The Structure of the Potent Muscarinic Agonist L-(+)-Acetyl-β-methylcholine Iodide

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CRYSTALS of the potent agonist of acetylcholine on the post-ganglionic parasympathetic nervous system, L-(+)-acetyl-β-methylcholine iodide,[1] $Me_3N^+CH_2{\cdot}CHMeO{\cdot}CO{\cdot}Me\ I^-$, are orthorhombic, space-group D_2^4-$P2_12_12_1$, $a = 28{\cdot}156 \pm 0{\cdot}027$, $b = 7{\cdot}601 \pm 0{\cdot}006$, $c = 5{\cdot}941 \pm 0{\cdot}005$ Å, $Z = 4$. The conformation of the molecule has been determined by *X*-ray

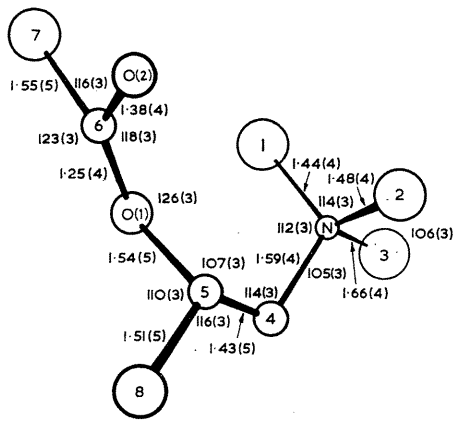

FIGURE. *Structure of* L(+)*-acetyl-β-methylcholine iodide with some interatomic distances and angles with standard deviations in units of the least significant digit given in brackets.*

diffraction analysis. The diffraction data were measured with Mo-*K* radiation using a computer-controlled four-circle diffractometer, a total of 3153 measurements being taken, reducing to 860 independent observed $[I \geqslant 3\sigma(I)]$ diffraction maxima. The data were not corrected for absorption and were standardized and scaled by a linear interpolation between periodic measurements of a normalized standard diffraction maximum. The structure was analysed by Patterson and Fourier methods and refined by iterative least-squares using anisotropic thermal parameters for the iodine atom and an overall thermal parameter for the other atoms, neglecting the hydrogen atoms. $R = 0{\cdot}07$. This structure analysis is not very good, as can be seen from the large deviations of bond distances and angles from expected values. Attempts to move atoms in order to provide more acceptable distances and angles have failed; in terms of the data the structure always refines to the one shown. The analysis is, however, good enough to provide the conformation of the molecule for comparison with those of other cholinergic molecules.

The Figure shows the general conformation of the molecule with certain interatomic distances and angles. The standard deviations of these distances and angles are indicated in parentheses in terms of the least significant digit given for each item.

The conformation proposed for this molecule[2] on the basis of the structures of acetylcholine bromide[3] and muscarine[4] is not completely correct. In the Table are listed various torsion angles for this compound acetyl-β-methylcholine iodide, lactoylcholine iodide,[5] muscarine,[4] and acetylcholine bromide.[3] Except for acetylcholine bromide, the conformations of the molecules are very similar. The O(1)–C(5)–C(4)–N torsion angle of 85° is consistent with that found in all reported N^+–C–C–O groups.[3,6]

The β-methyl group is essentially an extension of the C(3)–N–C(4)–C(5) extended chain. This position for this methyl group, which is similar to that of a ring carbon atom in the muscarinic agonist muscarine,[4] is that previously suggested for this compound.[2] The C(6)–O(1)–C(5)–C(4) torsion angle in L-(+)-acetyl-β-methylcholine is

Observed torsion angles of some cholinergic molecules. (*Standard deviations of these angles have not been determined but are probably about* 15°)

	C(8)–C(5)–C(4)–N	O(1)–C(5)–C(4)–N	C(6)–O(1)–C(5)–C(4)	O(2)–C(6)–O(1)–C(5)	C(7)–C(6)–O(1)–C(5)
L-Acetyl-β-methylcholine iodide	−152	+85	−147	+14	+175
L-Lactoylcholine iodide[5]	—	+85	+157	+1	+173
L-Muscarine iodide[4]	−168	+73	+144	—	−136
Acetylcholine bromide[3]	—	+77	+79	0	+167

−145°, 70° from the corresponding but fixed equivalent torsion angle in muscarine. In secondary esters, the carbonyl oxygen atom normally is *syn*-planar to the C(5) hydrogen atom,[7] [τ C(6)–O(1)–C(5)–C(4) = − 120°] and in most muscarinic agonists τ C(6)–O(1)–C(5)–C(4) is between +146° and 180°.[5] In acetyl-β-methylcholine this torsion angle is determined by interaction between the carbonyl oxygen atom and hydrogen atoms on the β-carbon atom C(5) and on the β-methyl group C(8) which forces τ C(6)–O(1)–C(5)–C(4) to be larger than usual.

The absolute configuration of this active enantiomer determined by Beckett[1] is consistent with the absolute configuration of the active enantiomers of muscarine[8] and that of the absolute configuration of the active enantiomer and isomer of 2-methyl-4-trimethylammoniummethyl-1,3-dioxolan.[9]

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