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Stereochemistry of Muscarinic Antagonists. IV.* Conformational Flexibility of the Cholinergic Antagonist (3,3-Diphenylpropyl)trimethylammonium Iodide

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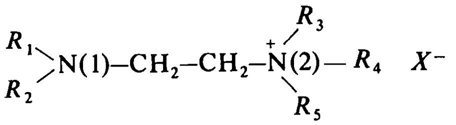
$C_{18}H_{24}NI$ is triclinic, space group $P\bar{1}$, with a = 19·600 (8), b = 9·930 (4), c = 9·606 (4) Å, α = 95·83 (5), β = 104·18 (4), γ = 79·90 (6)°, Z = 4. The structure was refined to R = 0·049 for 3040 counter reflexions. The two molecules of the asymmetric unit show similar conformations. The backbone chains are almost zigzag planar. The dihedral angles between the phenyl rings are 88·2 and 83·5° for molecules (I) and (II) respectively. The pairs of distances between the N^+ ion and the centres of the two phenyl rings are 6·32, 5·29 Å and 5·29, 6·37 Å for (I) and (II) respectively.

Introduction

In the series of substances capable of interaction with the muscarine receptor, the change-over from a substance with mimetic to one with antagonistic activity is often obtained by introducing aromatic or hydroaromatic rings of higher alkyls into the agonistic molecule. Besides the cationic head, these are precisely the groups which are regarded as the biggest contributors to the affinity of the antagonist molecule for the receptor (Ariens, 1966).

It is, therefore, interesting to examine, on the basis of intramolecular distances between the groups capable of interaction with the biological partner, whether optimal steric conditions exist as far as affinity is concerned. X-ray studies have already been carried out on several compounds (Zanotti, Del Pra, Cano & García-Blanco, 1976; Zanotti, Rueda, Del Pra & Cano, 1977*a*,*b*) which belong to a series of substances with general formula (1) exhibiting remarkable atropine-like activity (Pratesi, Villa, Ferri, Grana & Sossi, 1969).



$$R_1R_2N(1)\text{–}CH_2\text{–}CH_2\text{–}\overset{+}{N}(2)R_3R_4R_5\quad X^-$$

(1)

They show competitive antagonism towards acetylcholine and their activity is systematically greater both when N(1) is CH and when R_1 and R_2 are phenyl and cyclohexyl groups.

The analysis of the triclinic form (Del Pra & Mammi, 1967) of (3,3-diphenylpropyl)trimethylammonium iodide is reported here.

Experimental

Transparent {100} plates were prepared by evaporation of an acetone solution under reduced pressure in a dry atmosphere. Preliminary photographs showed that the crystals are triclinic. A second crystalline modification was obtained from ethanol solution as transparent needle-shaped monoclinic crystals, elongated along **c** (Del Pra & Mammi, 1967).

Lattice constants of the triclinic form were obtained by least squares from the setting angles of 60 reflections measured on a four-circle diffractometer with Mo $K\alpha$ radiation, monochromatized by a graphite crystal. The intensities were collected from a crystal 0·3 × 0·2 × 0·3 mm on a Philips PW 1100 four-circle diffractometer operating in the ω-scan mode (scan width = 1·4°; scan speed = 0·06° s^{-1}). 4335 independent reflections up to θ = 22° were measured, of which 3040 had $I > 2\sigma$, σ being calculated from the counting statis-

Table 1. *Crystal data (standard deviations in parentheses refer to the least significant digit)*

$C_{18}H_{24}NI$
Space group $P\bar{1}$
λ(Mo $K\alpha$) = 0·7107 Å
a = 19·600 (8) Å
b = 9·930 (4)
c = 9·606 (4)
D_o = 1·36 g cm^{-3}
D_c = 1·36

M_r = 381·3
Z = 4
V = 1781·2 $Å^3$
α = 95·83 (5)°
β = 104·18 (4)
γ = 79·90 (6)
$F(000)$ = 768
μ(Mo $K\alpha$) = 17·3 cm^{-1}

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* Part III: Zanotti, Rueda, Del Pra & Cano (1977*b*).

tics. Two standard reflections were measured every 120 min. Intensities were corrected for Lorentz and polarization factors and were converted to an absolute scale by Wilson's method. Absorption and extinction were ignored. Crystal data are given in Table 1.

Structure determination and refinement

A Patterson synthesis revealed the positions of the two I^- ions, and all non-hydrogen atoms were located from subsequent difference maps ($R = 0{\cdot}18$). The structure was refined by full-matrix least squares to $R = 0{\cdot}07$. At this stage the H atoms were included at calculated positions with isotropic temperature parameters equivalent to the anisotropic ones of the atoms to which they are bonded (Hamilton, 1959). The correction for the real and imaginary parts of anomalous dispersion was applied to the I^- ions only (*International Tables for X-ray Crystallography*, 1968). The quantity minimized was $\sum w(|F_o| - |F_c|)^2$, where $w = 0{\cdot}55\{1 + [(|F_o| - 30)/15]^2\}^{-1}$ to give constant values of $w\Delta^2$ (where $\Delta = |F_o| - |F_c|$) independent of the value of $|F_o|$. The final R for all observed reflexions was 0·049 ($R_w = 0{\cdot}055$). 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.*

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

	Molecule (I)			Molecule (II)		
	x	*y*	*z*	*x*	*y*	*z*
H(C1)	354	345	754	717	200	766
H'(C1)	331	232	864	764	343	801
H(C2)	303	185	536	688	238	504
H'(C2)	264	115	659	740	374	542
H(C3)	243	412	573	796	73	623
H(C5)	191	579	692	864	395	569
H(C6)	153	682	902	968	467	734
H(C7)	136	549	1076	1035	320	920
H(C8)	182	313	1073	991	131	975
H(C9)	217	209	868	888	63	816
H(C11)	216	224	351	716	209	311
H(C12)	116	190	164	739	121	88
H(C13)	0	218	204	855	9	67
H(C14)	−19	298	439	944	−33	282
H(C15)	84	336	635	918	27	510
H'(C16)	475	298	888	644	306	929
H''(C16)	450	183	994	692	449	964
H'''(C16)	519	122	896	596	478	902
H'(C17)	399	−13	866	694	582	761
H''(C17)	367	−29	673	653	528	580
H'''(C17)	457	−71	769	599	607	700
H'(C18)	403	142	535	594	321	537
H''(C18)	451	271	638	588	236	689
H'''(C18)	493	95	635	540	406	657

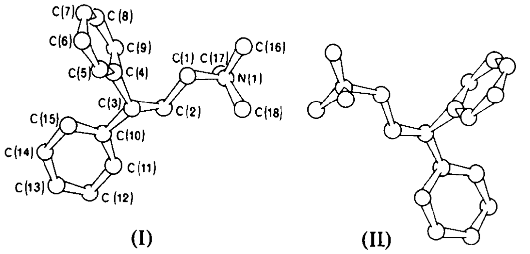

Fig. 1. A perspective view of the asymmetric unit.

Table 2. *Final positional parameters and e.s.d.'s for the heavy atoms*

	x	*y*	*z*		*x*	*y*	*z*
I(1)	0·34893 (3)	0·05984 (6)	0·20570 (7)	I'(1)	0·57263 (3)	0·40300 (6)	0·23259 (6)
N(1)	0·4162 (3)	0·1448 (7)	0·7635 (7)	N'(1)	0·6512 (3)	0·3957 (7)	0·7399 (6)
C(1)	0·3459 (4)	0·2374 (9)	0·7610 (9)	C'(1)	0·7205 (4)	0·3001 (9)	0·7309 (9)
C(2)	0·2842 (4)	0·2079 (8)	0·6385 (8)	C'(2)	0·7334 (4)	0·2750 (9)	0·5803 (9)
C(3)	0·2248 (5)	0·3290 (11)	0·6157 (10)	C'(3)	0·8023 (4)	0·1691 (9)	0·5836 (9)
C(4)	0·2034 (4)	0·3826 (10)	0·7601 (8)	C'(4)	0·8670 (4)	0·2228 (8)	0·6822 (7)
C(5)	0·1871 (5)	0·5223 (13)	0·7686 (15)	C'(5)	0·8909 (5)	0·3368 (9)	0·6546 (9)
C(6)	0·1648 (6)	0·5799 (12)	0·8903 (19)	C'(6)	0·9516 (7)	0·3773 (11)	0·7446 (14)
C(7)	0·1578 (6)	0·5035 (19)	0·9960 (13)	C'(7)	0·9879 (5)	0·2993 (16)	0·8616 (13)
C(8)	0·1807 (5)	0·3689 (16)	0·9912 (12)	C'(8)	0·9650 (6)	0·1874 (14)	0·8876 (11)
C(9)	0·2019 (5)	0·3101 (11)	0·8731 (11)	C'(9)	0·9044 (5)	0·1513 (9)	0·7995 (10)
C(10)	0·1578 (4)	0·2886 (10)	0·5077 (9)	C'(10)	0·8147 (4)	0·1279 (8)	0·4335 (9)
C(11)	0·1660 (5)	0·2458 (11)	0·3702 (9)	C'(11)	0·7640 (5)	0·1547 (9)	0·3075 (10)
C(12)	0·1086 (5)	0·2203 (10)	0·2616 (8)	C'(12)	0·7781 (7)	0·1068 (11)	0·1740 (10)
C(13)	0·0412 (5)	0·2390 (11)	0·2876 (10)	C'(13)	0·8431 (7)	0·0360 (11)	0·1670 (11)
C(14)	0·0323 (5)	0·2817 (12)	0·4226 (12)	C'(14)	0·8944 (6)	0·0113 (12)	0·2894 (13)
C(15)	0·0902 (5)	0·3048 (13)	0·5309 (10)	C'(15)	0·8800 (5)	0·0563 (12)	0·4206 (10)
C(16)	0·4691 (5)	0·1908 (11)	0·8938 (11)	C'(16)	0·6448 (5)	0·4061 (12)	0·8922 (10)
C(17)	0·4111 (6)	−0·0006 (11)	0·7720 (13)	C'(17)	0·6499 (6)	0·5327 (11)	0·6923 (14)
C(18)	0·4419 (5)	0·1623 (11)	0·6339 (11)	C'(18)	0·5891 (4)	0·3374 (10)	0·6490 (10)

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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 33299 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Results and discussion

A perspective view of the asymmetric unit showing the conformation and the numbering system of the two independent molecules is presented in Fig. 1. The final atomic parameters are reported in Tables 2 and 3.

Table 4 gives the bond lengths and angles for all non-hydrogen atoms, not corrected for thermal motion. Some least-squares planes and torsion angles are shown in Tables 5 and 6.

Bond lengths (mean standard deviation 0·01 Å) and angles (mean standard deviation 0·8°) are normal. Aromatic C—C bonds range from 1·34 to 1·40 Å; the mean, 1·37 Å, is shorter than the accepted value of 1·397 Å, the shortening probably being due to libration effects, as thermal motion of the benzene rings is large. The $C(sp^3)$—N^+ bonds average 1·48 Å in agreement with analogous compounds (Guy & Hamor, 1975, and references therein; Zanotti, Del Pra, Cano & Garcia-Blanco, 1976; Zanotti, Rueda, Del Pra &

Table 4. *Interatomic distances* (Å) *and valence angles* (°) *with e.s.d.'s in parentheses*

	Molecule (I)	Molecule (II)
N(1)—C(1)	1·51 (1)	1·53 (1)
N(1)—C(16)	1·50 (1)	1·49 (1)
N(1)—C(17)	1·48 (1)	1·47 (1)
N(1)—C(18)	1·49 (1)	1·48 (1)
C(1)—C(2)	1·51 (1)	1·52 (1)
C(2)—C(3)	1·56 (1)	1·55 (1)
C(3)—C(4)	1·50 (1)	1·53 (1)
C(3)—C(10)	1·55 (1)	1·52 (1)
C(4)—C(5)	1·37 (2)	1·37 (1)
C(5)—C(6)	1·38 (2)	1·38 (1)
C(6)—C(7)	1·37 (2)	1·40 (2)
C(7)—C(8)	1·33 (2)	1·34 (2)
C(8)—C(9)	1·35 (2)	1·36 (1)
C(9)—C(4)	1·37 (1)	1·37 (1)
C(10)—C(11)	1·38 (1)	1·38 (1)
C(11)—C(12)	1·37 (1)	1·40 (1)
C(12)—C(13)	1·38 (2)	1·36 (1)
C(13)—C(14)	1·37 (2)	1·36 (1)
C(14)—C(15)	1·37 (1)	1·37 (2)
C(15)—C(10)	1·38 (1)	1·37 (1)
C(1)—N(1)—C(16)	107·0 (6)	107·8 (6)
C(1)—N(1)—C(17)	112·2 (7)	111·9 (8)
C(1)—N(1)—C(18)	109·9 (6)	110·3 (6)
C(16)—N(1)—C(18)	107·9 (7)	108·1 (7)
C(16)—N(1)—C(17)	109·5 (7)	110·2 (8)
C(17)—N(1)—C(18)	110·2 (8)	108·5 (7)
N(1)—C(1)—C(2)	116·0 (7)	114·1 (6)
C(1)—C(2)—C(3)	110·0 (7)	109·1 (6)
C(2)—C(3)—C(4)	110·9 (7)	111·0 (6)
C(3)—C(4)—C(5)	111·2 (9)	122·3 (7)
C(3)—C(4)—C(9)	129·1 (9)	118·9 (8)
C(5)—C(4)—C(9)	119·7 (9)	118·7 (7)
C(4)—C(5)—C(6)	115·7 (12)	119·7 (8)
C(5)—C(6)—C(7)	123·1 (12)	119·0 (11)
C(6)—C(7)—C(8)	119·5 (13)	121·2 (10)
C(7)—C(8)—C(9)	118·2 (13)	118·7 (10)
C(8)—C(9)—C(4)	123·2 (11)	122·6 (10)
C(2)—C(3)—C(10)	110·8 (7)	112·2 (6)
C(4)—C(3)—C(10)	107·9 (8)	111·0 (7)
C(3)—C(10)—C(11)	115·9 (8)	124·3 (8)
C(3)—C(10)—C(15)	126·3 (8)	118·7 (7)
C(11)—C(10)—C(15)	117·4 (8)	116·9 (9)
C(10)—C(11)—C(12)	121·0 (9)	120·9 (9)
C(11)—C(12)—C(13)	120·3 (8)	119·8 (9)
C(12)—C(13)—C(14)	119·3 (8)	120·2 (10)
C(13)—C(14)—C(15)	119·9 (9)	119·7 (10)
C(14)—C(15)—C(10)	122·0 (9)	122·3 (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 $PX + QY + RZ = S$ in orthogonal space with X parallel to **a**, Z perpendicular to **a** in the *ac* plane, and Y perpendicular to the *ac* plane. Asterisks denote atoms not used in the plane calculations.

Plane 1: $0{\cdot}0730X + 0{\cdot}9527Y - 0{\cdot}2949Z = 1{\cdot}5128$

C(10)	0·002	C(13)	0·002
C(11)	0·004	C(14)	0·005
C(12)	−0·006	C(15)	−0·007
C(3)*	0·17		

Plane 2: $0{\cdot}8856X + 0{\cdot}1050Y + 0{\cdot}4524Z = 6{\cdot}0634$

C(4)	−0·03	C(7)	−0·05
C(5)	0·02	C(8)	0·03
C(6)	0·02	C(9)	0·01
C(3)*	−0·09		

Plane 3: $0{\cdot}5050X + 0{\cdot}8567Y - 0{\cdot}1047Z = 8{\cdot}3242$

C′(10)	−0·008	C′(13)	−0·005
C′(11)	0·012	C′(14)	0·008
C′(12)	−0·005	C′(15)	−0·002
C′(3)*	−0·07		

Plane 4: $0{\cdot}6228X - 0{\cdot}5655Y - 0{\cdot}5407Z = 5{\cdot}2304$

C′(4)	0·002	C′(7)	−0·002
C′(5)	0·005	C′(8)	0·009
C′(6)	−0·006	C′(9)	−0·009
C′(3)*	0·07		

Dihedral angles (°)

Plane 1/Plane 2	88·2
Plane 3/Plane 4	83·5

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 counterclockwise (Klyne & Prelog, 1960).

N(1)—C(1)—C(2)—C(3)	161·2
C(2)—C(1)—N(1)—C(16)	−179·2
C(1)—C(2)—C(3)—C(4)	50·9
C(1)—C(2)—C(3)—C(10)	170·8
C(2)—C(3)—C(4)—plane 2	35·7
C(2)—C(3)—C(10)—plane 1	59·0
N′(1)—C′(1)—C′(2)—C′(3)	176·1
C′(2)—C′(1)—N′(1)—C′(16)	−177·9
C′(1)—C′(2)—C′(3)—C′(4)	60·9
C′(1)—C′(2)—C′(3)—C′(10)	174·3
C′(2)—C′(3)—C′(4)—plane 4	62·0
C′(2)—C′(3)—C′(10)—plane 3	13·7

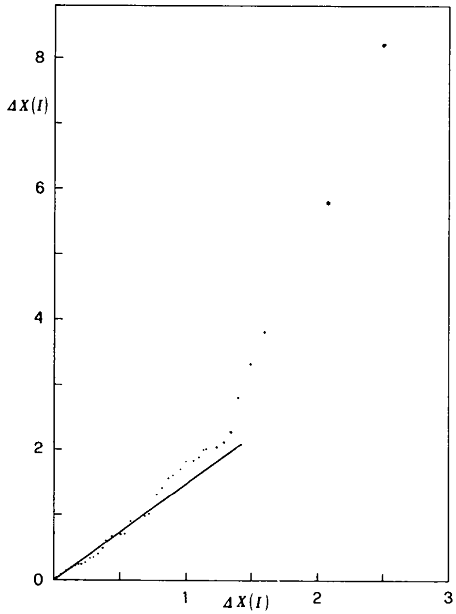

Fig. 2. Half-normal probability plot calculated with bond lengths, valence angles and internal rotation angles of the two independent molecules.

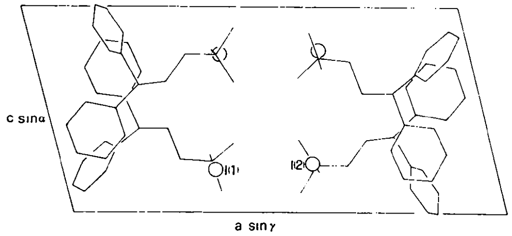

Fig. 3. The crystal structure projected down *b*.

Cano, 1977*a*,*b*). The phenyl rings are planar within experimental error. The dihedral angles between the rings are 88·2 and 83·5° for (I) and (II) respectively. The conformation of the remaining part of (I) is defined by rotation angles of 161·2 and 50·9° about C(1)–C(2) and C(2)–C(3) respectively; one methyl C atom is in the *trans* position (−179·2°) with respect to C(2), as is almost the case in (II) and in all muscarinic agonists (Baker, Chothia, Pauling & Petcher, 1971) and antagonists (Guy & Hamor, 1975; Zanotti, Del Pra, Cano & García-Blanco, 1976).

The dimensions of (II) are similar to those of (I) (Tables 4 and 6). In addition the pair of distances between the quaternary N atom and the centres of the two phenyl rings are 6·32, 5·29 Å and 5·29, 6·37 Å for (I) and (II) respectively; similar values have been observed in many anticholinergic agents (Guy & Hamor, 1975; Zanotti, Rueda, Del Pra & Cano, 1977*b*).

A half-normal probability plot (Abrahams & Keve, 1971) was calculated in order to compare the structural and conformational parameters of the two independent molecules. The resulting plot (Fig. 2) indicates that the dimensions of the two molecules are very similar; the only differences arise from the relative positions of the phenyl rings with respect to the central chain, and from the positions of the two I^- ions relative to the cationic heads. The plot is linear with a slope of about 1·5, suggesting that the e.s.d.'s have been underestimated.

Table 7. *The shorter* $N^+\cdots I^-$ *contact distances* (Å)

I(1)–N(1)	4·646 (6)
I(1)–N(2)	4·606 (7)
I(2)–N(1)	4·530 (7)
I(2)–N(2)	4·550 (7)

Packing

The packing (Fig. 3) is determined by Coulombic and van der Waals forces. Ionic layers, almost parallel to (100), alternate with others in which there are only hydrophobic parts of the molecule and where the phenyl rings are responsible for the cohesion. The shorter $I^- \cdots N^+$ distances are reported in Table 7. All other intermolecular distances are as expected for standard van der Waals values.

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