans* isomers are the antiestrogens) is now seen to be consistent and does provide insight into the molecular mode of action and optimal attributes for ovulation inducing agents (Ernst, Hite, Cantrell, Richardson & Benson, 1975).

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