Stereochemistry of Anticholinergic Agents. Part III.[1] Crystal and Molecular Structure of Piperidolate (*N*-Ethyl-3-piperidyl Diphenylacetate) Hydrochloride

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Crystals of the title compound are monoclinic, space group $P2_1/c$, with $Z = 4$ in a cell of dimensions $a = 9{\cdot}60$, $b = 15{\cdot}46$, $c = 13{\cdot}49$ Å (all ±0·01 Å), $\beta = 98{\cdot}6° \pm 0{\cdot}05°$. The structure was determined by Fourier and least-squares methods from three-dimensional *X*-ray counter-data and refined by least squares to *R* 6·4% for 1339 structure amplitudes. The piperidine ring is in the chair conformation with the ester group oriented axially. The acetylcholine-like portion adopts a conformation similar to, but somewhat more compact than, that of acetylcholine in crystals of the bromide salt.

N-ETHYL-3-PIPERIDYL diphenylacetate hydrochloride (piperidolate hydrochloride) is a synthetic anticholinergic drug [2] structurally related both to acetylcholine and to the anticholinergics adiphenine hydrochloride and glycopyrronium bromide whose solid-state conformations we have already described.[1,3] Its activity, as measured [2] by the inhibitory effect on acetylcholine-induced spasms of the guinea pig ileum *in vitro* is similar to that of adiphenine, but weaker than that of atropine and certain other synthetic drugs. We now report the crystal structure analysis of piperidolate hydrochloride as part of our study of the stereochemistry of cholinergic antagonists.

EXPERIMENTAL

Crystallographic Measurements.—Piperidolate hydrochloride (M.C.P. Pharmaceuticals) was recrystallised from butan-2-one. Cell dimensions were measured initially from oscillation and Weissenberg photographs, the final cell dimensions and intensity data 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, of dimensions 0·5 × 0·15 × 0·3 mm, was set up about the unique axis (*b*), and of 3015 reflections scanned within the range $0{\cdot}1 \leqslant \sin\theta/\lambda \leqslant 0{\cdot}60$, 1339, having $I > 2{\cdot}5\sigma(I)$, were considered observed and were used in the structure analysis. The ω-scan technique was used, taking 120 steps of 1 s at intervals of 0·01° for each reflection. For the fifth and higher layer-lines, a variable scan-range technique was employed, $\Delta\omega$ being calculated by the expression $(A + B \sin\mu/\tan\theta)°$, with $A = 0{\cdot}9$ and $B = 0{\cdot}5$. Backgrounds were measured for 30 s at each end of the scan. In converting intensities into structure amplitudes, the polarisation factor appropriate to monochromated radiation was used. Absorption corrections were not applied.

Crystal Data.—$C_{21}H_{25}NO_2$,HCl, $M = 359{\cdot}9$. Monoclinic, $a = 9{\cdot}60 \pm 0{\cdot}01$, $b = 15{\cdot}46 \pm 0{\cdot}01$, $c = 13{\cdot}49 \pm 0{\cdot}01$ Å, $\beta = 98{\cdot}6 \pm 0{\cdot}05°$, $U = 1979{\cdot}6$ Å^3, $Z = 4$, $D_c = 1{\cdot}207$, $F(000) = 768$. Systematic absences: $h0l$ when l is odd, $0k0$ when k is odd, space group $P2_1/c$ (C_{2h}^5). Mo-K_α radiation, $\lambda = 0{\cdot}71069$ Å; μ (Mo-K_α) = 2·1 cm^{-1}.

Structure Analysis.—The co-ordinates of the chloride ion were obtained from a three-dimensional Patterson synthesis and structure factors calculated (*R* 54%). The phase angles were used with the observed structure amplitudes to evaluate a three-dimensional electron-density distribution from which the positions of the atoms in the ester group and the piperidine ring were located. A second electron-density map based on these atomic parameters (*R* 41%) enabled location of all non-hydrogen atoms.

Least-squares refinement of the positional and isotropic thermal parameters reduced *R* to 14%, and the atoms were then allowed to vibrate anisotropically. Hydrogen atom positions were located from a Fourier difference synthesis and were included in subsequent calculations in their theoretical positions [assuming C(sp^3)–H 1·10, C(sp^2)–H 1·08, and N–H 1·04 Å] but their parameters were not refined. Refinement was terminated when the calculated shifts were all $<0{\cdot}1\sigma$, the final *R* being 6·4% for the 1339 observed structure amplitudes.

The weighting scheme used in the final cycles of refinement was: $w^{\frac{1}{2}} = 1{\cdot}0$ if $|F_o| \leqslant 24{\cdot}8$ and $w^{\frac{1}{2}} = 24{\cdot}8/|F_o|$ if $|F_o| > 24{\cdot}8$, chosen to give approximately constant values for the average of $\Sigma w(|F_o| - |F_c|)^2$ when taken in groups of

[1] Part II, J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1973, 1875.

[2] J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Amer. Chem. Soc.*, 1952, **74**, 1485.

[3] J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1973, 942.

increasing $|F_o|$ and increasing sin θ/λ. Atomic scattering factors were taken from ref. 4, except for those of hydrogen, which were taken from ref. 5.

All computations were performed on the Birmingham University KDF 9 computer. The major crystallographic programs used in the analysis are listed and acknowledged in ref. 3. Final observed and calculated structure factors are listed in Supplementary Publication No. SUP 20871 (9 pp., 1 microfiche).†

RESULTS AND DISCUSSION

Atomic parameters and molecular dimensions are listed in Tables 1—4. Figure 1 shows a view of the piperidolate cation as seen along the crystallographic c^* axis, and also indicates the atomic numbering scheme used.

TABLE 1

Fractional atomic co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses

	x	y	z
C(1)	−5667(7)	397(4)	−2716(5)
C(2)	−6776(8)	343(5)	−2162(6)
C(3)	−8170(8)	401(6)	−2628(8)
C(4)	−8459(11)	506(7)	−3638(9)
C(5)	−7411(13)	566(6)	−4204(7)
C(6)	−6009(8)	511(5)	−3747(5)
C(7)	−3452(7)	−513(4)	−2485(5)
C(8)	−2104(9)	−510(5)	−2757(5)
C(9)	−1423(9)	−1290(7)	−2923(6)
C(10)	−2092(10)	−2071(6)	−2852(6)
C(11)	−3425(9)	−2083(5)	−2599(6)
C(12)	−4104(7)	−1315(5)	−2416(5)
C(13)	−4116(7)	339(4)	−2256(5)
C(14)	−3907(7)	487(5)	−1135(5)
C(15)	−3753(8)	1616(5)	119(5)
C(16)	−2180(8)	1595(4)	478(4)
C(17)	−1986(8)	3133(4)	−39(5)
C(18)	−3566(9)	3144(5)	−416(6)
C(19)	−4356(8)	2516(5)	150(6)
C(20)	144(8)	2228(6)	251(6)
C(21)	835(9)	1372(7)	125(7)
O(1)	−4036(5)	1341(3)	−935(3)
O(2)	−3621(5)	−57(3)	−495(4)
N	−1406(6)	2239(4)	−85(4)
Cl	−1457(2)	1993(1)	−2323(1)
H[C(2)]	−6529	268	−1343
H[C(3)]	−9019	347	−2173
H[C(4)]	−9574	538	−3977
H[C(5)]	−7652	688	−5030
H[C(6)]	−5147	524	−4195
H[C(8)]	−1550	111	−2803
H[C(9)]	−380	−1279	−3137
H[C(10)]	−1584	−2673	−3011
H[C(11)]	−3976	−2701	−2527
H[C(12)]	−5151	−1322	−2213
H[C(13)]	−3548	863	−2599
H[C(15)]	−4281	1180	587
H¹[C(16)]	−1988	1752	1285
H²[C(16)]	−1787	935	370
H¹[C(17)]	−1833	3360	755
H²[C(17)]	−1440	3587	−480
H¹[C(18)]	−3981	3804	−373
H²[C(18)]	−3711	2954	−1232
H¹[C(19)]	−4319	2729	930
H²[C(19)]	−5502	2497	−201
H¹[C(20)]	330	2392	1066
H²[C(20)]	648	2718	−158
H¹[C(21)]	1988	1417	152
H²[C(21)]	550	1151	−661
H³[C(21)]	485	884	648
H[N]	−1573	2051	−842

† See Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, Index issue.

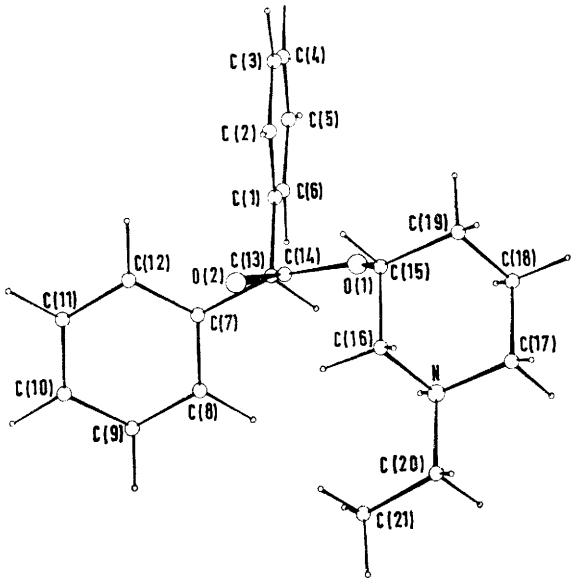

FIGURE 1 Drawing of the piperidolate cation as seen along c^*

The sample of piperidolate used was racemic. There is however evidence [6] that, in contrast to cholinomimetic molecules such as acetyl-β-methylcholine, where biological activity is critically dependent on absolute configuration, the activity of anticholinergic analogues of

TABLE 2

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

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	419	402	328	5	24	23
C(2)	443	562	635	7	−13	1
C(3)	308	974	886	94	77	−137
C(4)	669	897	877	248	−303	−18
C(5)	1115	670	472	150	−259	74
C(6)	648	540	416	60	0	77
C(7)	390	466	305	14	44	−24
C(8)	672	640	406	24	87	−68
C(9)	500	959	572	85	70	−163
C(10)	761	706	591	356	−100	−264
C(11)	640	599	667	140	−48	−126
C(12)	443	529	490	40	96	−141
C(13)	403	404	331	8	−3	−62
C(14)	409	381	467	10	42	−86
C(15)	558	567	321	−28	166	−34
C(16)	627	438	208	−1	−7	−50
C(17)	711	384	454	−65	42	−26
C(18)	716	419	612	124	58	71
C(19)	585	527	597	121	168	−153
C(20)	436	1053	549	−93	−68	−39
C(21)	585	1220	722	386	20	−91
O(1)	492	452	430	7	34	−31
O(2)	742	450	415	23	24	41
N	539	540	220	−13	−42	−12
Cl	667	840	321	−253	71	17

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

[4] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.

[5] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

acetylcholine is not influenced to a very great extent by the absolute configuration of the choline portion.† It seems likely, therefore, that the two enantiomers present in the crystals analysed do not differ greatly in activity.

TABLE 3

Molecular dimensions

(*a*) Bonded distances (Å) with standard deviations ($\times 10^3$) in parentheses

C(1)–C(2)	1·391(10)	C(7)–C(13)	1·514(9)
C(2)–C(3)	1·394(11)	C(13)–C(14)	1·513(9)
C(3)–C(4)	1·358(13)	C(14)–O(1)	1·357(8)
C(4)–C(5)	1·354(14)	C(14)–O(2)	1·207(8)
C(5)–C(6)	1·396(12)	C(15)–O(1)	1·470(8)
C(1)–C(6)	1·392(9)	C(15)–C(16)	1·515(10)
C(7)–C(8)	1·396(10)	C(15)–C(19)	1·509(10)
C(8)–C(9)	1·400(11)	C(16)–N	1·512(8)
C(9)–C(10)	1·373(12)	C(17)–N	1·495(9)
C(10)–C(11)	1·372(12)	C(20)–N	1·488(9)
C(11)–C(12)	1·394(10)	C(17)–C(18)	1·525(11)
C(7)–C(12)	1·398(10)	C(18)–C(19)	1·508(11)
C(1)–C(13)	1·527(9)	C(20)–C(21)	1·501(13)

(*b*) Bond angles (deg.); mean standard deviation 0·5°

C(6)–C(1)–C(2)	117·3	C(1)–C(13)–C(14)	111·9
C(2)–C(1)–C(13)	123·7	C(7)–C(13)–C(14)	109·8
C(6)–C(1)–C(13)	118·9	C(13)–C(14)–O(1)	110·1
C(1)–C(2)–C(3)	120·9	C(13)–C(14)–O(2)	126·3
C(2)–C(3)–C(4)	119·9	O(1)–C(14)–O(2)	123·6
C(3)–C(4)–C(5)	121·1	C(14)–O(1)–C(15)	117·7
C(4)–C(5)–C(6)	119·6	O(1)–C(15)–C(16)	109·5
C(5)–C(6)–C(1)	121·1	O(1)–C(15)–C(19)	106·1
C(12)–C(7)–C(8)	117·5	C(19)–C(15)–C(16)	112·3
C(8)–C(7)–C(13)	119·1	C(15)–C(16)–N	111·5
C(12)–C(7)–C(13)	123·4	N–C(17)–C(18)	110·7
C(7)–C(8)–C(9)	120·4	C(17)–C(18)–C(19)	112·0
C(8)–C(9)–C(10)	121·2	C(18)–C(19)–C(15)	110·8
C(9)–C(10)–C(11)	119·1	C(16)–N–C(17)	111·9
C(10)–C(11)–C(12)	120·6	C(16)–N–C(20)	112·5
C(11)–C(12)–C(7)	121·2	C(17)–N–C(20)	111·0
C(1)–C(13)–C(7)	112·5	N–C(20)–C(21)	114·4

(*c*) Torsion angles (deg.); * mean standard deviation 0·7°

C(2)–C(1)–C(13)–C(14)	−17·2
C(6)–C(1)–C(13)–C(14)	162·8
C(8)–C(7)–C(13)–C(14)	−97·5
C(12)–C(7)–C(13)–C(14)	80·8
C(2)–C(1)–C(13)–C(7)	107·0
C(6)–C(1)–C(13)–C(7)	−73·0
C(8)–C(7)–C(13)–C(1)	137·2
C(12)–C(7)–C(13)–C(1)	−44·5
C(1)–C(13)–C(14)–O(1)	−75·6
C(1)–C(13)–C(14)–O(2)	106·7
C(7)–C(13)–C(14)–O(1)	158·8
C(7)–C(13)–C(14)–O(2)	−19·0
C(13)–C(14)–O(1)–C(15)	−175·2
O(2)–C(14)–O(1)–C(15)	2·6
C(14)–O(1)–C(15)–C(16)	74·1
C(14)–O(1)–C(15)–C(19)	−164·5
O(1)–C(15)–C(16)–N	64·1
O(1)–C(15)–C(19)–C(18)	−65·8
C(19)–C(15)–C(16)–N	−53·6
C(15)–C(16)–N–C(17)	54·4
C(16)–N–C(17)–C(18)	−55·1
N–C(17)–C(18)–C(19)	55·8
C(17)–C(18)–C(19)–C(15)	−54·8
C(18)–C(19)–C(15)–C(16)	53·8
C(15)–C(16)–N–C(20)	−179·8
C(18)–C(17)–N–C(20)	178·2
C(16)–N–C(20)–C(21)	59·8
C(17)–N–C(20)–C(21)	−173·8

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

† However, if the acyl portion contains a chiral centre, anticholinergic activity is critically dependent on the absolute configuration of this centre.[6]

The diagrams and the atomic co-ordinates refer to the enantiomer with a + *synclinal* conformation for the O–C–C–N^+ group [*cf.* Table 3(*c*); torsion angle O(1)–C(15)–C(16)–N 64·1°], corresponding to the conformation

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)

$$0{\cdot}063x + 15{\cdot}336y + 1{\cdot}643z = 0{\cdot}129$$

C(1) 0·001, C(2) 0·000, C(3) −0·003, C(4) 0·003, C(5) −0·002, C(6) −0·001

Plane (*b*): C(7)—(12)

$$-2{\cdot}385x + 0{\cdot}799y - 12{\cdot}402z = 3{\cdot}870$$

C(7) 0·006, C(8) −0·009, C(9) 0·007, C(10) −0·003, C(11) −0·003, C(12) 0·000

Plane (*c*): C(13)—(15), O(1), O(2)

$$-9{\cdot}525x - 1{\cdot}819y + 2{\cdot}421z = 3{\cdot}339$$

C(13) 0·026, C(14) −0·019, C(15) 0·029, O(1) −0·025, O(2) −0·001

Plane (*d*): C(15)—(19), N

$$-0{\cdot}093x + 4{\cdot}406y + 12{\cdot}806z = 1{\cdot}117$$

C(15) 0·217, C(16) −0·218, C(17) −0·232, C(18) 0·231, C(19) −0·225, N 0·226

Plane (*e*): C(15)—(18)

$$-2{\cdot}906x + 4{\cdot}704y + 12{\cdot}659z = 1{\cdot}995$$

C(15) −0·006, C(16) 0·006, C(17) −0·006, C(18) 0·006, C(19) −0·645, N 0·641

(*b*) Dihedral angles (deg.)

(*a*)–(*b*)	94·0	(*b*)–(*c*)	77·9
(*a*)–(*c*)	96·9	(*b*)–(*d*)	155·5
(*a*)–(*d*)	66·3	(*c*)–(*d*)	89·6

of the more active enantiomer of acetyl-β-methylcholine which in the crystal structure [7] of the iodide salt has the O–C–C–N^+ torsion angle 85°.‡ As far as the molecular parameters listed in Tables 3 and 4 are concerned, only the signs of the torsion angles are affected by the choice of enantiomer.

The piperidine ring adopts the chair conformation with ring torsion-angles in the range 53·6—55·8°, mean 54·6°, typical [8] of this type of ring. The *N*-ethyl group is equatorial and the ester group axial, so that the O–C–C–N^+ conformation is *synclinal* with torsion angle O(1)–C(15)–C(16)–N 64·1° (see earlier). A similar conformation is observed in the crystal structures of most molecules containing this group,[9] although in cases

‡ This enantiomer of piperidolate has the (*R*)-configuration at the chiral centre C(15), with the C(15)–C(19) bond — *synclinal* with respect to the C(16)–N^+ bond. In the acetyl-β-methylcholine iodide structure, the β-methyl group is *antiplanar* with respect to the nitrogen atom and the configuration, accordingly (*S*). Such an arrangement is not possible for piperidolate since the nitrogen atom and C(19) form part of a piperidine ring.

[6] B. W. J. Ellenbroek, R. J. F. Nivard, J. M. van Rossum, and E. J. Ariens, *J. Pharm. Pharmacol.*, 1965, **17**, 393; R. W. Brimblecombe, D. M. Green, T. D. Inch, and B. J. Thompson, *ibid.*, 1971, **23**, 745.

[7] C. Chothia and P. Pauling, *Chem. Comm.*, 1969, 626.

[8] C. Altona and M. Sundaralingam, *Tetrahedron*, 1970, **26**, 925.

[9] E. Shefter, in 'Cholinergic Ligand Interactions,' eds. D. J. Triggle, J. F. Moran, and E. A. Barnard, Academic Press, New York, 1971.

where the geometry is not constrained by ring systems, the corresponding torsion angles are somewhat greater, *e.g.* 84·7 in acetylcholine chloride,[10] 77 in acetylcholine bromide,[11] and 83·3° in adiphenine hydrochloride.[3] The arrangement about the O(1)–C(15) bond is such that C(14) is *synclinal* to C(16), and *antiplanar* to C(19) with torsion angles C(14)–O(1)–C(15)–C(16) 74·1 and C(14)–O(1)–C(15)–C(19) −164·5°. This conformation is very similar to that occurring in other molecules containing an acetylcholine-like system where the nitrogen atom forms part of a ring system, to which the ester oxygen atom is directly linked. Thus in the crystal structures of quinuclidinyl benzilate hydrobromide,[12] quinuclidinyl di-(2-thienyl)glycolate,[13] and glycopyrronium bromide,[1] these torsion angles are all within the ranges 65·4—85·2° and −156·8 to −174·7°, respectively. It differs, however, from the orientation normally observed in the crystal structures of secondary esters where these two torsion angles are approximately equal (±120°).[14] The effect of the smaller C–O–C–CN angle is to decrease the distance between the nitrogen atom, and atoms O(2), C(13), and C(14) of the ester group. The C–O–C–CN^+ grouping of acetylcholine bromide has a similar conformation, but in crystals of the chloride salt the arrangement is *antiplanar* and this conformation, typical [14] of primary esters, is also observed in the acetylcholine-like system of adiphenine hydrochloride. The ester group, C(13)—(15), O(1), O(2), is planar to within 0·035 Å [Plane (*c*), Table 4] and adopts the normal *antiplanar* conformation, as do the ester groups of all the previously mentioned molecules.

Overall, the acetylcholine-like portion of piperidolate is more compact than is generally observed. The distances $N^+ \cdots O(1)$, $N^+ \cdots O(2)$, $N^+ \cdots C(14)$, and $N^+ \cdots C(13)$ are 2·96, 4·13, 3·75, and 4·66 Å, compared with more typical values of 3·26, 4·80, 4·40, and 5·38 Å in acetylcholine chloride,[10] or 3·23, 4·51, 4·22, and 5·41 Å in glycopyrronium bromide. This is mainly due to the relatively small O–C–C–N^+ torsion angle in piperidolate.

The biological activity of molecules containing an acetylcholine-like portion is critically dependent on the nature of the acyl group [15] (*cf.* footnote† p. 103), in our numbering system, the nature of the substituents on C(13). The orientations of the phenyl substituents on C(13) relative to one another, and to the ester group and the piperidine ring, are governed by the conformations about the bonds linking C(13) to C(1), C(7), and C(14). The arrangement about C(13)–C(14) is such that the bond to phenyl ring C(7)–(12) is *synplanar* with respect to the C=O bond, which is consistent with that generally observed for C_β–C_α–C=O groups.[16] In adiphenine hydrochloride, which has the same acyl system as piperidolate, the conformation is rather different. Relative to piperidolate, the bonds to the two phenyl rings are rotated clockwise through *ca.* 49° about C(13)–C(14), so that they are oriented plus and minus *synclinal* to the C=O bond, torsion angles 58·7 and −67·4°. The arrangement about bonds C(1)–C(13) and C(7)–C(13) is also different in adiphenine, one phenyl ring being rotated clockwise through 23°, and the other 42° anti-clockwise, compared to the conformation in piperidolate. The orientations of the phenyl rings are probably affected to a considerable extent by the crystal packing forces.

The acyl portion of quinuclidinyl benzilate hydrobromide has a hydroxy-substituent on C(13) but is otherwise the same. The conformation about C(13)–C(14) here is, however, different. The C(13)–OH bond is *synplanar* with respect to C=O, and the bonds to the two phenyl substituents accordingly plus and minus *anticlinal* to the C=O bond. The orientations about the corresponding bonds in quinuclidinyl di-(2-thienyl)glycolate and glycopyrronium bromide which also have a hydroxy-substituent at this site but different ring substituents, are similar, with the hydroxy-group *synplanar* to the carbonyl oxygen atom. The preference for this arrangement in the crystal structures of these molecules may be due to intramolecular hydrogen bonding between the hydroxy-group and the carbonyl oxygen atom, although the geometry does not seem favourable for a strong interaction (*cf.* discussions in refs. 1, 12, and 13).

However, despite these conformational differences, in each of the five structures, at least one of the ring substituents has its mean plane perpendicular to the plane of the ester group to within 16°. The inter-ring angles are also similar, deviating from 90° by a maximum of 15·5°.

Bond lengths and angles (mean σ 0·01 Å and 0·5°) are generally as expected. The short length of certain of the bonds in the phenyl rings is probably due to the effect of thermal libration, since no corrections for this were applied. The mean aromatic bond length is 1·385 Å compared with the accepted value of 1·394 Å.[17] Lengths and angles within the ester group are in good agreement with those normally observed for esters in a wide variety of different molecules.[18] The angle at the ester oxygen atom O(1) (117·7°) is, however, slightly larger than the corresponding angle in most ester structures (*ca.* 115—116°), and this may be due to repulsive interactions between the piperidine ring and the carbonyl oxygen atom.

The crystal structure is illustrated in Figure 2 and the shorter intermolecular distances are listed in Table 5. The $N^+ \cdots Cl^-$ distance (3·04 Å) indicates a strong hydro-

[10] J. K. Herdklotz and R. L. Sass, *Biochem. Biophys. Res. Comm.*, 1970, **40**, 583.
[11] F. G. Canepa, P. J. Pauling, and H. Sörum, *Nature*, 1966, **210**, 907.
[12] A. Meyerhöffer and D. Carlström, *Acta Cryst.*, 1969, *B*, **25**, 1119.
[13] A. Meyerhöffer, *Acta Cryst.*, 1970, *B*, **26**, 341.
[14] A. McL. Mathieson, *Tetrahedron Letters*, 1965, 4137.
[15] R. B. Barlow, ' Introduction to Chemical Pharmacology,' Methuen, London, 1964.
[16] J. D. Dunitz and P. Strickler, in ' Structural Chemistry and Molecular Biology,' eds. A. Rich and N. Davidson, Freeman, San Francisco, 1968.
[17] *Chem. Soc. Special Publ.*, No. 18, 1965.
[18] A. McL. Mathieson and H. K. Welsh, *Acta Cryst.*, 1965, **18**, 953; B. H. Bracher and R. W. H. Small, *ibid.*, 1967, **23**, 410.

gen bond, and hydrogen atom H[N] in its calculated position lies close to the $N^+ \cdots Cl^-$ line (angle $H-N^+ \cdots Cl^-$ 12°). Other distances correspond to normal van der Waals interactions.

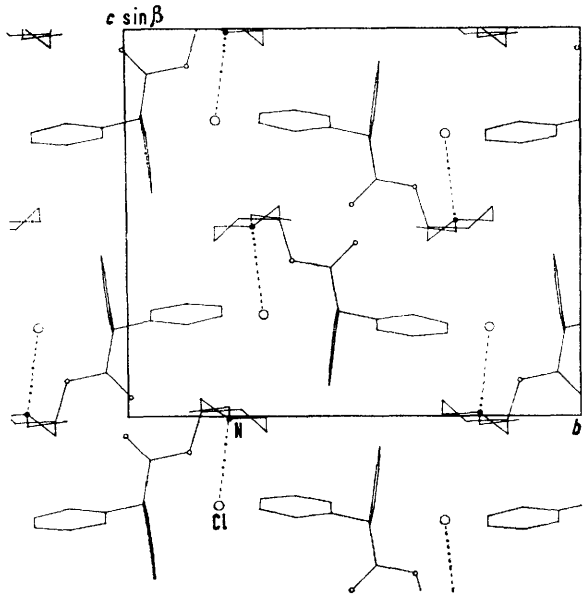

FIGURE 2 The crystal structure viewed along the *a* axis

TABLE 5

Intermolecular contacts (<3·8 Å), excluding hydrogen atoms

N · · · Cl	3·04	C(12) · · · C(18^{V})	3·51
O(1) · · · Cl	3·47	C(14) · · · O(2^{III})	3·53
C(20) · · · Cl	3·60	C(2) · · · O(2^{III})	3·57
C(13) · · · Cl	3·62	C(15) · · · O(2^{III})	3·58
C(17) · · · Cl^{I}	3·63	C(11) · · · C(18^{V})	3·65
C(17) · · · Cl	3·65	C(9) · · · C(21^{IV})	3·73
C(16) · · · Cl^{I}	3·66	C(10) · · · C(20^{IV})	3·73
C(10) · · · Cl^{II}	3·68	O(1) · · · O(2^{III})	3·74
O(2) · · · O(2^{III})	3·14	C(11) · · · O(1^{V})	3·79
C(21) · · · O(2^{IV})	3·34		

Superscripts refer to the following equivalent positions:

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

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