Stereochemistry of Anticholinergic Agents. Part VII.[1] Crystal and Molecular Structure of 3-(2-Methylpiperidino)-1-phenylpropyl Phenyl Ether Methiodide

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Crystals of the title compound are orthorhombic, space group $P2_12_12_1$ with $a = 11.41 \pm 0.01$, $b = 10.24 \pm 0.01$, $c = 17.92 \pm 0.02$ Å, 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* 3.4% for 1779 observed amplitudes. Estimated standard deviations for bond lengths, bond angles, and torsion angles average 0.015 Å, 0.9°, and 1.3°. The 3-(2-methylpiperidino)-1-phenylpropyl grouping adopts the characteristic claw-like arrangement observed in other potent anticholinergic agents.

3-(2-METHYLPIPERIDINO)-1-PHENYLPROPYL phenyl ether methiodide (I) was synthesized by Yoshida and coworkers [2] in the course of a study of the anticholinergic properties of a number of 3-(*NN*-disubstituted-amino)-1-phenylpropyl phenyl ethers. They found that the activity of (I) was 46.2% of that of atropine sulphate, as measured by the inhibition of acetylcholine-induced spasms of isolated guinea-pig ileum.[2] Unlike the acetylcholine-related anticholinergics [3] whose crystal structures have been described [1,4] previously, the atom chain connecting the ring substituents to the cationic head does not contain an ester group, nor does it contain the O–C–C–N$^+$ grouping of acetylcholine.

EXPERIMENTAL

Crystallographic Measurements.—Cell dimensions were measured initially from oscillation and Weissenberg photographs, final cell dimensions and intensities being measured with a Stoe two-circle computer-controlled diffractometer by use of graphite-monochromated Mo-K_α radiation and a scintillation counter. The crystal used in the analysis had dimensions 0.5 × 0.4 × 0.4 mm and was mounted about the crystallographic *c* axis. The ω-scan technique was used in the data collection, with 140 steps of 1 s at intervals of 0.01° for each reflection on layers *hk*0—7. For reflections on the higher layers a variable scan-range technique was employed, as described previously.[5] Backgrounds were measured for 30 s at each end of the scan. Four standard reflections from the zero layer were remeasured after each layer of data collection. No significant variation of intensity was observed. Of 2 127 reflections scanned within the range $0.1 < \sin\theta/\lambda < 0.6$, 1 779, for which $I > 2.5\sigma(I)$, were used in the structure analysis. Intensities were converted to structure amplitudes in the usual way, but absorption corrections were not applied.

Crystal Data.—$C_{22}H_{30}INO$, $M = 451.4$, Orthorhombic, $a = 11.41 \pm 0.01$, $b = 10.24 \pm 0.01$, $c = 17.92 \pm 0.02$ Å, $U = 2\,093.7$ Å^3, $D_m = 1.438$, $Z = 4$, $D_c = 1.432$, $F(000) = 920$. Systematic absences: *h*00 with *h* odd, 0*k*0 with *k* odd, 00*l* with *l* odd, space group $P2_12_12_1$ (D_2^4). Mo-K_α radiation, $\lambda = 0.71069$ Å; μ(Mo-K_α) = 15.6 cm^{-1}.

Structure Analysis.—The co-ordinates of the iodide ion were obtained from a three-dimensional Patterson synthesis and refined by least squares to *R* 24%. The *x* and *z* co-ordinates were both close to the pseudo-special value of 0.25 and the electron-density map phased on the iodide

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[3] R. B. Barlow, 'Introduction to Chemical Pharmacology,' Methuen, London, 1964, p. 221.

[4] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1974, 1126, and references therein.

[5] J. J. Guy and T. A. Hamor, *Acta Cryst.*, 1974, **B30**, 2277.

position exhibited four-fold pseudosymmetry. A chemically reasonable fragment of six of the lighter atoms could, however, be identified and when these atoms were included in the phasing calculations the resulting electron-density map no longer exhibited pseudosymmetry and all the remaining atoms (apart from hydrogen atoms) could be located. Least-squares refinement of positional and isotropic thermal parameters reduced R to 9.0%. The atoms were now allowed to vibrate anisotropically and the refinement continued until all calculated shifts were $<0.1\sigma$. Hydrogen atoms were located from a difference synthesis and were included in the calculations in their theoretical positions (assuming C–H 1.1 Å, and normal valency angles) but their parameters were not refined. The final value of R is 3.4% for the 1 779 reflections used in the analysis.*

The weighting scheme employed in the final cycles of least-squares refinement was $w^{\frac{1}{2}} = |F_0|/11.5$ if $|F_0| < 11.5$, $w^{\frac{1}{2}} = 1.0$ if $11.5 \leqslant |F_0| \leqslant 47.0$, and $w^{\frac{1}{2}} = 47.0/|F_0|$ if $|F_0| > 47.0$. Atomic scattering factors were taken from ref. 6.

Computations were carried out on the Birmingham University 1906A computer. The major computer programs used in the analysis are listed in ref. 5.

RESULTS AND DISCUSSION

The stereochemistry of the cation of (I), apart from absolute configuration, is illustrated in Figure 1, which shows a stereoscopic view along the b axis and also the atomic numbering scheme used. Final atomic coordinates are in Table 1, and thermal parameters in Table 2. Molecular dimensions calculated from the parameters in Table 1 are in Table 3 and the results of mean plane calculations are in Table 4. Estimated standard deviations average 0.015 Å for lengths, 0.9° for bond angles, and 1.3° for torsion angles.

The packing arrangement is illustrated in Figure 2 which shows a view of the unit cell projected along the b axis. The shorter intermolecular contact distances are in Table 5. These correspond to normal van der Waals interactions.

In the cation of (I) the phenyl rings are each planar and the mean of the bond lengths within the rings is 1.380 Å in reasonable agreement with the accepted[7] aromatic bond length of 1.394 Å. The piperidyl ring is in the chair conformation with ring torsion angles in the range 52.2—59.9°, mean 55.7°, similar to that of the piperidyl ring in the crystal structure of piperidolate hydrochloride.[8] The mean carbon–carbon bond length in the ring is 1.511 Å and the four C–N$^+$ bond lengths average 1.532 Å, also in good agreement with previous results.[8] The phenylpropyl phenyl ether moiety is in the equatorial position [torsion angles C(15)–N–C(16)–C(17) 171 and C(15)–N–C(20)–C(19) 177°] with the N-methyl group axial. Methyl carbon atom C(22) is equatorial.

The chain of atoms C(7)–O–C(13)–C(14)–C(15)–N linking phenyl ring C(7)—(12) and the piperidyl ring adopts a conformation close to fully extended all-*trans*. The apparently large bond angle at oxygen (118.5°) is typical of aromatic ethers and is probably due to an electronic rather than a steric effect. It may be compared with values of 118° in *p,p'*-dimethoxybenzophenone[9] and 118.3° in *o*-ethoxybenzoic acid[10] (both mean values taken over two crystallographically independent molecules). The C(7)–O and O–C(13) bond lengths are also similar to those commonly found[9,10] in aromatic ethers. The angle C(14)–C(15)–N (115.7°) is larger than might be expected at an sp^3-hybridised carbon atom and may indicate some repulsive forces between the piperidyl ring and the rest of the molecule. Similar large C–C–N$^+$ angles also occur in the crystal structures of penthienate bromide[4] and benactyzine hydrochloride.[11]

X-Ray crystallographic studies of atropine hydrobromide[12] and of a number of potent anticholinergic

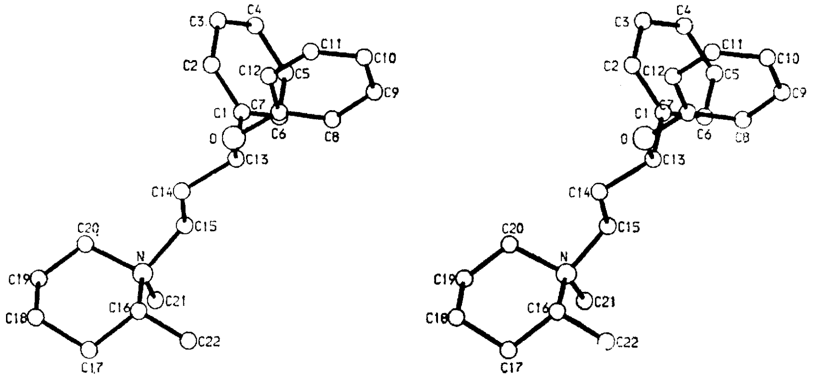

FIGURE 1 Stereoscopic view of the cation (I) along the b axis

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* Observed and calculated structure amplitudes and phase angles are published in Supplementary Publication SUP No. 21309 (9 pp., 1 microfiche). See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1973, Index issue.

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[9] H. G. Norment and I. L. Karle, *Acta Cryst.*, 1962, **15**, 873.

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substances formally derived from acetylcholine by incorporation of two ring substituents in the acyl group and ethyl groups on the nitrogen atom, or with the nitrogen atom forming part of a ring system, have shown that in the solid state these adopt a characteristic shape which may be likened[1] to that of a claw. The extremities of the 'claw' are formed by the cationic head and one of the ring substituents situated on the same side of the mean plane of the ester group as the onium nitrogen atom (or sulphur atom in the case of hexasonium[1]). The mean plane of this ring is generally steeply inclined to the ester plane, and the

TABLE 1

Fractional atomic co-ordinates (× 10^4), with estimated standard deviations in parentheses

	x	*y*	*z*
C(1)	5 345(9)	2 710(9)	−167(6)
C(2)	4 691(9)	2 640(11)	488(6)
C(3)	4 885(10)	3 503(12)	1 062(6)
C(4)	5 725(12)	4 470(12)	975(8)
C(5)	6 357(10)	4 543(11)	322(8)
C(6)	6 180(9)	3 672(11)	−238(6)
C(7)	6 001(9)	−128(9)	−161(6)
C(8)	7 153(9)	263(9)	−258(6)
C(9)	8 032(10)	−456(12)	105(6)
C(10)	7 763(9)	−1 489(11)	564(6)
C(11)	6 614(10)	−1 829(11)	662(8)
C(12)	5 738(10)	−1 194(11)	306(6)
C(13)	5 169(7)	1 712(11)	−801(5)
C(14)	4 024(9)	1 923(11)	−1 237(6)
C(15)	4 142(7)	3 153(9)	−1 679(6)
C(16)	3 109(10)	2 197(11)	−2 830(8)
C(17)	2 067(10)	2 354(15)	−3 373(8)
C(18)	962(14)	2 638(16)	−2 953(9)
C(19)	1 047(10)	3 782(14)	−2 403(9)
C(20)	2 026(9)	3 523(14)	−1 892(8)
C(21)	3 597(12)	4 584(11)	−2 683(8)
C(22)	4 180(12)	2 001(15)	−3 244(9)
N	3 244(6)	3 336(8)	−2 311(5)
O	5 058(6)	414(8)	−505(5)
I	7 432(1)	3 407(1)	−2 392(0)
H[C(2)]	4 026	1 884	543
H[C(3)]	4 354	3 445	1 568
H[C(4)]	5 845	5 138	1 436
H[C(5)]	7 006	5 322	273
H[C(6)]	6 719	3 727	−735
H[C(8)]	7 374	1 086	−631
H[C(9)]	8 940	−185	16
H[C(10)]	8 473	−2 007	826
H[C(11)]	6 406	−2 630	1 058
H[C(12)]	4 825	−1 509	348
H[C(13)]	5 930	1 790	−1 210
H^1[C(14)]	3 291	1 967	−799
H^2[C(14)]	3 826	1 050	−1 582
H^1[C(15)]	4 027	3 978	−1 273
H^2[C(15)]	5 026	3 173	−1 896
H[C(16)]	2 960	1 321	−2 455
H^1[C(17)]	1 945	1 440	−3 701
H^2[C(17)]	2 244	3 158	−3 764
H^1[C(18)]	721	1 783	−2 563
H^2[C(18)]	194	2 830	−3 293
H^1[C(19)]	246	3 969	−2 067
H^2[C(19)]	1 241	4 705	−2 720
H^1[C(20)]	1 819	2 605	−1 610
H^2[C(20)]	2 107	4 318	−1 498
H^1[C(21)]	3 400	5 350	−2 300
H^2[C(21)]	4 510	4 600	−2 700
H^3[C(21)]	2 900	4 860	−3 090
H^1[C(22)]	4 400	2 820	−3 500
H^2[C(22)]	4 075	1 200	−3 670
H^3[C(22)]	4 800	1 720	−2 850

TABLE 2

Anisotropic thermal parameters (× 10^4) for the heavier atoms

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	514	437	513	103	−57	77
C(2)	465	563	677	24	−85	68
C(3)	720	593	663	182	−63	−13
C(4)	772	585	753	182	−203	−151
C(5)	554	521	892	−37	−97	−12
C(6)	558	490	656	57	−50	1
C(7)	603	387	535	19	−48	−42
C(8)	555	422	510	−38	16	2
C(9)	576	536	593	59	−19	−60
C(10)	708	567	669	144	−47	72
C(11)	796	491	809	30	−5	184
C(12)	628	578	670	−105	53	66
C(13)	507	648	482	−113	−73	85
C(14)	627	566	552	−100	−179	98
C(15)	376	511	616	−41	−100	12
C(16)	825	509	681	68	−75	86
C(17)	642	1 197	800	−130	−316	481
C(18)	951	971	1 025	191	−474	−59
C(19)	637	925	1 190	185	−73	199
C(20)	488	722	975	2	4	62
C(21)	954	509	792	−126	−167	260
C(22)	686	831	1 210	73	11	−6
N	564	453	559	−78	−154	161
O	601	443	776	−67	−147	5
I	543	587	702	−38	161	−26

Temperature factors are in the form: $T = \exp[-2\pi^2(U_{11}h^2a^{*2} + \cdots + 2U_{12}hka^*b^* + \cdots)]$.

TABLE 3

Molecular dimensions

(*a*) Bonded distances (Å) with standard deviations in parentheses

C(1)–C(2)	1.394(11)	C(13)–O	1.437(11)
C(2)–C(3)	1.375(11)	O–C(7)	1.386(12)
C(3)–C(4)	1.387(14)	C(13)–C(14)	1.537(12)
C(4)–C(5)	1.377(9)	C(14)–C(15)	1.495(14)
C(5)–C(6)	1.359(11)	C(15)–N	1.538(12)
C(6)–C(1)	1.376(14)	N–C(16)	1.501(15)
C(7)–C(8)	1.386(17)	C(16)–C(17)	1.543(15)
C(8)–C(9)	1.403(12)	C(17)–C(18)	1.498(17)
C(9)–C(10)	1.376(12)	C(18)–C(19)	1.534(17)
C(10)–C(11)	1.367(17)	C(19)–C(20)	1.469(21)
C(11)–C(12)	1.352(11)	C(20)–N	1.591(14)
C(12)–C(7)	1.408(14)	N–C(21)	1.497(12)
C(1)–C(13)	1.541(11)	C(16)–C(22)	1.444(18)

(*b*) Selected non-bonded distances (Å)

N · · · O	4.87	N · · · Centre of ring C(1)–(6)	5.65
N · · · C(13)	3.86	N · · · Centre of ring C(7)–(12)	7.50

(*c*) Bond angles (deg.); mean standard deviation 0.9°

C(1)–C(2)–C(3)	120.7	C(1)–C(13)–C(14)	113.1
C(2)–C(3)–C(4)	119.1	O–C(13)–C(14)	104.0
C(3)–C(4)–C(5)	121.0	C(13)–C(14)–C(15)	108.1
C(4)–C(5)–C(6)	119.8	C(14)–C(15)–N	115.7
C(5)–C(6)–C(1)	120.3	C(15)–N–C(20)	104.4
C(6)–C(1)–C(2)	119.1	C(15)–N–C(16)	115.5
C(7)–C(8)–C(9)	117.9	N–C(16)–C(17)	112.9
C(8)–C(9)–C(10)	121.5	C(16)–C(17)–C(18)	110.6
C(9)–C(10)–C(11)	119.1	C(17)–C(18)–C(19)	114.7
C(10)–C(11)–C(12)	121.7	C(18)–C(19)–C(20)	108.1
C(11)–C(12)–C(7)	119.8	C(19)–C(20)–N	113.0
C(12)–C(7)–C(8)	120.0	C(20)–N–C(16)	107.2
C(2)–C(1)–C(13)	121.1	C(15)–N–C(21)	104.7
C(6)–C(1)–C(13)	119.8	C(20)–N–C(21)	110.0
C(1)–C(13)–O	110.7	C(16)–N–C(21)	114.5
C(13)–O–C(7)	118.5	N–C(16)–C(22)	109.9
C(8)–C(7)–O	125.2	C(17)–C(16)–C(22)	110.0
C(12)–C(7)–O	114.8		

TABLE 3 (*Continued*)

(*d*) Selected torsion angles (deg.);* mean standard deviation 1.3°

C(2)–C(1)–C(13)–O	−42.7
C(6)–C(1)–C(13)–O	135.8
C(2)–C(1)–C(13)–C(14)	73.5
C(6)–C(1)–C(13)–C(14)	−108.0
C(8)–C(7)–O–C(13)	−20.8
C(12)–C(7)–O–C(13)	161.2
C(7)–O–C(13)–C(14)	172.2
C(1)–C(13)–O–C(7)	−66.0
O–C(13)–C(14)–C(15)	−170.1
C(1)–C(13)–C(14)–C(15)	69.8
C(13)–C(14)–C(15)–N	163.7
C(14)–C(15)–N–C(16)	−50.1
C(14)–C(15)–N–C(20)	67.4
C(14)–C(15)–N–C(21)	−176.9
C(15)–N–C(16)–C(17)	171.0
C(15)–N–C(16)–C(22)	−65.8
C(15)–N–C(20)–C(19)	177.1
C(21)–N–C(16)–C(17)	−67.2
C(21)–N–C(16)–C(22)	55.9
C(21)–N–C(20)–C(19)	65.2
N–C(16)–C(17)–C(18)	−53.5
C(16)–C(17)–C(18)–C(19)	52.2
C(17)–C(18)–C(19)–C(20)	−55.3
C(18)–C(19)–C(20)–N	58.2
C(19)–C(20)–N–C(16)	−59.9
C(20)–N–C(16)–C(17)	55.2
C(22)–C(16)–C(17)–C(18)	−176.6

* Sign convention as defined by W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521.

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 co-ordinates relative to the cell axes

Plane (*a*): C(1)—(6)

$$7.852x - 6.256y + 7.018z = 2.382$$

C(1) −0.002, C(2) 0.009, C(3) −0.008, C(4) −0.000, C(5) 0.007, C(6) −0.006, C(13) −0.043

Plane (*b*): C(7)—(12)

$$0.829x - 6.367y - 13.979z = 0.800$$

C(7) −0.005, C(8) 0.013, C(9) −0.010, C(10) −0.003, C(11) 0.012, C(12) −0.008, O −0.062

Plane (*c*): C(13)—(15)

$$4.245x - 5.352y - 13.750z = 2.379$$

C(1) 1.331, C(7) −0.459, N −0.389, O −0.241

Plane (*d*): C(16)—(20), N

$$2.173x + 8.385y - 9.709z = 5.493$$

C(16) 0.228, C(17) −0.204, C(18) 0.205, C(19) −0.239, C(20) 0.262, N −0.253

Plane (*e*): C(16), C(18), C(19), N

$$1.964x + 6.280y - 13.819z = 5.914$$

C(16) 0.013, C(18) −0.012, C(19) 0.012, N −0.012, C(17) −0.631, C(20) 0.689

(*b*) Dihedral angles (deg.)

(*a*)–(*b*)	82.9	(*b*)–(*c*)	18.2
(*a*)–(*c*)	74.0	(*b*)–(*d*)	94.2
(*a*)–(*d*)	125.5		

$N^+(S^+) \cdots$ centre-of-ring distances are in the range 5.1—6.1 Å. This is illustrated by drawings of the hexasonium, penthienate, glycopyrronium, and atropine cations as viewed in a direction perpendicular to their ester planes, which have been presented[1,4,5] elsewhere. In the crystal structures of these potent anticholinergics the onium atom to centre-of-ring distances are 6.0, 5.2, 5.9, and 6.1 Å.

Despite the difference in chemical structure, in particular the absence of an ester group from the chain of atoms connecting the cationic head and the ring substituents, the overall shape of the cation (I) is similar. The extremities of the 'claw' may be considered to consist of the N^+-methylpiperidino-ring system and phenyl ring C(1)—(6). The phenyl ring is inclined at an angle of 74° to the plane of atoms C(13)—(15) and the nitrogen to centre-of-ring distance is 5.65 Å. Interestingly, the situation of the ether oxygen atom relative to the 'claw' is roughly similar to that of the hydroxy-group in the crystal structures of penthienate, glycopyrronium, and atropine.

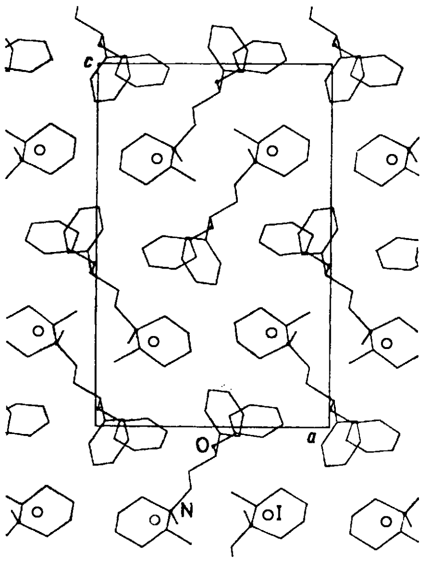

FIGURE 2 The crystal structure projected along the *b* axis

TABLE 5

Intermolecular contacts <3.8 Å for the heavier atoms [<4.0 Å for contacts involving I]

$C(3) \cdots C(20^{I})$	3.53	$C(5) \cdots C(14^{I})$	3.77
$C(9) \cdots C(3^{I})$	3.58	$C(4) \cdots C(20^{I})$	3.78
$C(9) \cdots C(2^{I})$	3.61	$C(11) \cdots C(5^{III})$	3.78
$C(3) \cdots C(19^{I})$	3.61	$C(3) \cdots C(18^{I})$	3.79
$C(8) \cdots C(2^{I})$	3.63	$I \cdots C(16^{II})$	3.95
$C(8) \cdots C(3^{I})$	3.66	$I \cdots C(15)$	3.97
$C(21) \cdots O^{II}$	3.69	$C(11) \cdots I^{IV})$	4.00
$C(21) \cdots C(13^{II})$	3.76		

The superscripts refer to the following equivalent positions:

I $\frac{1}{2} + x, \frac{1}{2} - y, -z$ III $x, -1 + y, z$
II $1 - x, \frac{1}{2} + y, -\frac{1}{2} - z$ IV $1\frac{1}{2} - x, -y, \frac{1}{2} + z$

The results obtained for (I), therefore, illustrate the importance of the overall shape and size of a cation in determining its capacity to bind to the cholinergic receptor. It seems probable that the binding groups are the cationic head and the ring substituent which form the extremities of the ' claw.' Although it is certainly dangerous to extrapolate conformational results obtained in the solid state for molecules which possess considerable flexibility, to their conformation in solution or when interacting with a receptor, the consistency of the relationship between structure and anticholinergic activity would, however, seem to indicate that the crystallographic results are meaningful in this case.

We thank Dr. A. Yoshida for supplying the crystals used in the analysis, Professors M. Stacey and J. C. Robb for their interest in this work, and the University of Birmingham for the award of a Research Scholarship (to J. J. G.).

[**4/2375** *Received*, **13***th November*, **1974**]