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Stereochemistry of Muscarinic Antagonists. III.[*] Crystal and Molecular Structure of *N*-(3,3-Diphenylpropyl)-*N*-methylpiperidinium Iodide

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$C_{21}H_{28}NI$ is monoclinic, space group *Pn*, with a = 8·430 (1), b = 10·835 (2), c = 10·854 (2) Å, β = 98° 45 (1)′, Z = 2. The structure was refined to R = 0·070 for 3080 counter reflexions. The molecular conformation is defined by the N(1)–C(7)–C(8)–C(9) torsion angle of −159·7°, with the methyl group axial to the piperidyl ring and synclinal (65·3°) with respect to C(8). The two phenyl rings make an angle of 80·9° to each other. The distances between the N^+ ion and the centres of the two phenyl rings are 5·44 and 6·33 Å.

Introduction

N-(3,3-Diphenylpropyl)-*N*-methylpiperidinium iodide (CH$\varphi\varphi$PIP), a synthetic anticholinergic drug, closely related to acetylcholine, exhibits atropine-like activity at the parasympathetic postganglionic (muscarinic) receptor (Pratesi, 1964; Pratesi, Villa, Ferri, Grana & Sossi, 1969). The antagonism to acetylcholine is competitive in type (Pratesi, 1964), but the nature of the receptor–ligand interaction is not fully understood (Moran & Triggle, 1971).

Comparison of the crystal structures of a number of anticholinergic agents (Guy & Hamor, 1975; Pauling & Petcher, 1970) showed close stereochemical similarities between these molecules and with acetylcholine in the conformation suggested (Baker, Chothia, Pauling & Petcher, 1971) as corresponding to muscarinic activity. We report here the structure of the title compound as part of continuing studies on the stereochemistry of anticholinergic agents (Del Pra & Mammi, 1967; Del Pra, Mammi, Valle, Pratesi & Villa, 1973; Zanotti, Del Pra, Cano & García-Blanco, 1976; Zanotti, Rueda, Del Pra & Cano, 1977).

Experimental

Crystals of CH$\varphi\varphi$PIP, elongated along **a**, were obtained by slow evaporation of ethanolic solutions under reduced pressure, in a dry atmosphere. Photographs showed that the crystals are monoclinic, space group *Pn* (Del Pra & Mammi, 1967). Lattice constants were obtained by least squares from the setting angles of 43 reflexions measured on a diffractometer with Mo $K\alpha$ radiation monochromatized by a graphite crystal. The intensities were collected from a crystal 0·27 × 0·22 × 0·37 mm on a Philips PW 1100 four-circle diffractometer with the $\theta/2\theta$ scan mode (scan width 1·50°, scan speed 0·24° s^{-1}). 4325 independent reflexions up to θ = 35° were measured, of which 3080 had $I > 2\sigma$, σ being calculated from counting statistics. Two standard reflections were measured every 90 min. Intensities were corrected for Lorentz and polarization factors and converted to an absolute scale by Wilson's method. Absorption and extinction corrections were applied with *AGNOSTC*, written by Coppens, Leiserowitz & Rabinovich, modified by Hamilton, Edwards & Cahen.

Crystal data are in Table 1.

Table 1. *Crystal data*

$C_{21}H_{28}NI$
Space group *Pn*
λ(Mo $K\alpha$) = 0·7107 Å
a = 8·430 (1) Å
b = 10·835 (2)
c = 10·854 (2)
β = 98° 45 (1)′

Z = 2
V = 979·86 Å^3
D_o = 1·42 g cm^{-3}
D_c = 1·43
$F(000)$ = 428
μ(Mo $K\alpha$) = 16·4 cm^{-1}

Structure determination and refinement

A Patterson synthesis revealed the position of the I atom and a subsequent electron density map located all

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[*] Part II: Zanotti, Rueda, Del Pra & Cano (1977).

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non-hydrogen atoms ($R = 0{\cdot}25$). The structure was refined by full-matrix least squares, allowing the atoms to vibrate anisotropically; R fell to 0·08. At this stage the coordinates of the H atoms were calculated and included in the refinement with isotropic thermal parameters equivalent to those of the atoms to which they are bonded (Hamilton, 1959). The correction for the real and imaginary parts of the anomalous dispersion was applied for I (*International Tables for X-ray Crystallography*, 1968). The quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$, $w = 2{\cdot}4/\sigma$, where $\sigma = 1 + [(|F_o| - 25)/7]^2$ to give constant values of $w\Delta^2$, independent of the value of $|F_o|$. The final R for the 3080 observed reflexions was 0·07.

The calculations were carried out on the CYBER 76 computer of the Centro di Calcolo Interuniversitario dell'Italia Nord Orientale with the XRAY system (Stewart, Kundell & Baldwin, 1970). The scattering factors were those of Cromer & Waber (1965) for I⁻, and those of *International Tables for X-ray Crystallography* (1968) for all other atoms.

Results and discussion

A perspective view of the molecule with the numbering system is presented in Fig. 1.

Final parameters are reported in Tables 2 and 3.* In Table 4 the bond lengths and angles for non-hydrogen atoms are given. All C—H lengths are in the range 0·99–1·11 Å. Some least-squares planes and torsion angles are shown in Tables 5 and 6 respectively.

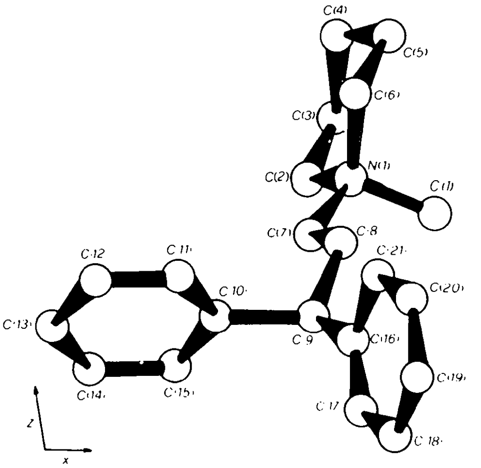

Fig. 1. A perspective view of the molecule.

Table 2. *Atomic coordinates* (×10⁴)

	x	y	z
I	0	1351·8 (4)	0
N	10081 (7)	1575 (5)	4209 (6)
C(1)	11629 (9)	1355 (8)	3720 (8)
C(2)	9147 (10)	364 (7)	4210 (8)
C(3)	9921 (23)	−574 (7)	5167 (14)
C(4)	10218 (13)	17 (9)	6456 (8)
C(5)	11206 (12)	1144 (9)	6469 (7)
C(6)	10379 (10)	2085 (8)	5518 (7)
C(7)	9038 (8)	2461 (6)	3353 (7)
C(8)	9686 (9)	3766 (7)	3278 (7)
C(9)	8872 (13)	4376 (10)	2072 (10)
C(10)	7044 (8)	4499 (6)	2052 (6)
C(11)	6396 (12)	5428 (10)	2717 (10)
C(12)	4728 (10)	5544 (7)	2625 (8)
C(13)	3748 (10)	4747 (9)	1888 (9)
C(14)	4388 (11)	3839 (9)	1228 (10)
C(15)	6016 (10)	3713 (8)	1302 (8)
C(16)	9569 (8)	5602 (7)	1816 (7)
C(17)	9497 (10)	5937 (11)	605 (9)
C(18)	10169 (16)	7025 (12)	227 (12)
C(19)	10829 (12)	7856 (10)	1157 (14)
C(20)	10948 (12)	7534 (9)	2389 (12)
C(21)	10333 (12)	6407 (8)	2745 (9)

Table 3. *Atomic coordinates for hydrogen atoms* (×10³)

	x	y	z	U
H′(C1)	1138	97	278	58
H″(C1)	1226	225	368	58
H‴(C1)	1239	73	433	58
H′(C2)	794	59	443	53
H″(C2)	904	−5	329	53
H′(C3)	909	−137	518	58
H″(C3)	1105	−89	490	58
H′(C4)	909	20	679	71
H″(C4)	1091	−69	711	71
H′(C5)	1136	157	741	56
H″(C5)	1240	93	623	56
H′(C6)	922	234	580	48
H″(C6)	1114	292	554	48
H′(C7)	886	206	241	56
H″(C7)	787	252	369	56
H′(C8)	942	432	408	50
H″(C8)	1099	374	329	50
H(C9)	909	381	128	36
H(C11)	711	603	326	41
H(C12)	428	623	310	48
H(C13)	254	482	185	53
H(C14)	366	327	70	54
H(C15)	646	305	82	41
H(C17)	890	540	−4	57
H(C18)	1009	718	−66	60
H(C19)	1121	865	87	68
H(C20)	1146	812	306	62
H(C21)	1046	616	365	56

Bond lengths (mean standard deviation 0·013 Å) and angles (mean standard deviation 0·8°) have their expected values (Guy & Hamor, 1975). Aromatic C—C bonds range from 1·357 to 1·412 Å; the mean, 1·386 Å, is shorter than the accepted value of 1·397 Å, the shortening probably being due to libration effects.

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32696 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Bond distances* (Å) *and angles* (°)

C(1)–N(1)	1·500 (10)	C(1)–N(1)–C(2)	109·8 (0·6)
N(1)–C(2)	1·531 (9)	C(1)–N(1)–C(6)	111·2 (0·6)
C(2)–C(3)	1·526 (15)	C(1)–N(1)–C(7)	109·7 (0·6)
C(3)–C(4)	1·509 (17)	N(1)–C(2)–C(3)	113·9 (0·8)
C(4)–C(5)	1·507 (14)	C(2)–C(3)–C(4)	110·9 (0·7)
C(5)–C(6)	1·540 (12)	C(3)–C(4)–C(5)	110·9 (0·9)
C(6)–N(1)	1·509 (10)	C(4)–C(5)–C(6)	110·7 (0·7)
N(1)–C(7)	1·520 (9)	C(5)–C(6)–N(1)	112·5 (0·7)
C(7)–C(8)	1·523 (10)	C(6)–N(1)–C(2)	109·0 (0·6)
C(8)–C(9)	1·532 (12)	C(2)–N(1)–C(7)	107·0 (0·5)
C(9)–C(10)	1·544 (13)	N(1)–C(7)–C(8)	116·1 (0·5)
C(10)–C(11)	1·397 (13)	C(7)–C(8)–C(9)	109·2 (0·6)
C(11)–C(12)	1·400 (13)	C(8)–C(9)–C(10)	111·4 (0·8)
C(12)–C(13)	1·366 (12)	C(8)–C(9)–C(16)	113·8 (0·7)
C(13)–C(14)	1·375 (14)	C(9)–C(10)–C(11)	121·5 (0·7)
C(14)–C(15)	1·370 (13)	C(9)–C(10)–C(15)	119·2 (0·7)
C(15)–C(10)	1·387 (10)	C(10)–C(11)–C(12)	119·7 (0·8)
C(9)–C(16)	1·495 (13)	C(11)–C(12)–C(13)	119·7 (0·9)
C(16)–C(17)	1·357 (12)	C(12)–C(13)–C(14)	120·5 (0·8)
C(17)–C(18)	1·396 (17)	C(13)–C(14)–C(15)	120·7 (0·8)
C(18)–C(19)	1·403 (18)	C(14)–C(15)–C(10)	120·3 (0·8)
C(19)–C(20)	1·371 (20)	C(15)–C(10)–C(11)	119·2 (0·7)
C(20)–C(21)	1·403 (14)	C(9)–C(16)–C(17)	117·2 (0·8)
C(21)–C(16)	1·412 (12)	C(9)–C(16)–C(21)	124·5 (0·8)
		C(16)–C(17)–C(18)	123·4 (0·9)
		C(17)–C(18)–C(19)	117·7 (1·1)
		C(18)–C(19)–C(20)	120·0 (1·1)
		C(19)–C(20)–C(21)	121·0 (1·1)
		C(20)–C(21)–C(16)	119·2 (0·9)
		C(21)–C(16)–C(17)	118·3 (0·8)

Table 5. *Deviations* (Å) *of the atoms from some least-squares planes in the molecule, with their dihedral angles*

The equations of the planes are in the form $AX + BY + CZ = D$, where X,Y,Z are coordinates referred to orthogonal Å space. An asterisk denotes an atom not used in the plane calculation.

Plane 1: $-0{\cdot}11217X - 0{\cdot}62573Y + 0{\cdot}77193Z = -1{\cdot}97904$

C(10)	0·001	C(13)	0·002
C(11)	0·001	C(14)	0·001
C(12)	−0·003	C(15)	−0·003
C(9)*	−0·07	H(C13)	0·03
H(C11)*	−0·01	H(C14)*	0·006
H(C12)*	−0·02	H(C15)*	−0·001

Plane 2: $0{\cdot}89578X - 0{\cdot}44375Y - 0{\cdot}02577Z = 4{\cdot}22601$

C(16)	−0·01	C(19)	−0·02
C(17)	−0·01	C(20)	−0·00
C(18)	0·03	C(21)	0·02
C(9)*	0·003	H(C19)*	−0·07
H(C17)*	−0·09	H(C20)*	−0·01
H(C18)*	0·05	H(C21)*	0·07

Dihedral angles (°)

Plane 1–Plane 2	81·0
Plane C(8)C(9)C(10)–Plane 1	76·1
Plane C(8)C(9)C(16)–Plane 2	29·5

The $C(sp^3)$–N^+ bonds average 1·515 Å, in good agreement with previous values (Zanotti, Del Pra, Cano & García-Blanco, 1976; Guy & Hamor, 1975; Zanotti, Rueda, Del Pra & Cano, 1977).

The two phenyl rings are planar within experimental error and the angle between them is 80·9°.

The piperidyl ring assumes the chair conformation with torsion angles in the range 52·7–57·4° (mean 55°). Its C–C lengths (average 1·52 Å) have values similar to those in analogous compounds (Guy & Hamor, 1975).

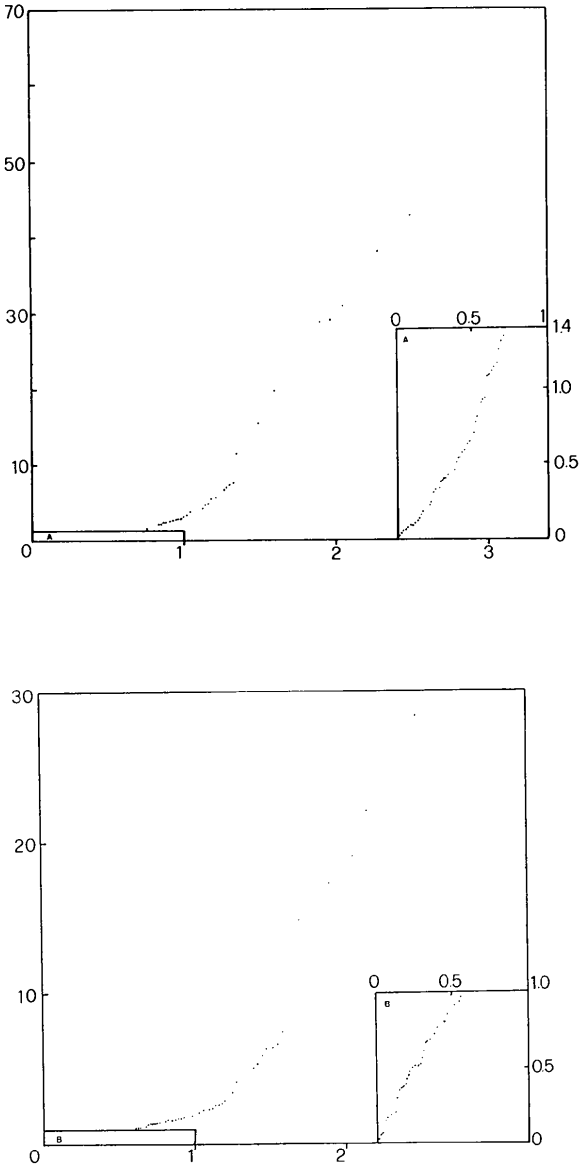

Fig. 2. Half-normal probability plots calculated with bond lengths, valence angles and internal rotation angles to compare CHφφPIP with the two solid-state conformations of φφPIP. The inset on the right represents the enlargement of the first part of the plot.

The conformational features of the remaining part of the molecule are defined by rotation angles of −159·7 and −62·9° about C(7)–C(8) and C(8)–C(9) respectively; in addition the methyl C atom, which is axial with respect to the piperidyl ring, assumes the synclinal conformation with respect to C(8). This arrangement does not resemble that found in the first compound of this series (Zanotti, Del Pra, Cano & García-Blanco, 1976) and in other antagonists (Baker, Chothia, Pauling & Petcher, 1971; Guy & Hamor, 1975), but agrees with the solid-state conformations of a synthetic anticholinergic drug previously examined (Zanotti, Rueda, Del Pra & Cano, 1977).

The distances between the quaternary N atom and the centres of the two phenyl rings are 5·44 and 6·33 Å; similar values have been observed in many anticholinergic agents (Guy & Hamor, 1975; Zanotti, Rueda, Del Pra & Cano, 1977).

Half-normal probability plots (Abrahams & Keve, 1971) were calculated to compare the structural and conformational parameters of CH$\varphi\varphi$PIP with those of the previously reported isosteric antagonist, *N*-(2-diphenylaminoethyl)-*N*-methylpiperidinium bromide, $\varphi\varphi$PIP (Zanotti, Rueda, Del Pra & Cano, 1977), which exhibits two solid-state conformations. The resulting plots (Fig. 2) show that the conformation of CH$\varphi\varphi$PIP is quite different from either of those of $\varphi\varphi$PIP.

Table 6. *Torsion angles* (°)

The torsion angle of the bonded group *A*–*X*–*Y*–*B* is the angle between the planes *A*–*X*–*Y* and *X*–*Y*–*B*. It is positive if clockwise and negative if anticlockwise (Klyne & Prelog, 1960).

C(1)–N(1)–C(7)–C(8)	65·3
N(1)–C(7)–C(8)–C(9)	−159·7
C(7)–C(8)–C(9)–C(10)	−62·9
C(7)–C(8)–C(9)–C(16)	172·1
C(7)–N(1)–C(2)–C(3)	171·9
N(1)–C(2)–C(3)–C(4)	−54·0
C(2)–C(3)–C(4)–C(5)	55·0
C(3)–C(4)–C(5)–C(6)	−56·7
C(4)–C(5)–C(6)–N(1)	57·4
C(5)–C(6)–N(1)–C(2)	−54·0
C(6)–N(1)–C(2)–C(3)	52·7

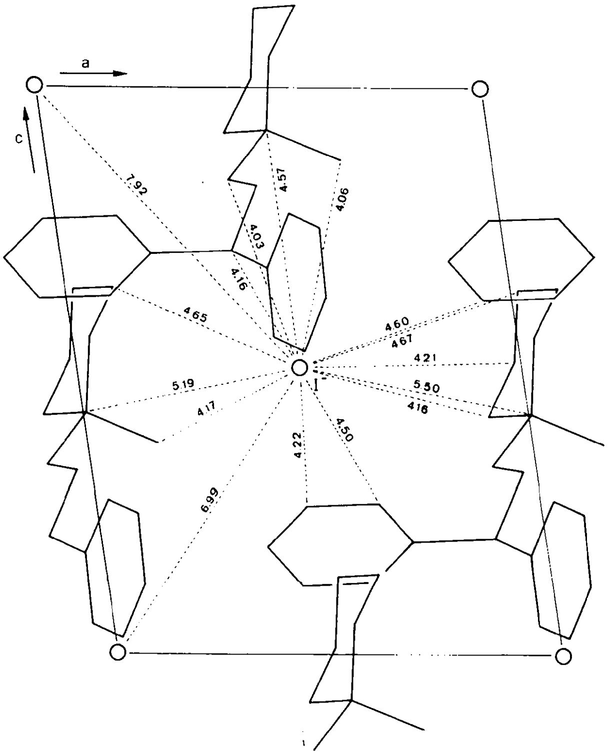

Fig. 3. The crystal structure projected down **b**.

Packing

The packing is determined by Coulombic and van der Waals forces. The 4·57 Å $I^-\cdots N^+$ distance is the shortest allowed by steric hindrance. The more relevant distances are reported in Fig. 3.

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References*

Abrahams, S. C. & Keve, E. T. (1971). *Acta Cryst.* A**27**, 157–165.

Baker, R. W., Chothia, C. H., Pauling, P. & Petcher, T. J. (1971). *Nature, Lond.* **230**, 439–445.

Cromer, D. T. & Waber, J. T. (1965). *Acta Cryst.* **18**, 104–109.

Del Pra, A. & Mammi, M. (1967). *Ric. Sci.* **37**, 1181.

Del Pra, A., Mammi, M., Valle, G., Pratesi, P. & Villa, L. (1973). *Farm. Ed. Sci.* **9**, 675–680.

Guy, J. J. & Hamor, T. A. (1975). *J. Chem. Soc. Perkin* II, pp. 1074–1078.

Hamilton, W. C. (1959). *Acta Cryst.* **12**, 609–610.

International Tables for X-ray Crystallography (1968). Vol. III, 2nd ed., pp. 201–209, 213–216. Birmingham: Kynoch Press.

Klyne, W. & Prelog, V. (1960). *Experientia*, **16**, 521–523.

Moran, J. F. & Triggle, D. J. (1971). In *Cholinergic Ligand Interactions*, edited by D. J. Triggle, J. F. Moran & E. A. Barnard. New York: Academic Press.

Pauling, P. J. & Petcher, T. J. (1970). *Nature, Lond.* **228**, 673–674.

Pratesi, P. (1964). *Postepy Hig. Med. Dosw.* **18**, 969.

Pratesi, P., Villa, L., Ferri, V., Grana, E. & Sossi, A. (1969). *Farm. Ed. Sci.* **24**, 313.

Stewart, J. M., Kundell, F. A. & Baldwin, J. C. (1970). XRAY 70 system. Computer Science Center, Univ. of Maryland, College Park, Maryland.

Zanotti, G., Del Pra, A., Cano, F. H. & García-Blanco, S. (1976). *Cryst. Struct. Commun.* **5**, 811–814.

Zanotti, G., Rueda, D. R., Del Pra, A. & Cano, F. H. (1977). *Cryst. Struct. Commun.* **6**, 79–83.