

Crystal and Molecular Structure of Arecoline Methiodide

BY D. J. H. MALLARD AND D. P. VAUGHAN

Department of Clinical Pharmacology, University of Birmingham Medical School, Birmingham B15 2TJ, England

AND T. A. HAMOR

Department of Chemistry, The University, Birmingham B15 2TT, England

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Arecoline methiodide crystallizes in the monoclinic space group $P2_1/n$ (C_{2h}^5), with $a=9.705$ (10), $b=8.88$ (1), $c=13.97$ (1) Å, $\beta=100.00$ (5)° and $Z=4$. The structure was determined by Patterson and Fourier methods from three-dimensional X-ray counter data and refined by least-squares calculations to $R=4.5\%$ for 1617 observed amplitudes. Estimated standard deviations for bond lengths, bond angles and torsion angles average 0.01 Å, 0.6° and 1.0°. The N,N -dimethyl-2,5,6-trihydropyridinium ring is in a half-chair-like conformation. The angle between the mean plane of the ester group and the planar four-atom portion of the ring system is 6.6°.

Introduction

The majority of potent muscarinic agonists contain a quaternary ammonium moiety, maximal pharmacological activity occurring with a trimethylammonium group. Substitution of a methyl group by any other group, e.g. ethyl, diminishes muscarinic activity, and successive replacement of methyl groups by hydrogen to produce the corresponding tertiary, secondary and primary ammonium salts diminishes the activity radically (Friedman, 1967). However, the naturally occurring muscarinic agonist arecoline (*Areca cathechu*), N -methyl-2,5,6-trihydropyridine 3-methylcarboxylate, with activity 1.4 times greater than that of carbachol, is an exception, in that it is a tertiary amine which on methylation becomes *less* active by a factor of *ca.* 40. Furthermore, while arecoline is only a weak nicotinic agonist, arecoline methiodide is a hundredfold more active nicotinic agonist (Burgen, 1964).

We have therefore determined the crystal structure of arecoline methiodide to obtain a fuller understanding of structure-activity relationships for both muscarinic and nicotinic agonists. The crystal structure of the tertiary ammonium salt, arecoline hydrobromide, has been determined previously (Baker, Chothia, Pauling & Petcher, 1971).

Experimental

Arecoline base (Sigma Chemicals) was quaternized with methyl iodide in redistilled ether. The resulting precipitate was recrystallized from ethanol, giving rod-like crystals. Approximate cell dimensions were determined from oscillation and Weissenberg photographs. Final cell dimensions and intensity data were measured on a Stoe two-circle computer-controlled diffractometer with graphite-monochromated Mo $K\alpha$ radiation.

The crystal had approximate dimensions $0.3 \times 0.25 \times 0.3$ mm and was set about **b**. From 2575 reflexions scanned in the range $0.1 \leq \sin \theta/\lambda \leq 0.60$, 1617 [$I > 2.5\sigma(I)$] were considered to be observed and were used in the structure analysis. The ω -scan method was employed, with a stepping interval of 0.01° and a step-time of 1 s. For layers $h0l-h3l$, the scan range was 1.2°. Reflexions on the fourth and higher layers were measured by a variable ω -scan technique as described previously (Mallard, Vaughan & Hamor, 1974). Appropriate correction factors were applied to convert the intensities to structure amplitudes. No absorption correction was applied.

Crystal data

$C_9H_{16}NO_2I$, $M=297.1$. Monoclinic, $a=9.705$ (10), $b=8.884$ (10), $c=13.969$ (10) Å, $\beta=100.00$ (0.05)°, $U=1186.1$ Å³, $Z=4$, $D_m=1.684$, $D_c=1.664$ g cm⁻³, $F(000)=584$. Systematic absences: $0k0$, k odd; $h0l$, $h+l$ odd; space group $P2_1/n$ (C_{2h}^5). * Mo $K\alpha$ radiation, $\lambda=0.71069$ Å; $\mu(\text{Mo } K\alpha)=20.3$ cm⁻¹.

Determination of the structure

The coordinates of the iodide ion were obtained from a Patterson synthesis. Structure factors were calculated ($R=53.0\%$) and the phase angles and observed amplitudes were used to produce an electron density map from which the positions of all the atoms in the asymmetric unit could be determined (apart from the hydrogen atoms). Refinement of positional and isotropic temperature parameters by least-squares analysis produced an R of 7.2%. Refinement was continued with the atoms vibrating anisotropically until calculated shifts

* Equivalent positions for this non-standard orientation are: $\pm(x, y, z)$; $\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z$.

were $<0.1\sigma$. H atoms (excluding those of the methyl groups) were included in the calculations in their theoretical positions, but their parameters were not refined. The final R was 4.5% for the 1617 observed reflexions.* Final atomic coordinates are listed in Table 1, and thermal parameters in Table 2. Scattering factors were taken from Hanson, Herman, Lea & Skillman (1964), except those for the H atoms which were from Stewart, Davidson & Simpson (1965).

Table 1. Fractional atomic coordinates ($\times 10^4$) with estimated standard deviations in parentheses

	x	y	z
N(1)	1437 (9)	2559 (8)	1090 (6)
C(2)	1223 (12)	2878 (10)	15 (7)
C(3)	2131 (12)	1899 (10)	-477 (7)
C(4)	3314 (12)	1284 (12)	-19 (8)
C(5)	3808 (12)	1463 (11)	1055 (8)
C(6)	2966 (12)	2624 (11)	1499 (8)
C(7)	817 (12)	1051 (12)	1279 (8)
C(8)	640 (13)	3758 (13)	1567 (8)
C(9)	1629 (12)	1676 (12)	-1538 (8)
C(10)	1876 (12)	490 (12)	-3027 (10)
O(1)	2337 (10)	702 (9)	-1949 (8)
O(2)	618 (10)	2365 (9)	-1973 (6)
H ¹ [C(2)]	1471	4076	-100
H ² [C(2)]	111	2683	-304
H[C(4)]	3973	635	-446
H ¹ [C(5)]	3710	357	1406
H ² [C(5)]	4923	1789	1184
H ¹ [C(6)]	3111	2433	2298
H ² [C(6)]	3365	3757	1373
I	1980 (1)	2070 (1)	4362 (1)

Table 2. Anisotropic thermal parameters ($\times 10^4$) for the heavier atoms

Temperature factors are in the form:

$$T = \exp[-2\pi^2(U_{11}h^2a^{*2} + \dots + 2U_{12}hka^*b^* + \dots)]$$

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	441	330	305	-38	-85	57
C(2)	488	454	233	36	-3	44
C(3)	331	376	379	-17	27	32
C(4)	447	418	390	-29	-40	50
C(5)	487	510	387	152	-107	-1
C(6)	370	496	377	21	-67	-77
C(7)	638	400	497	-172	24	35
C(8)	556	530	417	61	66	-151
C(9)	401	555	324	-29	75	67
C(10)	808	1073	303	163	-54	-113
O(1)	751	753	378	214	21	-94
O(2)	571	938	357	200	-62	26
I	557	430	451	52	60	32

Local versions of the Zalkin Fourier program *FORDAP* and the Busing, Martin & Levy full-matrix least-squares and function-and-error programs, *ORFLS* and *ORFFE*, were used in the computations, which were carried out on the University of Birmingham ICL 1906A Computer.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30833 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Discussion

The stereochemistry of the *N*-methylarecolinium cation is illustrated in Fig. 1 which also shows the atomic numbering scheme. Molecular parameters are listed in Tables 3 and 4. Mean estimated standard deviations for bond lengths, bond angles and torsion angles are 0.01 Å, 0.6° and 1.0°, respectively. A view of the crystal structure along y is shown in Fig. 2. Intermolecular distances (listed in Table 5) are unexceptional, apart from a short contact of 3.04 Å between C(6) and the carbonyl oxygen atom of the cation related by an n glide plane. C-H...O hydrogen bonding is probably not involved, since the H¹[C(6)]...O distance (2.48 Å) is *ca.* 0.2 Å greater than where hydrogen bonding of this type has been postulated (Hamilton & Ibers, 1968).

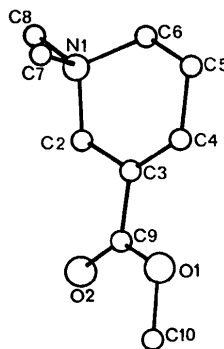


Fig. 1. The *N*-methylarecolinium cation viewed along the y axis.

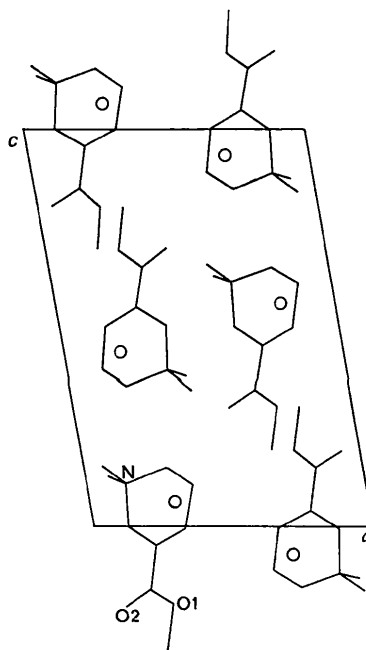


Fig. 2. The crystal structure projected along the y axis. Circles denote iodide ions.

Table 3. Distances and angles

(a) Bond distances (Å) with estimated standard deviations in parentheses

C(2)—N(1)	1.507 (9)	C(6)—N(1)	1.496 (10)
C(2)—C(3)	1.490 (10)	C(7)—N(1)	1.510 (8)
C(3)—C(4)	1.331 (10)	C(8)—N(1)	1.534 (9)
C(3)—C(9)	1.491 (9)	C(9)—O(1)	1.299 (9)
C(4)—C(5)	1.502 (10)	C(9)—O(2)	1.225 (9)
C(5)—C(6)	1.514 (11)	C(10)—O(1)	1.506 (9)

(b) Selected non-bonded distances (Å)

N(1)···C(10)	6.13	C(7)···O(1)	6.08
N(1)···C(9)	3.79	C(7)···O(2)	5.09
N(1)···O(1)	4.78	C(8)···C(10)	6.30
N(1)···O(2)	4.22	C(8)···C(9)	4.78
C(7)···C(10)	7.33	C(8)···O(1)	4.99
C(7)···C(9)	4.96	C(8)···O(2)	4.66

(c) Bond angles (°); mean standard deviation 0.6°

C(2)—N(1)—C(6)	109.2	C(4)—C(3)—C(9)	122.0
C(2)—N(1)—C(7)	110.5	C(3)—C(4)—C(5)	122.4
C(2)—N(1)—C(8)	108.0	C(4)—C(5)—C(6)	112.3
C(6)—N(1)—C(7)	111.5	N(1)—C(6)—C(5)	112.8
C(6)—N(1)—C(8)	110.4	C(3)—C(9)—O(1)	114.9
C(7)—N(1)—C(8)	107.1	C(3)—C(9)—O(2)	121.5
N(1)—C(2)—C(3)	111.1	O(1)—C(9)—O(2)	123.6
C(2)—C(3)—C(4)	123.2	C(9)—O(1)—C(10)	115.9
C(2)—C(3)—C(9)	114.8		

(d) Torsion angles (°); mean standard deviation 1.0°. Also present in the crystal are the centrosymmetrically related rotamers with torsion angles of opposite sign.

C(2)—C(3)—C(4)—C(5)	3.0
C(2)—C(3)—C(9)—O(1)	-173.2
C(2)—N(1)—C(6)—C(5)	-61.4
C(2)—C(3)—C(9)—O(2)	6.4
C(3)—C(2)—N(1)—C(6)	51.5
C(3)—C(2)—N(1)—C(7)	171.7
C(3)—C(2)—N(1)—C(8)	-71.4
C(3)—C(4)—C(5)—C(6)	-10.3
C(3)—C(9)—O(1)—C(10)	-178.3
C(4)—C(5)—C(6)—N(1)	39.7
C(4)—C(3)—C(2)—N(1)	-24.1
C(4)—C(3)—C(9)—O(1)	7.9
C(4)—C(3)—C(9)—O(2)	-172.6
C(5)—C(6)—N(1)—C(7)	180.0
C(5)—C(6)—N(1)—C(8)	61.0
C(5)—C(4)—C(3)—C(9)	-178.2
C(10)—O(1)—C(9)—O(2)	2.2

Table 4. Mean-plane calculations

(a) Deviations (Å) of atoms from least-squares planes. In the equations of the planes, x , y and z are fractional coordinates relative to the cell axes.

Plane (1)	C(3), C(9), O(1), O(2), C(10)						
	$6.304x + 6.529y - 4.253z = 2.777$						
C(3)	-0.009,	C(9)	0.001,	O(1)	0.004,	O(2)	0.017,
C(10)	-0.013						
Plane (2)	C(2)—(5)						
	$5.440x + 7.177y - 3.865z = 2.719$						
C(2)	-0.006,	C(3)	0.005,	C(4)	-0.012,	C(5)	0.012,
N(1)	0.522,	C(6)	-0.198,	C(9)	0.036,	C(10)	0.178,
O(1)	0.191,	O(2)	-0.077				

(b) Dihedral angle

(1)—(2)	6.64°
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Table 5. Intermolecular contacts (excluding hydrogen atoms)

Distances involving only the lighter atoms are listed up to 3.8 Å, and those involving the iodide ion up to 4.0 Å.

C(6)···O(2 ⁱ)	3.04	C(7)···O(1 ⁱⁱ)	3.70
C(5)···O(2 ⁱ)	3.17	C(9)···C(10 ⁱⁱⁱ)	3.78
C(7)···C(9 ⁱⁱ)	3.46	C(4)···I ^{iv}	3.88
C(7)···O(2 ⁱⁱ)	3.54	C(10)···I ^v	3.93
O(2)···C(10 ⁱⁱⁱ)	3.69	C(5)···I ^v	4.00

Symmetry code

i	$\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z$	iv	$\frac{1}{2} - x, -\frac{1}{2} + y, \frac{1}{2} - z$
ii	$-x, -y, -z$	v	$x, y, -1 + z$
iii	$\frac{1}{2} - x, \frac{1}{2} + y, -\frac{1}{2} - z$		

The *N,N*-dimethyl-2,5,6-trihydropyridinium ring adopts a half-chair-like conformation. The four atoms C(2)—C(5) are coplanar to within 0.012 Å and N(1) and C(6) are situated on opposite sides of the mean plane through these atoms at distances of 0.522 and 0.198 Å. The ester side chain is planar to within 0.017 Å and has the antiplanar conformation [torsion angle C(3)—C(9)—O(1)—C(10) = -178.3°] typical of esters. The angle between the ester plane and the plane of atoms C(2)—C(5) is 6.6°, such that O(2) is synplanar with respect to C(2) [torsion angle C(2)—C(3)—C(9)—O(2) = 6.4°] and O(1) synplanar with respect to C(4) [torsion angle C(4)—C(3)—C(9)—O(1) = 7.9°].

Bond lengths generally agree well with expected values (Sutton, 1965). C(3)—C(9) has a length of 1.491 Å, in good agreement with the accepted value (Cruickshank, 1962) for a single bond between sp^2 -hybridized C atoms so that there does not seem to be any appreciable conjugation between the carbonyl group and the C(3)—C(4) double bond. Bond lengths in the ester group are, however, somewhat anomalous. Thus C(9)—O(1) is slightly shorter and C(9)—O(2) and C(10)—O(1) slightly longer than is normally found in esters.

In interpreting the biological activity of acetylcholine and related compounds, the distances from the cationic head to the ester and carbonyl oxygen atoms and the terminal methyl group appear to be of importance (Chothia, 1970; Beers & Reich, 1970; Baker *et al.*, 1971). Arecoline does not contain the $N^+ - C - C - O - C(=O) - C$ system of acetylcholine. However, similar functional groups are present. The distances N(1)···O(1), O(2) and C(10) are 4.78, 4.22 and 6.13 Å, which may be compared with the distances between the corresponding atoms in acetylcholine which are 3.26, 4.80 and 5.38 Å, as measured in crystals of the chloride salt (Herdklotz & Sass, 1970), in which acetylcholine adopts a conformation similar to that observed in solution (Culvenor & Ham, 1966; Partington, Feeney & Burgen, 1972). The only similarity, therefore, is the $N \cdots O$ (carbonyl) separation. For arecoline hydrobromide (Baker *et al.*, 1971) the only structural parameters quoted are the distances between N and the atoms of the ester group. Mean values for the two crystallographically independent cations present in the crystal are $N \cdots O(1)$ 4.27 ± 0.01; $N \cdots O(2)$ 4.82 ± 0.08, $N \cdots C(9)$

3.79 ± 0.05 and $N \cdots C(10) 6.16 \pm 0.02$ Å. These indicate that, compared with arecoline methiodide, the ester group is rotated *ca.* 180° about C(3)–C(9).

It does not, however, seem possible to rationalize the differences in biological activity between the tertiary and quaternary arecoline salts on the basis of the difference in orientation of the ester side chain. This orientational difference may well be due to packing forces rather than an intramolecular effect of the additional *N*-methyl substituent in the quaternary salt. The somewhat anomalous bond lengths in the ester group would, in fact, be consistent with some degree of disorder, involving a small contribution (*ca.* 1–5%) from the rotamer in which the ester group is rotated through 180° about C(3)–C(9), corresponding to the conformation observed for arecoline hydrobromide. This would suggest that the two conformations have roughly similar energies. The comparatively high thermal parameters of O(1), O(2) and C(10) would also be consistent with the possible disorder.

It is nevertheless of interest that in the conformation adopted by arecoline methiodide, the $N^+ - C - C(=O) - OMe$ system could present a surface to the receptor somewhat similar to the 'carbonyl side' of acetylcholine as defined by Chothia (1970). It is this side of the acetylcholine cation which is considered to interact with the nicotinic receptor.

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The Crystal Structure of Hypoxanthine Gold(III) Tetrachloride Dihydrate

BY MINO R. CAIRA, LUIGI R. NASSIMBENI AND ALLEN L. RODGERS

Department of Physical Chemistry, University of Cape Town, Rondebosch, South Africa

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The structure of $(C_5H_3N_4O)^+(AuCl_4)^- \cdot 2H_2O$ has been determined from single-crystal X-ray diffraction data collected on a four-circle diffractometer. The analysis was carried out with 2145 independent reflexions and refined by full-matrix least-squares calculations to a final *R* of 0.06. The crystals are monoclinic, space group $P2_1/c$, with $a = 7.767$ (5), $b = 11.338$ (5), $c = 15.678$ (5) Å, $\beta = 97.47^\circ$ and $Z = 4$. The structure is ionic. The Au atom is coordinated in a square-planar arrangement to four Cl atoms. The hypoxanthine cations are linked *via* $NH \cdots N$ and $NH \cdots O$ hydrogen bonds. Short contact distances involving some of the Cl atoms and two hydrate O atoms are reported.

Introduction

The crystal structure of the title compound is one of a series of X-ray determinations on compounds resulting from the interaction of purines with metals of the Ahrlund, Chatt & Davies (1958) triangle. Hypoxanthine itself occurs naturally in higher animals and is

involved in the enzymatic degradation of purines to uric acid.

Experimental section

Molar solutions of hypoxanthine and sodium chloraurate ($NaAuCl_4 \cdot 2H_2O$), dissolved in molar HCl, were mixed in equal proportions. On standing for several