The Crystal Structure of L-(+)-*cis*-2-(*S*)-Methyl-4-(*R*)-trimethylammonium-methyl-1,3-dioxolan Iodide

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Summary The structure of the potent muscarinic agonist L-(+)-*cis*-2-methyl-4-trimethylammonium-methyl-1,3-dioxolan has been determined by a three-dimensional *X*-ray diffraction study of crystals of the iodide.

CRYSTALS of L-(+)-*cis*-2-(*S*)-methyl-4-(*R*)-trimethylammonium-methyl-1,3-dioxolan iodide, a potent agonist of acetylcholine at the parasympathetic postganglionic (muscarinic) junction,[1] are orthorhombic, space group $P2_12_12_1$,

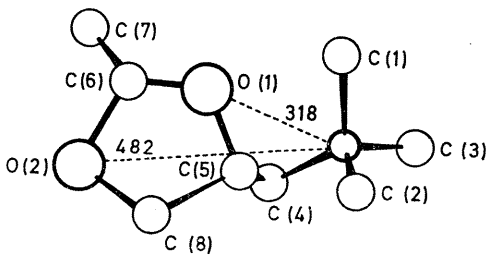

FIGURE. L-(+)-cis-2-(S)-*Methyl*-4-(R)-*trimethylammonium-methyl*-1,3-*dioxolan, projected on the plane* C(5)–O(1)–C(6)–O(2).

$a = 1214 \pm 1$, $b = 1413 \pm 2$, $c = 719 \pm 1$ pm, $Z = 4$. Three dimensional diffraction data were collected on a computer-controlled four-circle diffractometer[2] using zirconium-filtered Mo–K_α radiation in the range $2\theta \leqslant 30°$, and unfiltered Mo–K radiation in the range $25° \leqslant 2\theta \leqslant 45°$. One hemisphere of data collected in this fashion gave 3723 measurements, which, after correction for Lorentz and polarisation effects and for long-term variation in the intensity of the incident radiation by means of periodic measurement of a standard diffraction maximum, yielded 395 unique observed $[I \geqslant 3\sigma(I)]$ diffraction maxima. Absorption and extinction corrections were not made. The structure was solved by Patterson and Fourier methods, phased on the iodine atom, and refined by multiple cycles of least-squares to a present value of $R = 0{\cdot}087$.

The molecule is shown in the Figure, in the absolute configuration established by chemical methods.[3] We have not attempted to verify this by consideration of anomalous scattering effects. The five-membered ring C(5)–O(1)–C(6)–O(2)–C(8) is not planar, but is in the 'half-chair' configuration with C(8) 35pm out of the plane of C(5)–O(1) C(6)–O(2), on the side of the plane opposite to the methyl and trimethylammonium-methyl groups. In this position, C(8) is part of a planar extended chain C(8)–C(5)–C(4)–N–C(3) in which the maximum deviation from planarity is 6pm for C(5). The torsion angles C(6)–O(1)-C(5)–C(4) and C(6)–O(1)–C(5)–C(8) are 100° and −22° respectively. The torsion angles about the C(5)–C(4) bond are O(1)–C(5)–C(4)–N = 68° and C(8)–C(5)–C(4)–N = 178°. In muscarine,[4] the five-membered ring is also in the half-chair conformation, but the atom C(9) corresponding to C(8) in

this dioxolan is out of the plane of C(5)–O(1)–C(6)–C(8) on the *same* side of the plane as the methyl and trimethylammonium-methyl groups. This results in torsion angles C(6)–O(1)–C(5)–C(4) = 144° and C(6)–O(1)–C(5)–C(9) = 23°. The atom C(9), however, is also part of a planar extended chain C(9)–C(5)-C(4)–N–C(3), and both structures have the nitrogen atom *synclinal* to the ether oxygen atom O(1). The torsion angles O(1)–C(5)–C(4)–N and C(9)–C(5)–C(4)–N of muscarine are 73° and 168° respectively, very similar to the corresponding torsion angles of this 1,3-dioxolan. The conformation of this 1,3-dioxolan and those of other muscarinic agonists have already been discussed,[5–7] and the present structure is very close to that predicted by Pauling.[5] It differs only from that conformation and the observed conformation of muscarine in the position of C(8), with a consequent change in certain torsion angles. While this difference does not affect the overall conformation of these molecules a great deal, it may be that in solution the position of C(8) changes relative to the rest of the ring, resulting in identical conformations for this 1,3-dioxolan and muscarine. The *synclinal* conformation of the nitrogen relative to the ester or ether oxygen atom of muscarinic agonists appears now to be well established, though the orientation of the acetyl or ring groups relative to the trimethylammoniummethyl group appears to be variable.

We thank the M.R.C. for the support of this work, Professor Belleau for providing the crystals, and Miss M. Dellow for data processing assistance.

(*Received, August 18th*, 1969; *Com.* 1262.)

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