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Stereochemistry of Muscarinic Antagonists. I. Crystal and Molecular Structure of (2-Diphenylaminoethyl)trimethylammonium Iodide

BY G. ZANOTTI AND A. DEL PRA

Biopolymer Research Centre, Università di Padova, 35100 *Padova, Italy*

AND F. H. CANO AND S. GARCÍA-BLANCO

Departamento de Rayos X, Instituto 'Rocasolano', CSIC, Serrano 119, *Madrid* 6, *Spain*

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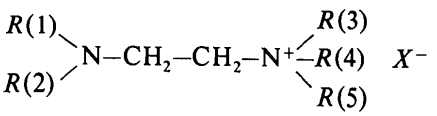
Crystals of (2-diphenylaminoethyl)trimethylammonium iodide, $C_{17}H_{23}N_2I$, are monoclinic, space group $P2_1/a$, with four molecules in a cell having the dimensions $a = 19{\cdot}137$ (7), $b = 7{\cdot}400$ (1), $c = 12{\cdot}872$ (6) Å, $\beta = 106°3$ (1)′. Intensity data were collected on a four-circle diffractometer with Mo $K\alpha$ radiation. The structure was solved by the heavy-atom method and refined by a full-matrix least-squares program to a final R value of 0·048 for 3142 observed reflexions. The N(2)–C(2)–C(1)–N(1)–C(17) chain is almost planar with a zigzag conformation, and the two phenyl rings make an angle of 70·6° with each other. The distances between the N^+ ion and the centres of the two phenyl rings are 5·60 and 5·72 Å respectively.

Introduction

Quaternary ammonium salts, such as:



(I)

where $R(1)$ and $R(2)$ may be aryl or aralkyl residues and $R(3)$, $R(4)$ and $R(5)$ are alkyl residues, exhibit atropine-like activity at the muscarinic receptor (Pratesi, Villa, Grana & Lilla, 1963 and references therein). This property is more marked than in the corresponding bitertiary free bases and it is fully preserved by replacing N by the isosteric methynic group ≡CH. Although the chemical constitution of these compounds is quite different from that of the agonistic drugs such as acetylcholine and muscarine, their antagonism against the latter compounds is reported to be of a competitive type (Pratesi, 1964). In spite of the number of studies on the structure of many anticholinergic agents made in the last few years (Guy & Hamor, 1975*a*,*b* and references therein; Meyerhöffer, 1970; Baker, Chothia, Pauling & Petcher, 1971 and references therein; *etc.*) the nature of the receptor–ligand interaction is not fully understood.

We are studying, by means of X-ray analysis, a number of compounds similar to (I) in order to contribute to the better understanding of the correlation between molecular conformation and pharmacological activity. Here we present the final crystallographic results of (2-diphenylaminoethyl)trimethylammonium iodide, the first compound of the series exhibiting remarkable atropine-like activity (Pratesi, Villa, Ferri, Grana & Sossi, 1969). A preliminary account of this crystal structure has already been given (Zanotti, Del Pra, Cano & García-Blanco, 1976).

Experimental

Transparent needle-shaped crystals of (2-diphenylaminoethyl)trimethylammonium iodide, elongated along **b**, were obtained by slow evaporation of the solvent from a solution of absolute ethanol under reduced constant pressure, in a dry atmosphere. Preliminary photographic data showed that the crystals are monoclinic, space group $P2_1/a$ (Del Pra & Mammi, 1967).

Lattice constants were obtained from a least-squares analysis of the setting angles of 36 reflexions measured on a four-circle diffractometer with Mo $K\alpha$ radiation monochromatized by a graphite crystal. The intensities were collected from a crystal of approximate dimensions 0·21 × 0·53 × 0·12 mm, on a Philips PW 1100 four-circle diffractometer operating in the $\theta/2\theta$ scan mode (scan width = 1·60°, scan speed = 0·03° s^{-1}). 4840 independent reflexions up to $\theta = 30°$ were measured, of which 3142 had intensities greater than twice their standard deviation (σ), σ being calculated from the counting statistics of the measurements. During the data collection three standard reflexions were measured every 90 min to check the stability of the crystal and electronics. Intensities were corrected for Lorentz and polarization factors and were converted to the absolute scale by Wilson's method. Absorption and extinction corrections were applied with the program *AGNOSTC* written by Coppens,

Table 1. *Crystal data*

$C_{17}H_{23}N_2I$	
Space group $P2_1/a$	$Z = 4$
λ(Mo $K\alpha$) = 0·7107 Å	V = 1749·58 Å^3
a = 19·137 (7) Å	D_o = 1·40 g cm^{-3}
b = 7·400 (1)	D_c = 1·42
c = 12·872 (6)	F(000) = 768 e
β = 106° 3 (1)′	μ(Mo $K\alpha$) = 18·1 cm^{-1}

Leiserowitz & Rabinovich and modified by Hamilton, Edwards & Cahen. Crystal data are given in Table 1.

Structure determination and refinement

A Patterson synthesis revealed the position of the I atom, and the positions of the non-hydrogen atoms were derived from the subsequent electron density map. The R value was 0·25. The structure was refined by full-matrix least-squares methods and the R value was reduced to 0·06. At this stage a difference map yielded the positions of all the H atoms. These were then included in the refinement with isotropic temperature factors equivalent to the anisotropic ones of the atoms to which the H are bonded (Hamilton, 1959); the correction for the real and imaginary parts of the anomalous dispersion was applied for I only (*International Tables for X-ray Crystallography*, 1968). The refinement was carried out minimizing the quantity $\Sigma w(|F_o| - |F_c|)^2$, $w = 32/\sigma$, where $\sigma = 25 + |F_o| + 0{\cdot}008|F_o|^2 + 10 \sin\theta$, to give constant values of $w\Delta^2$ (where $\Delta = |F_o| - |F_c|$), independent of the value of $|F_o|$. The final R value for all observed reflexions was 0·048.

The calculations were carried out on the CYBER 76 computer of the 'Centro di Calcolo Interuniversitario dell'Italia Nord Orientale' with the XRAY system of crystallographic programs (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 showing its conformation and the numbering system is presented in Fig. 1. The final structural parameters, with their e.s.d.'s, of the non-hydrogen and H atoms are reported in Tables 2 and 3 respectively;* in Table 4 the bond lengths and valence angles for all non-hydrogen atoms, not corrected for changes due to thermal vibrations, are given. All the C—H lengths are in the range 0·8–1·2 Å. Some least-squares planes and torsion angles are shown in Tables 5 and 6 respectively.

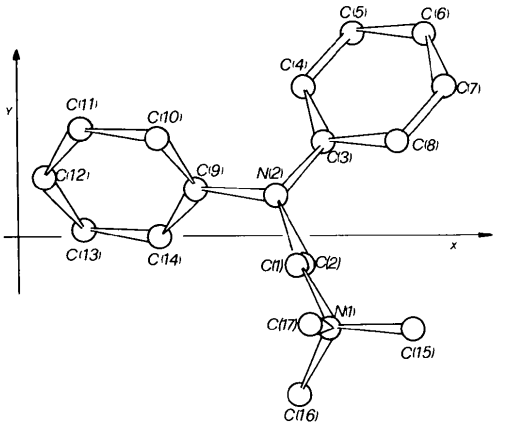


Fig. 1. Perspective view of the cation.

Bond lengths (mean standard deviation 0·006 Å) and angles (mean standard deviation 0·4°) generally are quite normal. Aromatic C—C bonds range from 1·362–1·395 Å; the mean, 1·377 Å, is shorter than the accepted value of 1·397 Å, the shortening being probably due to libration effects as the thermal motion of the atoms of the benzene rings is large. The C(sp^3)—N^+ bonds average 1·503 Å, in good agreement with analogous compounds (Guy & Hamor, 1973, 1974, 1975*a*,*b*). The amine group N(2)C(2)C(3)C(9) is approximately planar; the N atom is at a distance of

Table 2. *Final positional parameters* ($\times 10^4$) *and their standard deviations for non-hydrogen atoms*

	x	y	z
I	1487·9 (2)	2217·9 (5)	1251·4 (3)
N(1)	5896 (2)	−2366 (4)	9269 (2)
N(2)	5374 (2)	995 (5)	6950 (3)
C(1)	5573 (2)	−723 (5)	8627 (3)
C(2)	5639 (3)	−720 (6)	7455 (3)
C(3)	5865 (2)	2392 (5)	6928 (3)
C(4)	5654 (2)	3802 (6)	6188 (3)
C(5)	6134 (2)	5170 (6)	6122 (3)
C(6)	6835 (2)	5170 (7)	6800 (4)
C(7)	7041 (2)	3793 (8)	7523 (4)
C(8)	6569 (2)	2425 (6)	7595 (3)
C(9)	4611 (2)	1184 (6)	6462 (3)
C(10)	4220 (3)	2518 (6)	6788 (4)
C(11)	3474 (3)	2699 (8)	6302 (5)
C(12)	3132 (3)	1521 (10)	5512 (5)
C(13)	3515 (3)	196 (9)	5179 (5)
C(14)	4249 (3)	18 (7)	5638 (4)
C(15)	6709 (2)	−2390 (7)	9495 (4)
C(16)	5587 (2)	−4080 (5)	8717 (4)
C(17)	5712 (2)	−2255 (6)	10341 (3)

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32669 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Fractional coordinates* ($\times 10^3$) *and thermal parameters* ($\times 10^3$) *for the hydrogen atoms*

	x	*y*	*z*	*U*
H′(C1)	507 (4)	−063 (9)	867 (5)	40
H″(C1)	576 (3)	027 (9)	945 (5)	40
H′(C2)	617 (5)	−082 (10)	748 (5)	47
H″(C2)	544 (4)	−168 (10)	708 (6)	47
H(C4)	521 (3)	383 (10)	576 (5)	44
H(C5)	606 (3)	618 (10)	555 (5)	42
H(C6)	714 (4)	573 (10)	647 (5)	50
H(C7)	749 (4)	384 (11)	799 (5)	53
H(C8)	672 (4)	158 (10)	802 (5)	48
H(C10)	447 (4)	315 (11)	736 (6)	54
H(C11)	327 (4)	349 (12)	671 (6)	71
H(C12)	273 (4)	180 (12)	523 (6)	73
H(C13)	330 (4)	−037 (11)	467 (6)	72
H(C14)	457 (4)	−079 (11)	552 (5)	55
H′(C15)	687 (4)	−249 (9)	888 (6)	54
H″(C15)	685 (4)	−148 (11)	984 (5)	54
H‴(C15)	692 (4)	−340 (11)	1003 (5)	54
H′(C16)	509 (4)	−396 (10)	853 (5)	44
H″(C16)	580 (3)	−409 (10)	813 (5)	44
H‴(C16)	567 (4)	−489 (9)	916 (5)	44
H′(C17)	524 (4)	−218 (9)	1023 (6)	48
H″(C17)	591 (4)	−121 (10)	1070 (5)	48
H‴(C17)	598 (4)	−323 (10)	1082 (5)	48

only 0·01 Å from the plane through the three C atoms and its valence angles have values very close to 120°. This indicates that N(2) has sp^2 hybridization, as in many anticholinergic drugs, *e.g.* hexasonium, penthienate, glycopirronium and atropine (Guy & Hamor, 1975*b*). The two phenyl rings are planar within experimental error and are tilted from the plane of aminic group by 17·6° (plane 1) and 58·6° (plane 2); the dihedral angle between the rings is 70·6°. Partial conjugation seems therefore possible only between N(2) and phenyl ring 1. The conformation of the remaining part of the molecule is defined by rotation angles of 83·2 and 174·6° around the N(2)–C(2) and C(2)–C(1) bonds, respectively; one methyl C is in the *trans* position (173·8°) with respect to C(2), as in almost all the muscarinic agonists examined by Baker, Chothia, Pauling & Petcher (1971). The distances between the quaternary N and the centres of the two phenyl rings are 5·72 and 5·60 Å. Comparison of this structure with those of many anticholinergic agents (Meyerhöffer & Carlström, 1969; Pauling & Petcher, 1969, 1970; Guy & Hamor, 1975*b* and references

Table 4. *Intramolecular bond distances and angles with e.s.d.'s in parentheses*

N(1)–C(1)	1·502 (5) Å	C(1)–N(1)–C(15)	111·1 (0·4)°
C(1)–C(2)	1·549 (7)	C(1)–N(1)–C(16)	112·3 (0·3)
C(2)–N(2)	1·451 (6)	C(1)–N(1)–C(17)	107·0 (0·4)
N(2)–C(3)	1·403 (6)	C(15)–N(1)–C(16)	109·5 (0·4)
N(2)–C(9)	1·425 (6)	C(15)–N(1)–C(17)	108·5 (0·3)
C(3)–C(4)	1·394 (5)	C(16)–N(1)–C(17)	108·5 (0·3)
C(4)–C(5)	1·385 (7)	N(1)–C(1)–C(2)	113·8 (0·4)
C(5)–C(6)	1·380 (6)	C(1)–C(2)–N(2)	108·9 (0·4)
C(6)–C(7)	1·362 (7)	C(2)–N(2)–C(3)	120·1 (0·4)
C(7)–C(8)	1·377 (7)	C(2)–N(2)–C(9)	118·0 (0·4)
C(8)–C(3)	1·380 (5)	N(2)–C(3)–C(4)	119·9 (0·3)
C(9)–C(10)	1·374 (7)	C(3)–C(4)–C(5)	121·3 (0·4)
C(10)–C(11)	1·395 (7)	C(4)–C(5)–C(6)	120·4 (0·4)
C(11)–C(12)	1·360 (9)	C(5)–C(6)–C(7)	118·4 (0·5)
C(12)–C(13)	1·363 (10)	C(6)–C(7)–C(8)	121·8 (0·4)
C(13)–C(14)	1·369 (8)	C(7)–C(8)–C(3)	121·0 (0·4)
C(14)–C(9)	1·392 (6)	C(8)–C(3)–C(4)	117·2 (0·4)
N(1)–C(15)	1·501 (5)	N(2)–C(9)–C(10)	121·0 (0·4)
N(1)–C(16)	1·492 (5)	C(9)–C(10)–C(11)	120·6 (0·5)
N(1)–C(17)	1·519 (6)	C(10)–C(11)–C(12)	119·4 (0·6)
		C(11)–C(12)–C(13)	120·5 (0·5)
		C(12)–C(13)–C(14)	120·7 (0·6)
		C(13)–C(14)–C(9)	120·0 (0·5)
		C(14)–C(9)–C(10)	118·8 (0·4)

Table 5. *Some least-squares planes in the molecule, with dihedral angles between the planes and distances* (Å) *of atoms to the respective planes*

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

Plane 1 $-0{\cdot}5133X + 0{\cdot}5285Y + 0{\cdot}6762Z = 2{\cdot}2486$

C(3)	−0·001	C(6)	0·002
C(4)	0·002	C(7)	−0·001
C(5)	−0·002	C(8)	0·001
N(2)*	−0·04	H(C4)*	0·02
H(C5)*	−0·11	H(C6)*	−0·41
H(C7)*	0·06	H(C8)*	−0·05

Plane 2 $-0{\cdot}3857X - 0{\cdot}6187Y + 0{\cdot}6844Z = 2{\cdot}4154$

C(9)	0·004	C(12)	0·006
C(10)	0·003	C(13)	0·002
C(11)	−0·008	C(14)	−0·006
N(2)*	0·008	H(C12)*	−0·11
H(C10)*	0·09	H(C13)*	−0·08
H(C11)*	0·18	H(C14)*	0·01

Plane 3 $-0{\cdot}3611X + 0{\cdot}3428Y + 0{\cdot}8672Z = 4{\cdot}8833$

N(2)	0·009	C(3)	−0·003
C(2)	−0·003	C(9)	−0·003

Dihedral angles (°) between planes

1–2	70·6
2–3	58·6
1–3	17·6

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).

C(17)–N(1)–C(1)–C(2)	173·8
N(1)–C(1)–C(2)–N(2)	174·6
C(1)–C(2)–N(2)–C(3)	83·2
C(1)–C(2)–N(2)–C(9)	95·2

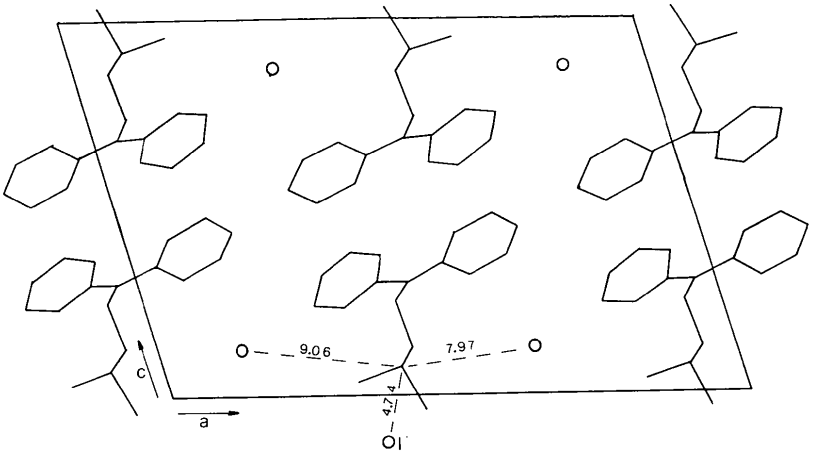


Fig. 2. The crystal structure projected down **b**.

therein) shows marked similarities between these molecules although they are subjected to very different crystal packing forces. This suggests that intramolecular forces impose a preferred conformation on many such antagonist molecules.

In the conformation postulated (Baker, Chothia, Pauling & Petcher, 1971) for acetylcholine as being relevant to muscarinic activity and to interaction with the receptor, the only groups believed to interact with the receptor are the $-N^+(CH_3)_3$ cationic head and the methyl of the ester group, the former by electrostatic and the latter by van der Waals forces. The relation of the plane containing the H atoms of the methyl group to the cationic head in acetylcholine is very similar to that of the benzene ring and the charged N atom in this compound, in atropine and in many other anticholinergic agents. The N^+–plane distances are, moreover, very similar (in the range 5·1–6·1 Å) suggesting that both acetylcholine and many antagonists interact with the muscarinic receptor in similar ways and at the same site. The extent to which results obtained in the solid state or in solution can be extrapolated to predict the conformation of flexible molecules interacting with receptors in biological systems is open to question (Maunter, Dexter & Low, 1972). Nevertheless our results are consistent with the view that anticholinergic agents compete with acetylcholine for the same receptors but that the critical interaction is mainly between the terminal substituents and neighbouring accessory receptor areas. The effect of this interaction with the accessory receptor areas is then believed to be transmitted in some way to the part of the receptor area relevant to cholinergic stimulation causing some change in its properties which prevents it from interacting with acetylcholine (Ariens & Simonis, 1967).

Packing

The crystal packing (Fig. 2) is due to Coulombic and van der Waals forces. Ionic layers, roughly parallel to (100), alternate with layers in which there are only hydrophobic parts of the molecules and where the phenyl rings are responsible for the intermolecular interactions. In the 'polar' region each anion is surrounded by four cations approximately tetrahedrally. The $I^- \cdots N^+$ (4·74 Å) distance is the shortest allowed by the steric hindrance of the three methyl groups: the shortest distance between the I atom and the methyl H atoms is 3·1 Å, which is shorter than the sum of van der Waals radii (3·25 Å). All other intermolecular distances are as expected for standard van der Waals values.

The molecular packing coefficient (Kitaigorodsky, 1973) is 0·72.

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Etude Cristallographique de $Cr_{1-x}V_xN$ à Basse Température

PAR M. NASR EDDINE

Université Libanaise, Faculté des Sciences, Hadeth, Beyrouth, Liban

E. F. BERTAUT

Laboratoire de Cristallographie, BP 166, *Centre de Tri* 38042, *Grenoble CEDEX, France*

ET M. ROUBIN ET J. PÂRIS

Faculté des Sciences de Lyon, 69100 *Villeurbanne, France*

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The solid solutions $Cr_{1-x}V_xN$, at room temperature, have a face-centred-cubic NaCl-type structure. X-ray diffraction shows that only the compounds with $x < \frac{1}{3}$ present an orthorhombic deformation below a temperature $T_D(x)$ for part of the sample. The fraction of deformed sample, $p(x, T)$, decreases with increasing x for T constant (5K) and increases for x constant ($x < \frac{1}{3}$) with decreasing T.

I. Introduction

Les nitrures de chrome et de vanadium possèdent à la température ambiante une structure cubique à faces centrées type NaCl. Les paramètres de la maille sont: $a' = 4{,}1480 \pm 0{,}0005$ Å pour CrN, $a' = 4{,}1360 \pm 0{,}0005$ Å pour VN.

Dans une autre note (Nasr Eddine & Bertaut, 1977) nous avons étudié les solutions solides $Cr_{1-x}V_xN$ par diffraction de neutrons à basse température; nous avons trouvé que les composés tels que $x < \frac{5}{16}$ présentent à basse température une structure antiferromagnétique de quatrième espèce (Corliss, Elliot & Hastings, 1960) identique à celle observée dans CrN pur. Les composés tels que $x > \frac{6}{16}$ ne présentent aucun ordre magnétique à longue distance. Dans ce papier, nous étudierons par diffraction de rayons X, à température variable, les propriétés cristallographiques de ces solutions solides.

II. Structure cristallographique à l'ambiante

L'ensemble des diagrammes de rayons X, obtenus pour différentes valeurs de la concentration en vanadium, x, présentent les mêmes ensembles de raies observées dans le cas de CrN et de VN purs; ils s'indexent tous dans une maille cubique à faces centrées type NaCl dont le paramètre a' dépend de la concentration x (Fig. 1).

D'autre part, l'absence, dans les diagrammes, de toute raie de surstructure, confirme le résultat proposé (Nasr Eddine & Bertaut, 1977), à savoir l'absence de