Acta Cryst. (1979). B**35**, 1120–1123

The Crystal and Molecular Structure of the Acetylcholine antagonist (*RS*)-4-Dimethylamino-2-butynyl 2-Cyclohexyl-2-hydroxy-2-phenylacetate Hydrochloride

By Narayandas Datta[†], Panchali Mondal and Peter Pauling

William Ramsay, Ralph Forster and Christopher Ingold Laboratories, University College London, Gower Street, London WC1, England

(*Received* 27 *July* 1978; *accepted* 10 *January* 1979)

Abstract

The structure of the title compound, $C_{20}H_{28}NO_3^+.Cl^-$, has been determined by single-crystal X-ray diffraction. Crystals are monoclinic, space group $P2_1/c$, with four formula units in a unit cell ($Z = 4$) with dimensions $a =$ 17·164 (8), $b =$ 8·109 (4), $c =$ 14·541 (7) Å and $\beta =$ 91·81 (4)°. The structure was solved by direct methods and refined by full-matrix least squares to a final R value of 0·071. The ester group is planar. The angle between the phenyl ring and the mean plane of the cyclohexyl ring is 71°. The phenyl group makes an angle of 66° and the mean plane of the cyclohexyl group an angle of 79° with the plane of the ester.

Introduction

The title compound, $C_{20}H_{28}NO_3^+.Cl^-$, is an anticholinergic substance synthesized by Inch & Brimblecombe (1971). The crystal structure has been analysed as part of a systematic study of substances affecting the peripheral and central nervous systems.

Experimental

A sample of the compound was kindly supplied by Dr T. Inch. The large, colourless, optically perfect plate crystals were prepared by recrystallization from acetone in a controlled atmosphere of ether, or during slow diffusion of ether vapour. The crystals are plates elongated along the c axis and show the forms {100}, {010} and {011}. Space group, preliminary cell parameters, and Laue symmetry $2/m$ were determined from oscillation and Weissenberg photographs. The refined cell parameters and standard deviations were obtained by a least-squares refinement of the angular parameters of twelve reflections accurately aligned on a computer-controlled four-circle Stoe diffractometer (Busing, Ellison, Levy, King & Rosebury, 1968). The density of single crystals was measured by flotation.

Crystal data

(*RS*)-4-Dimethylamino-2-butynyl 2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride, $C_{20}H_{28}NO_3^+.Cl^-$, M_r = 365·66, a = 17·164 (8), b = 8·109 (4), c = 14·541 (7) Å, β = 91·81 (4)°, V = 2022·35 Å^3, D_m = 1·205, D_x = 1·201 Mg m^{-3}, Z = 4. Systematic absences: $h0l$ for $l = 2n + 1$; $0k0$ for $k = 2n + 1$. Space group $P2_1/c$, λ(Mo $K\alpha$) = 0·7107 Å, μ(Mo $K\alpha$) = 0·225 mm^{-1}.

Data collection and processing

Three-dimensional X-ray intensity data from a small crystal (0·28 × 0·25 × 0·15 mm) were collected on a computer-controlled Stoe four-circle diffractometer using Mo $K\alpha$ radiation with a graphite monochromator (002). A coupled θ–2θ step scan with $\Delta 2\theta =$ 0·04°, a counting time of 5 s per step and a peak width of 1·6° were used. In the range 2θ = 5–45° 3108 diffraction maxima covering one quarter of reciprocal space ($hk\pm l$) were collected. This number reduced to 1052 symmetry-independent observed data having $I \geq 3\sigma(I)$. The data were corrected for Lorentz and polarization effects, but not for absorption or extinction.

Structure determination and refinement

The structure was solved by direct methods with the program *MULTAN* (Germain, Main & Woolfson, 1971). Normalized structure factors $|E|$ were calculated from the observed structure factors by the K-curve method described by Karle & Hauptman (1953,

---

[†] Deceased 17 June 1976.

0567-7408/79/051120-04$01.00

1956). The E map calculated from the set of phases with the highest combined figure of merit showed all the 28 non-hydrogen atoms.

Refinement began with a residual, R, of 0·35 for the 1052 observed data. Three cycles of isotropic full-matrix least-squares refinement reduced R to 0·127 and a further three cycles of anisotropic full-matrix refinement of all non-hydrogen atoms gave an R value of 0·099. A difference Fourier synthesis at this stage clearly indicated all H-atom positions. The observed H atoms were included as a fixed contribution to the calculated structure factors. The isotropic thermal parameters (U_{iso}) for all H atoms were fixed at 0·063 Å^2. Two additional cycles of anisotropic refinement of non-hydrogen atoms (with fixed parameters for H atoms) converged to an R value of 0·071 and all non-hydrogen parameter shifts were $\leq 0 \cdot 1\sigma$. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 4I/\sigma^2$, where $\sigma = \sigma(I) + 0 \cdot 06I$. The term $0 \cdot 06I$ was included in the estimate of σ to allow for the random long-term fluctuation in intensity measurement of a standard reflection which was measured after every 25 observations. Atomic scattering factors for neutral C, N, O and the chloride ion were those of Cromer & Waber (1965) and for H from *International Tables for X-ray Crystallography* (1962). The final positional parameters for non-hydrogen atoms are listed in Table 1 and H-atom positions in Table 2.*

Table 1. *Fractional coordinates* ($\times 10^4$) *derived from the least-squares refinement, with estimated standard deviations in parentheses*

	x	y	z
Cl(1)	4326 (2)	−1609 (4)	8595 (2)
N(1)	4331 (5)	−1535 (14)	6524 (6)
C(1)	3982 (12)	−3183 (20)	6333 (11)
C(2)	5015 (7)	−1391 (23)	6051 (10)
C(3)	3776 (10)	−213 (25)	6338 (9)
C(4)	3395 (8)	−363 (19)	5385 (9)
C(5)	3114 (7)	−326 (15)	4658 (8)
C(6)	2755 (6)	−282 (13)	3723 (7)
O(1)	2270 (4)	1177 (8)	3633 (4)
C(7)	2625 (7)	2534 (14)	3359 (6)
O(2)	3278 (5)	2594 (9)	3098 (5)
C(8)	2101 (6)	4075 (11)	3430 (6)
O(3)	2526 (4)	5474 (8)	3203 (4)
C(9)	1414 (6)	3895 (11)	2725 (6)
C(10)	780 (6)	2866 (12)	2862 (7)
C(11)	182 (6)	2797 (15)	2199 (9)
C(12)	219 (8)	3658 (17)	1405 (9)
C(13)	841 (8)	4677 (15)	1243 (8)
C(14)	1441 (6)	4762 (12)	1912 (8)
C(15)	1806 (6)	4184 (11)	4429 (6)
C(16)	1290 (6)	5666 (12)	4579 (7)
C(17)	988 (6)	5720 (14)	5544 (7)
C(18)	1681 (7)	5768 (13)	6250 (7)
C(19)	2224 (7)	4310 (14)	6098 (6)
C(20)	2505 (6)	4274 (12)	5122 (7)

Table 2. *Fractional coordinates* ($\times 10^3$) *for hydrogen atoms derived from the difference Fourier synthesis* (*column a*) *and by calculation* (*column b*)

	x		y		z	
	a	*b*	*a*	*b*	*a*	*b*
H(1)	434	445	−155	−147	713	722
H(2)	358	344	−226	−331	648	671
H(3)	390	439	−409	−415	677	656
H(4)	390	386	−347	−331	568	559
H(5)	533	528	−51	−17	633	619
H(6)	529	542	−246	−236	610	628
H(7)	491	489	−114	−152	537	531
H(8)	409	409	77	97	631	640
H(9)	340	333	−29	−27	676	686
H(10)	323	321	−27	−24	338	321
H(11)	249	239	−134	−139	369	361
H(12)	72	75	202	214	348	347
H(13)	−14	−31	201	206	238	232
H(14)	−1	−23	345	355	92	90
H(15)	101	86	492	538	72	63
H(16)	196	193	533	552	170	179
H(17)	161	147	304	305	453	455
H(18)	148	163	656	678	427	445
H(19)	95	80	556	560	418	408
H(20)	68	63	683	683	554	562
H(21)	68	63	474	462	561	566
H(22)	177	200	675	693	625	617
H(23)	143	146	555	571	682	695
H(24)	243	273	483	442	660	658
H(25)	212	191	370	317	652	624
H(26)	279	284	496	540	518	499
H(27)	272	288	320	319	520	503
H(28)	293	306	568	539	333	347

Description and discussion of the structure

Fig. 1 shows the atom-numbering scheme on a drawing of the molecule with depth cues. Bond distances and angles for a unique molecule are listed in Table 3. Table 2 contains two values for each H coordinate; one derived from the difference Fourier synthesis and one calculated using accepted stereochemical distances, angles and torsion angles. In Table 1, the parameters were derived by least squares using the H coordinates from the difference Fourier synthesis. The thermal parameters U_{11} for C(1) and U_{22} for C(2) and C(3) are large, and the distance N(1)—C(2) (Table 3) is very small. Upon calculation of interatomic distances, angles, and torsion angles for the H atoms bonded to C(1), C(2) and C(3), which are not presented here, it can be seen that the observed positions of H atoms bonded to C(2) are very poor. We interpret this to indicate that the refined parameters of C(2) are somewhat unreliable, and that the calculated H positions are more reliable than the observed, though

---

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34147 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

the latter were used in the heavy-atom least-squares refinement. Since all data on this compound have been lost, recalculation of the refinement or a new difference Fourier synthesis is impossible. Table 4 gives the mean-plane equations for certain groups of atoms in the molecule. It shows that the ester group formed by O(1), O(2), C(6), C(7), C(8) is planar. The cyclohexyl group [C(15)···C(20)] is in the chair conformation with the substituent atom C(8) in the equatorial position. The mean plane of the cyclohexyl group makes an angle of 79° with the plane of the ester and 71° with the phenyl group [C(9)···C(14)]. The phenyl group is planar and makes an angle of 66° with the ester plane. The conformation of the molecule is described in terms of selected torsion angles in Table 5. The angle τ[N(1)–C(3)–C(6)–O(1)] is −176°. The observed Cl(1)–N(1) and Cl(1)–H(1) bond lengths are 3·02 and 2·13 Å, respectively, significantly short in comparison with expected distances, presumably due to electrostatic bonding between the charged atoms. The bond lengths observed for the butyne group [C(3)···C(6)] are not significantly different from those found in an oxotremorine analogue {trimethyl[4-(2-oxopyrrolidin-1-yl)-2-butynyl]ammonium iodide} by Baker & Pauling (1973), and oxotremorine sesquioxalate by Clarke, Pauling & Petcher (1975). This group is not linear, the bond angle at C(4) being observed as 173·9 (2)° and at C(5) 179·8 (2)°. This non-linearity is also observed in an oxotremorine analogue by Baker & Pauling (1973) but not in oxotremorine sesquioxalate (Clarke, Pauling & Petcher, 1975). These three acetylenic compounds can be compared: the chief interesting difference, the addition of the phenyl ring in this substance, changes the activity from that of a cholinergic agonist (as are the other two compounds) to that of a cholinergic antagonist.

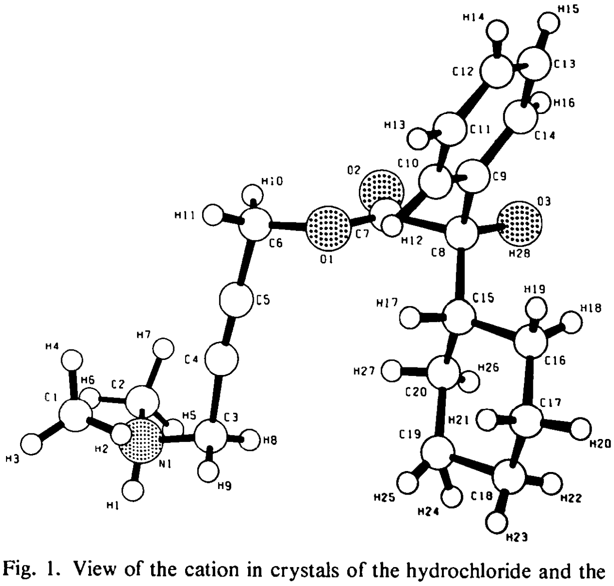

Fig. 1. View of the cation in crystals of the hydrochloride and the atomic numbering.

Most intermolecular contacts, neglecting H atoms, are >3·6 Å. The four contacts <3·6 Å involving O(2) and O(3) are: O(2)···C(3) at $(x, \frac{1}{2}-y, -\frac{1}{2}+z)$ 3·46, O(2)···C(2) at $(1-x, -y, 1-z)$ 3·28, O(3)···C(3) at $(x, \frac{1}{2}-y, -\frac{1}{2}+z)$ 3·51, O(3)···C(6) at $(x, 1+y, z)$ 3·55 Å. A close contact involving the chloride ion is: O(3)···Cl at $(x, \frac{1}{2}-y, -\frac{1}{2}+z)$ 3·26 Å. Fig. 2 shows the molecular packing viewed down the c axis with rotation about the orthonormal y axis of +45° and

Table 3. *Interatomic distances* (Å) *and angles* (°) *for non-hydrogen atoms with estimated standard deviations in parentheses in terms of the least significant figure given*

Cl(1)–N(1)	3·01 (1)	C(9)–C(10)	1·39 (1)
N(1)–C(1)	1·49 (1)	C(10)–C(11)	1·39 (1)
N(1)–C(2)	1·38 (1)	C(11)–C(12)	1·35 (1)
N(1)–C(3)	1·45 (1)	C(12)–C(13)	1·38 (1)
C(3)–C(4)	1·52 (1)	C(13)–C(14)	1·40 (1)
C(4)–C(5)	1·15 (1)	C(14)–C(9)	1·38 (1)
C(5)–C(6)	1·48 (1)	C(8)–C(15)	1·56 (1)
C(6)–O(1)	1·45 (1)	C(15)–C(16)	1·51 (1)
C(7)–O(1)	1·33 (1)	C(16)–C(17)	1·51 (1)
O(2)–C(7)	1·20 (1)	C(17)–C(18)	1·55 (1)
C(7)–C(8)	1·55 (1)	C(18)–C(19)	1·53 (1)
O(3)–C(8)	1·39 (1)	C(19)–C(20)	1·51 (1)
C(8)–C(9)	1·55 (1)	C(20)–C(15)	1·54 (1)
C(1)–N(1)–C(2)	109·0 (13)	C(8)–C(9)–C(14)	118·4 (10)
C(1)–N(1)–C(3)	111·7 (12)	C(9)–C(10)–C(11)	119·3 (10)
C(2)–N(1)–C(3)	114·0 (12)	C(10)–C(11)–C(12)	121·3 (11)
N(1)–C(3)–C(4)	111·8 (12)	C(11)–C(12)–C(13)	120·9 (12)
C(3)–C(4)–C(5)	173·9 (18)	C(12)–C(13)–C(14)	118·0 (11)
C(4)–C(5)–C(6)	179·8 (19)	C(9)–C(14)–C(13)	121·9 (10)
C(5)–C(6)–O(1)	109·0 (9)	C(8)–C(15)–C(16)	112·9 (8)
C(6)–O(1)–C(7)	115·9 (8)	C(8)–C(15)–C(20)	110·1 (8)
O(1)–C(7)–O(2)	125·0 (11)	C(16)–C(15)–C(20)	108·3 (8)
O(1)–C(7)–C(8)	112·2 (10)	C(15)–C(16)–C(17)	112·1 (9)
O(2)–C(7)–C(8)	122·8 (11)	C(16)–C(17)–C(18)	109·7 (9)
C(7)–C(8)–O(3)	109·4 (8)	C(17)–C(18)–C(19)	110·2 (6)
C(7)–C(8)–C(9)	108·2 (8)	C(18)–C(19)–C(20)	111·4 (9)
C(7)–C(8)–C(15)	108·4 (8)	C(15)–C(20)–C(19)	110·4 (8)
C(8)–C(9)–C(10)	123·1 (9)		

Table 4. *Equations of mean planes with displacements* (Å × 10^2) *of relevant atoms*

The equations are based on orthonormalized coordinates: X is parallel to the crystallographic a axis, Y is perpendicular to X in the plane ab, and Z is perpendicular to the plane ab and completes a right-handed set of axes X,Y,Z.

Plane (1): $0{\cdot}312X + 0{\cdot}207Y + 0{\cdot}927Z = 6{\cdot}817$
O(1) −8; C(6) 6; C(7) −3; C(8) 5; O(2) −1

Plane (2): $-0{\cdot}482X + 0{\cdot}762Y + 0{\cdot}432Z = 4{\cdot}473$
C(9) 1; C(10) −1; C(11) 1; C(12) −1; C(13) 0; C(14) 0

Plane (3): $0{\cdot}521X + 0{\cdot}837Y - 0{\cdot}166Z = 9{\cdot}168$
C(15) −26; C(16) 26; C(17) −24; C(18) 23; C(19) −24; C(20) 25

rotation about the orthonormal x axis of +15°.* The figures were produced using a modified version of the program *PLUTO* written by S. Motherwell, G. P. Jones and P. J. Pauling (unpublished).

All computations were carried out on the University College London IBM 360/651, the University of London CDC 6600 and our GT 44. The programs for the GT 44 were written by Douglas Richardson.

This work has been made possible by the support of the British Medical Research Council and the United States Public Health Service, National Institute of Mental Health (Grant MH 24284) and National Institute of Neurological and Communicative Disorders and Stroke (Grant NS 12021). We are most grateful to Douglas Richardson for computer programs, discussion and inspiration, to Mrs Ann Steward for assistance, Dr T. D. Inch for the sample, John Cresswell for taking photographs, and the referee for valuable comments.

Table 5. *Selected torsion angles* (°) *for non-hydrogen atoms*

N(1)–C(3)–C(4)–C(5)	−139	O(1)–C(7)–C(8)–O(3)	175
C(1)–N(1)–C(3)–C(4)	−51	O(1)–C(7)–C(8)–C(9)	−67
C(2)–N(1)–C(3)–C(4)	73	O(1)–C(7)–C(8)–C(15)	54
C(3)–C(4)–C(5)–C(6)	120	C(7)–C(8)–C(9)–C(10)	76
C(4)–C(5)–C(6)–O(1)	−158	C(7)–C(8)–C(15)–C(16)	179
C(5)–C(6)–O(1)–C(7)	88	C(9)–C(8)–C(15)–C(20)	177
C(6)–O(1)–C(7)–C(8)	−171		

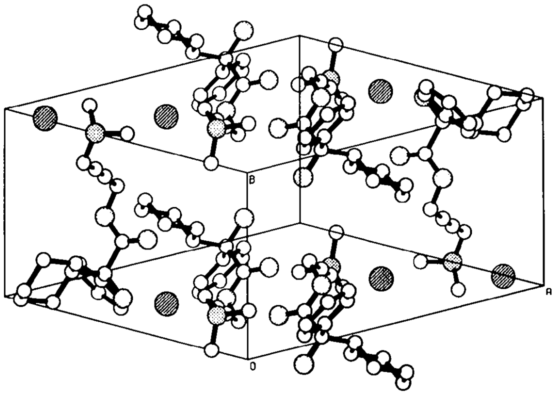

Fig. 2. Molecular packing viewed down the c axis with rotation about the orthonormal Y axis of 45° and rotation about the orthonormal X axis of 15°.

References

Baker, R. W. & Pauling, P. J. (1973). *J. Chem. Soc. Perkin Trans.* 2, pp. 1247–1249.
Busing, W. R., Ellison, R. D., Levy, H. A., King, S. P. & Rosebury, R. T. (1968). Report ORNL-143. Oak Ridge National Laboratory, Tennessee.
Clarke, P. J., Pauling, P. J. & Petcher, T. J. (1975). *J. Chem. Soc. Perkin Trans.* 2, pp. 774–778.
Cromer, D. T. & Waber, J. T. (1965). *Acta Cryst.* **18**, 104–109.
Germain, G., Main, P. & Woolfson, M. M. (1971). *Acta Cryst.* A**27**, 368–376.
Inch, T. D. & Brimblecombe, R. W. (1971). *J. Pharm. Pharmacol.* **23**, 813–815.
International Tables for X-ray Crystallography (1962). Vol. III. Birmingham: Kynoch Press.
Karle, J. & Hauptman, H. (1953). *Acta Cryst.* **6**, 131–141.
Karle, J. & Hauptman, H. (1956). *Acta Cryst.* **9**, 635–651.

---

* The orthonormal axes are defined as $x_o = a^*$, $y_o = c \times a^*$, $z_o = c$.

Acta Cryst. (1979). B**35**, 1123–1128

Pseudosymmetry in Cholesterol Monohydrate

By B. M. Craven

Crystallography Department, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, *USA*

(*Received* 23 *August* 1978; *accepted* 16 *January* 1979)

Abstract

Cholesterol monohydrate ($C_{27}H_{47}O.H_2O$) is triclinic, space group $P1$, with a = 12·39 (3), b = 12·41 (3), c = 34·36 (6) Å, α = 91·9 (1), β = 98·1 (1), γ = 100·8 (1)° and has eight molecules each of cholesterol and water in the unit cell. There are systematic absences in X-ray reflections hkl when h, k are both odd, and the diffraction symmetry is almost $2/m$. The crystal structure has a bilayer arrangement of cholesterols. Each side of the bilayer has a subcell containing two cholesterol molecules. The two similar subcells have repeats (a, $b/2$) and ($a/2$, b) with a common c direction. At the interface between subcell regions, which consists of a layer of hydrogen-bonded hydroxyl groups and water molecules, there is local twofold symmetry.

0567-7408/79/051123-06$01.00