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References

ABRAHAMS, S. C. & KEVE, E. T. (1971). *Acta Cryst.* A**27**, 157–165.
CHWANG, A. K. & SUNDARALINGAM, M. (1973). *Nature, New Biol.* **243**, 78–80.
COHEN, S. S. (1966). In *Progress in Nucleic Acid Research and Molecular Biology*, Vol. 5, edited by J. N. DAVIDSON & W. E. COHN. New York: Academic Press.
HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502–510.
International Tables for X-ray Crystallography (1962). Vol. III. Birmingham: Kynoch Press.
JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee.
LAI, T. F. & MARSH, R. E. (1972). *Acta Cryst.* B**28**, 1982–1989.
LARSON, A. C. (1967). *Acta Cryst.* **23**, 664–665.
SHERFINSKI, J. S. & MARSH, R. E. (1973). *Acta Cryst.* B**29**, 192–198.
SOUBEYRAN, O. L. & TOUGARD, P. (1973). *C. R. Acad. Sci. Paris. Ser. C*, **276**, 403–406.
STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.
SUNDARALINGAM, M. & CHWANG, A. K. (1973). Amer. Chem. Soc. Meeting, Chicago, Ill. Program and Abstracts.
TOLLIN, P., WILSON, H. R. & YOUNG, D. W. (1973*a*). *Nature, New Biol.* **247**, 49–50.
TOLLIN, P., WILSON, H. R. & YOUNG, D. W. (1973*b*). *Acta Cryst.* B**29**, 1641–1647.

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The Crystal Structure of *o*-Methyl β-Methylphenylcholine Ether Bromide

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The crystal structure has been determined from three-dimensional counter X-ray data. The material crystallizes in the monoclinic space group $P2_1/c$ with four molecules in the unit cell. The cell parameters are $a=9{\cdot}915$ (2), $b=9{\cdot}204$ (2), $c=18{\cdot}170$ (4) and $\beta=121{\cdot}45$ (2)°. The structure was solved by Patterson and Fourier syntheses using 2859 independent reflexions and refined by block-diagonal least-squares calculations to a final R value of 0·061. The N–C–C–O system adopts the positive synclinal (*gauche*) conformation. The remaining torsional angles are close to 180°.

Introduction

The pharmacological properties of *o*-methyl β-methylphenylcholine ether bromide (OMBEM TM1) are in sharp contrast to those of phenylcholine ether bromide itself and its α-methyl substituted derivatives. Whereas the latter are all potent ganglion stimulants, OMBEM TM1 is devoid of such activity (Hey, 1952; Clark & Jana, 1966; Clark, Dawes & Williams, 1968). It has been suggested on the basis of ultraviolet spectroscopic studies that a possible reason for this lack of activity is that β-methyl substituted derivatives cannot adopt a conformation in which the Ph–O–C group of atoms are coplanar (Clark & Williams, 1967). The present study shows this deduction to be most unlikely and moreover that the conformation adopted by the molecule in the crystal is close to that which has been suggested as necessary for pharmacological activity in acetylcholine and its analogues (Chothia, 1970).

Experimental

Systematic absences were found from Weissenberg photographs for $0k0$ when $k=2n+1$, and for $h0l$ when $l=2n+1$, indicating the space group $P2_1/c$. Three-dimensional intensity data were collected on a computer-controlled Enraf–Nonius CAD4 four-circle diffractometer and measured by the moving-crystal moving-counter technique in the range $3° \le \theta \le 70°$. A control reflexion measured every 40 min showed a maximum deviation of 6%. After correction for Lorentz and polarization effects, a statistical analysis (Wilson, 1942) was carried out to determine a mean temperature factor and an absolute scale factor. No absorption corrections were made.

Crystal data

$C_{13}H_{22}ON^+Br^-$; M.W. 288. Source: Dr E. R. Clark, Dept. of Pharmacology, University of Leeds. Crystal system: monoclinic. Space group: $P2_1/c$; $a=9{\cdot}915$ (2), $b=9{\cdot}204$ (2), $c=18{\cdot}170$ (4) Å, $\beta=121{\cdot}45$ (2)°; $V=1415$ Å^3, $Z=4$, $D_c=1{\cdot}351$, $D_m=1{\cdot}345$ g cm^{-3}. Radiation: Graphite monochromatized Cu $K\alpha$, $\lambda=1{\cdot}54051$ Å.

Structure determination and refinement

The position of the bromine atom in the asymmetric unit was found from a study of the Patterson–Harker section $(U,\frac{1}{2},W)$ and line $(0,V,\frac{1}{2})$ and confirmed by the general peak at (U,V,W). A three-dimensional

Table 1. *Final least squares parameters of the non-hydrogen atoms and their estimated standard deviations*

Fractional coordinates are $\times 10^5$. Thermal parameters are $\times 10^4$. The anisotropic temperature factor is of the form

$$\exp\{-2\pi^2(U_{11}a^{*2}h^2+U_{22}b^{*2}k^2+U_{33}c^{*2}l^2+2U_{12}a^*b^*hk+2U_{13}a^*c^*hl+2U_{23}b^*c^*kl)\}.$$

	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	$2U_{23}$	$2U_{13}$	$2U_{12}$
Br	40071 (5)	20457 (5)	12115 (3)	532 (3)	520 (3)	596 (3)	−251 (3)	805 (5)	292 (3)
C(1)	63208 (62)	67374 (52)	7922 (26)	675 (29)	530 (23)	362 (18)	70 (34)	532 (39)	108 (44)
C(2)	46089 (50)	61930 (51)	13630 (31)	346 (20)	492 (23)	686 (27)	111 (40)	424 (39)	83 (35)
C(3)	62537 (67)	83683 (47)	18321 (32)	830 (34)	321 (18)	659 (28)	−72 (38)	894 (53)	1 (43)
C(4)	74982 (42)	59973 (39)	23249 (20)	379 (18)	413 (18)	281 (15)	−141 (26)	371 (27)	−12 (29)
C(5)	76970 (40)	44214 (38)	21570 (20)	356 (17)	355 (16)	295 (15)	−43 (26)	340 (27)	4 (28)
C(6)	85938 (40)	32918 (38)	12777 (20)	295 (16)	334 (16)	329 (16)	15 (26)	318 (27)	55 (27)
C(7)	95617 (39)	34224 (39)	9285 (20)	296 (16)	364 (16)	307 (15)	56 (27)	289 (26)	36 (28)
C(8)	95419 (46)	23116 (43)	4087 (24)	396 (19)	409 (19)	412 (18)	99 (30)	477 (32)	170 (31)
C(9)	85888 (47)	11167 (41)	2196 (24)	433 (20)	387 (18)	390 (18)	3 (30)	400 (31)	183 (32)
C(10)	76185 (46)	9869 (41)	5602 (25)	445 (20)	331 (18)	491 (19)	35 (29)	496 (33)	−3 (30)
C(11)	76488 (46)	20708 (38)	11076 (25)	367 (19)	370 (19)	441 (19)	−12 (27)	461 (32)	−11 (27)
C(12)	85476 (63)	35747 (56)	30050 (27)	698 (30)	583 (26)	403 (20)	219 (39)	439 (42)	236 (47)
C(13)	5621 (53)	47590 (50)	11113 (28)	527 (23)	511 (24)	576 (23)	−104 (37)	702 (39)	−259 (38)
O	86592 (31)	44440 (28)	17762 (17)	423 (14)	396 (13)	461 (13)	−248 (22)	588 (23)	−142 (22)
N	61651 (40)	67979 (32)	15707 (20)	424 (17)	314 (14)	353 (14)	−46 (23)	382 (26)	34 (25)

Fourier synthesis was computed on the Leeds University 1906A computer by a modified version of a program originally written by Cruickshank, Pilling, Bujosa, Lovell & Truter (1961) with the phase angles specified by the bromine atoms. The resultant synthesis revealed the positions of all the non-hydrogen atoms. Six cycles of structure-factor block-diagonal least-squares (*SFLS*) isotropic refinement gave a residual $R=0{\cdot}21$. Three more cycles with anisotropic temperature factors for the bromine atom reduced R to 0·09 and a further four cycles with anisotropic temperature factors for all the atoms gave $R=0{\cdot}07$. At this stage the positions of the hydrogen atoms not bonded to the phenyl ring were found from a three-dimensional Fourier synthesis and a three-dimensional difference Fourier synthesis. The positions of the hydrogen atoms attached to the phenyl ring were obtained by calculation assuming a C–H bond length of 1·0 Å and the hydrogen atoms to be collinear with diametrically opposed carbon atoms in the phenyl ring. Another three cycles of *SFLS* refinement reduced the R index to 0·061. Two hydrogen atoms, *viz.* H(C10) and H″(C13) did not refine to sensible positions.

The coordinates of the non-hydrogen atoms are given in Table 1 together with their estimated standard deviations. The anisotropic temperature factors are also given in Table 1 and the positions and isotropic temperature factors of the hydrogen atoms in Table 2. The bond lengths and related e.s.d.'s and bond angles were calculated by a program written by Dr W. S. McDonald and the results are shown in Tables 3 and 4. The displacements of the phenyl ring atoms from the plane of best fit are shown in Table 5.*

* The calculated and observed structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30305 (49 pp., 1 microfiche). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Final least-squares parameters of the hydrogen atoms and their standard deviations*

Fractional coordinates are $\times 10^4$.

	x/a	y/b	z/c	U_{iso} ($\times 10^3$)
H(C1)	5891 (63)	5644 (64)	485 (33)	49 (15)
H′(C1)	5055 (71)	7121 (56)	305 (35)	43 (16)
H″(C1)	7381 (71)	7054 (56)	990 (36)	51 (16)
H(C2)	3910 (130)	6802 (122)	959 (80)	148 (41)
H′(C2)	4567 (64)	6316 (64)	1918 (32)	41 (15)
H″(C2)	5116 (201)	5501 (219)	1676 (95)	58 (75)
H(C3)	6325 (68)	8334 (66)	2396 (34)	53 (15)
H′(C3)	7104 (74)	8647 (75)	1829 (37)	39 (17)
H″(C3)	5462 (68)	8941 (65)	1290 (33)	55 (15)
H(C4)	7351 (44)	6139 (41)	2730 (22)	9 (8)
H′(C4)	8505 (54)	6502 (54)	2482 (27)	35 (11)
H(C5)	6559 (45)	3910 (41)	1728 (23)	2 (8)
H(C8)	149 (63)	2351 (62)	155 (32)	24 (13)
H(C9)	8363 (97)	336 (97)	285 (44)	93 (25)
H(C11)	7080 (78)	1828 (68)	1366 (38)	51 (18)
H(C12)	8962 (97)	2650 (100)	2896 (49)	118 (24)
H′(C12)	7830 (95)	3404 (96)	3410 (46)	80 (24)
H″(C12)	9368 (68)	4187 (66)	3489 (33)	48 (16)
H(C13)	1163 (67)	4943 (67)	1772 (34)	37 (16)
H′(C13)	1397 (144)	4690 (175)	1284 (77)	252 (53)

Table 3. *Bond lengths (e.s.d.'s in parentheses)*

N——C(1)	1·503 (6) Å
N——C(2)	1·493 (6)
N——C(3)	1·510 (5)
N——C(4)	1·511 (5)
C(4)—C(5)	1·516 (5)
C(5)—C(12)	1·530 (5)
C(5)—O	1·443 (4)
O——C(6)	1·374 (4)
C(6)—C(7)	1·406 (5)
C(7)—C(8)	1·385 (5)
C(8)—C(9)	1·372 (6)
C(9)—C(10)	1·395 (6)
C(10)–C(11)	1·398 (5)
C(11)–C(6)	1·391 (5)
C(7)—C(13)	1·505 (6)

Table 4. *Bond angles*

C(3)–N——C(4)	107·6 (3)°
C(1)–N——C(4)	111·4 (3)
C(2)–N——C(4)	110·4 (3)
N——C(4)—C(5)	115·4 (2)
C(4)–C(5)—C(12)	110·2 (3)
C(4)–C(5)—O	105·7 (3)
O——C(5)—C(12)	109·6 (3)
C(7)–C(6)—C(11)	120·6 (3)
C(6)–C(7)—C(8)	118·4 (3)
O——C(6)—C(11)	124·4 (3)
O——C(6)—C(7)	115·0 (3)
C(7)–C(8)—C(9)	121·7 (3)
C(6)–C(11)–C(10)	119·8 (3)
C(8)–C(9)—C(10)	120·2 (3)
C(9)–C(10)–C(11)	119·4 (3)
C(8)–C(7)—C(13)	121·8 (3)
C(6)–C(7)—C(13)	119·9 (3)
C(5)–O——C(6)	119·3 (3)

Table 5. *Displacements from plane of best fit through phenyl ring*

C(6)	−0·007 Å
C(7)	−0·005
C(8)	+0·009
C(9)	−0·001
C(10)	−0·011
C(11)	+0·014

There were 2859 accessible reflexions in the range $3° \leq \theta \leq 70°$ of which 241 were very weak and not used in the structure determination. These were assigned an intensity equal to one half of the minimum measured intensity and an additional cycle of *SFLS* refinement which included these reflexions gave a residual $R = 0{\cdot}066$.

Atomic form factors were taken from *International Tables for X-ray Crystallography* (1962). The weighting scheme used was

$$\sqrt{w} = \left[1 + \left(\frac{|F_o| - P_2}{P_1}\right)^2\right]^{-1/2}$$ (Mills & Rollett, 1961)

where $P_1 = |F\text{max}|/10$ and $P_2 = |F\text{max}|/40$.

Discussion

A perspective view of the molecule is shown in Fig. 1 which also illustrates the numbering of the atoms. The most important parameters of the structure are the torsional angles C(3)–N–C(4)–C(5), N–C(4)–C(5)–O, C(4)–C(5)–O–C(6), C(5)–O–C(6)–C(7) and these are listed in Table 6. The group of atoms C(3)–N–C(4)–C(5) forms an antiplanar extended chain with $\tau \sim 180°$. This is the angle expected from a consideration of van der Waals forces and steric hindrance effects (Chothia & Pauling, 1970). The group N–C(4)–C(5)–O adopts the *gauche* conformation, a feature which is commonly observed in acetylcholine-like molecules. It has been suggested (Sundaralingam, 1968) that this conformation is stabilized by electrostatic forces between N^+ and the ether oxygen, and by the possible formation of a hydrogen bond between one of the methyl carbons attached to the nitrogen and the ether oxygen. The corresponding distances of 3·16 and 2·95 Å in OMBEM TM1 are in accord with these contentions.

Table 6. *Torsion angles*

C(3)–N——C(4)–C(5)	−174·7°
N——C(4)–C(5)–O	+85·7
C(4)–C(5)–O——C(6)	−156·9
C(5)–O——C(6)–C(7)	+179·3

Values equal or close to 180° for the torsion angle C(5)–O–C(6)–C(7) have been ascribed to partial double-bond character of the O–C(6) bond in acetylcholine and its derivatives (Chothia & Pauling, 1969*a*, 1970). This is apparently true in OMBEM TM1 as well (where the O–C(6) bond length is 1·374 Å) even though the ester group of acetylcholine has been replaced by phenyl.

The torsion angle C(4)–C(5)–O–C(6) is −156·9°, which is close to that found in acetyl *β*-methylcholine (−147°). It has been suggested (Chothia & Pauling, 1969*b*) that this latter value is somewhat different from the normal value of 150–180° found in non *β*-substituted acetylcholine derivatives because of interaction between the carbonyl oxygen atom and hydrogen atoms on C(5) and on the *β*-methyl group. A similar situation pertains with the *β*-methylphenylcholines where the carbonyl oxygen of acetylcholine is replaced by C(11). In fact an examination of skeletal models shows that if the group of atoms C(5)–O–C(6)–C(7) is coplanar, or nearly so, as discussed above, then steric hindrance effects allow only a few values for τC(4)–C(5)–O–C(6). The value found in the crystal would seem to put the

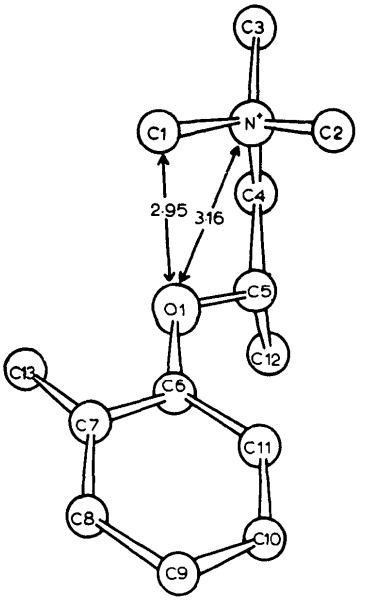

Fig. 1. Perspective view of *o*-methyl *β*-methylphenylcholine ether.

model under the least strain but even so we would consider that the distance between the hydrogen atoms on C(11) and C(5) and the distance between the hydrogen atoms on C(11) and the β-methyl group are smaller than would be normally acceptable. However, bond-angle measurements show that these close contacts are relieved in the crystal by increasing the C(11)–C(6)–O angle from the normal trigonal value to 124·4°.

In summary, there would seem to be good reasons for supposing that the conformation of OMBEM TM1, as described by the four torsional angles discussed above, is determined primarily by intramolecular forces. This would lead us to expect that the molecule would adopt a very similar conformation *in vivo*. In support of this view it has been found that molecules of β-methylphenylcholine ether in crystals of the bromide have an almost identical structure (manuscript in preparation). Moreover, both these compounds adopt a conformation in which the atoms C(5)–O–C(6)–C(7) are coplanar or very nearly so, and the hypothesis of Clark & Williams (1967) that their lack of pharmacological activity arises because they cannot adopt such a conformation now seems untenable.

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References

CHOTHIA, C. (1970). *Nature, Lond.* **225**, 36–38.
CHOTHIA, C. & PAULING, P. (1969*a*). *J. Chem. Soc.* (*D*), **12**, 626–627.
CHOTHIA, C. & PAULING, P. (1969*b*). *J. Chem. Soc.* (*D*), **13**, 746–747.
CHOTHIA, C. & PAULING, P. (1970). *Proc. Natl. Acad. Sci. U.S.*, **65**, 477–482.
CLARK, E. R., DAWES, P. M. & WILLIAMS, S. G. (1968). *Brit. J. Pharmacol.* **32**, 113–126.
CLARK, E. R. & JANA, M. DE L. S. A. (1966). *Brit. J. Pharmacol.* **27**, 135–144.
CLARK, E. R. & WILLIAMS, S. G. (1967). *J. Chem. Soc.* (*B*), pp. 859–866.
CRUICKSHANK, D. W. J., PILLING, D. E., BUJOSA, A., LOVELL, F. M. & TRUTER, M. R. (1961). *Symposium on Computer Methods*. Oxford: Pergamon Press.
HEY, P. (1952). *Brit. J. Pharmacol.* **7**, 117–129.
International Tables for X-ray Crystallography (1962). Vol. III. Birmingham: Kynoch Press.
MILLS, O. S. & ROLLETT, J. S. (1961). *Computing Methods and the Phase Problem in X-ray Crystal Analysis*, p. 107. London: Pergamon Press.
SUNDARALINGAM, M. (1968). *Nature, Lond.* **217**, 35–37.
WILSON, A. J. C. (1942). *Nature, Lond.* **150**, 151–152.

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The Crystal Structure of β-Methylphenylcholine Ether Bromide

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β-Methylphenylcholine ether bromide, $C_{12}H_{20}ON^+Br^-$, crystallizes as the hemihydrate in the orthorhombic space group $Pna2_1$ with 8 molecules in the unit cell (two molecules per asymmetric unit). The cell parameters are $a=14{\cdot}500$ (2), $b=28{\cdot}388$ (4) and $c=6{\cdot}829$ (1) Å. The structure was solved by three-dimensional Patterson and Fourier syntheses using 2505 independent reflexions collected on a computer-controlled four-circle diffractometer. It was refined by block-diagonal least-squares calculations to a final R index of 0·081. Both molecules in the asymmetric unit adopt a conformation in which the N–C–C–O system is positive synclinal (*gauche*) and the remaining torsional angles are close to 180°, although there are small differences in detail between the two molecules.

Introduction

A number of phenylcholine ether bromides are currently under investigation in our laboratory. These include two highly potent ganglion stimulants, phenylcholine ether bromide (TM1) and *o*-methylphenylcholine ether bromide (OME TM1), and two β-substituted derivatives which show no such activity, β-methylphenylcholine ether bromide (BEM TM1) and *o*-methyl β-methylphenylcholine ether bromide (OMBEM TM1) (Hey, 1952; Clark & Jana, 1966; Clark, Dawes & Williams, 1968).

It is hoped that these structural studies will help towards an understanding of why these compounds have such different pharmacological properties. X-ray intensity data have been collected for all these compounds and the structure of OMBEM TM1 has already been solved (see previous paper). The structures for BEM TM1 described below are similar to OMBEM TM1 although there are differences in detail.