Crystal and Molecular Structure of Benactyzine Hydrochloride (2-Diethylaminoethyl Benzilate Hydrochloride), an Antagonist of Acetylcholine in the Central and Peripheral Nervous Systems

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The crystal structure of the title compound (I) has been solved by direct methods. Crystals are triclinic, space group $P\bar{1}$, with a = 879·1(4), b = 1594·8(8), c = 709·1(6) pm, α = 95·73(1), β = 94·10(1), γ = 87·57(1)°, Z = 2. Data were collected on a diffractometer, and the structure was refined by full-matrix least-squares to R 0·104 (R' 0·160) for 2116 significant observations.

AMINO-ALCOHOL esters of aromatic-substituted glycolic acids, particularly of benzilic acid, are characterised by the production of psychic disturbances through antagonism of the transmission of nerve impulses by acetylcholine at muscarinic synapses in the brain. For this reason, they are frequently referred to as the

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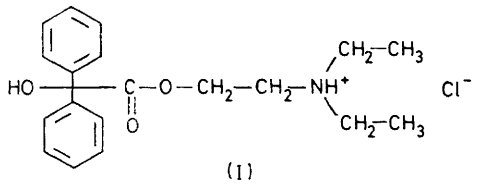
psychotomimetic glycolate esters. The use of drugs to produce psychic disturbances by this mechanism dates back to the ancient Egyptian civilisation, and the first well-documented use of belladonna alkaloids, as decoctions and smoke of *Solanacae* species, stems from the accounts of the sacred rites of the Delphic oracle. The two major alkaloids responsible for these effects are atropine and scopolamine, the crystal structures of which were determined [1,2] in order to elucidate their mechanism and site of action at muscarinic receptors in the peripheral nervous system. Out of interest in the psychic effects of these molecules, it was decided to determine the crystal structure of (I), benactyzine hydrochloride, a drug more specifically used for its CNS antagonism of acetylcholine.



(I)

Benactyzine is a potent peripheral muscarinic antagonist which also affects the CNS. In 1957 it was introduced as a sedative in the treatment of psychoneurotic disorders and has been suggested for the treatment of psychoses. The activity at peripheral muscarinic synapses tends to offset the therapeutic value of this drug in treatment of anxiety states, however, as its actions are very similar to those of atropine and scopolamine. Additionally, it is a mild antihistaminic, has a cardiac antifibrillatory effect, and is twice as potent as cocaine as a local anaesthetic.

EXPERIMENTAL

Crystal Data.—$C_{20}H_{25}NO_3$,HCl, $M = 363$. Triclinic, $a = 879{\cdot}1(4)$, $b = 1594{\cdot}8(8)$, $c = 709{\cdot}1(6)$ pm, $\alpha = 95{\cdot}73(1)$, $\beta = 94{\cdot}10(1)$, $\gamma = 87{\cdot}57(1)°$, $U = 985{\cdot}2 \times 10^6$ pm^3, $Z = 2$, $D_c = 1{\cdot}22$. Space group $P\bar{1}$ (C_i^1, No. 2). Mo-K_α radiation, $\lambda = 71{\cdot}07$ pm; μ(Mo-K_α) = 2·2 cm^{-1}.

A crystal of dimensions *ca.* 0·24 × 0·28 × 0·24 mm was selected from a batch of the commercial material (Ralph Emmanuel Ltd.). This was a parallelepiped of which it was shown, by preliminary precession photography, that the major faces corresponded to the {100}, {010}, and {001} zones of the triclinic cell. The crystal was transferred to a four-circle diffractometer and accurate cell and orientation parameters were derived by the method previously described.[3] Three-dimensional intensity data were collected by use of an ω—2θ scan and Zr-filtered Mo-K_α radiation for $2\theta < 45°$. 2592 Measurements, including periodic measurement of a standard reflection to check long-term intensity variations, yielded 2116 symmetry-independent diffraction maxima having $I \geqslant 3\sigma(I)$. Data were corrected for Lorentz and polarisation effects, and for absorption by a Gaussian quadrature procedure, before being placed on an absolute scale by means of a Wilson plot.

[1] P. Pauling and T. J. Petcher, *Nature*, 1970, **228**, 673.
[2] P. Pauling and T. J. Petcher, *Chem. Comm.*, 1969, 1001.
[3] P. Pauling and T. J. Petcher, *J.C.S. Perkin II*, 1973, 1342.
[4] R. E. Long, Thesis, University of California, Los Angeles, 1965.

An initial attempt to solve the structure by the heavy-atom method was made, but the Cl · · · Cl vector could not be located unambiguously in the Patterson synthesis, so further efforts were made with direct methods, by use of the REL [4] multisolution program. A selection of those data having $E \geqslant 1{\cdot}5$ was made, and used as input to the program, which automatically selects three origin-defining reflections and four other reflections which are systematically given phases of 0 or 180°, producing a total of 16 starting sets. Consistency indices are produced for the extension of each of the starting sets to phase all other reflections (in this case 322) from which likely sets, after exclusion of the completely consistent set with all phases positive, may be selected for the calculation of E maps. The E map calculated with the second most consistent set revealed all 25 atoms of the structure (Figure 1), and showed that the Cl · · · Cl vector in the Patterson was buried among many overlapping Cl · · · C and C · · · C vectors. The structure was refined by full-matrix least-squares, employing anisotropic temperature factors for chlorine, carbon, nitrogen, and oxygen, and a fixed overall isotropic temperature

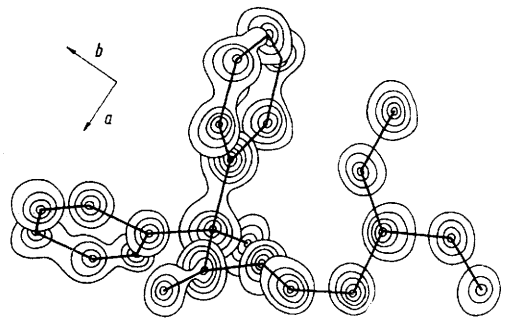


FIGURE 1 Final composite observed Fourier synthesis, projected down the c axis

factor of 5·5 for the hydrogen atoms, which were located in a difference-Fourier synthesis and then kept fixed, to

TABLE 1

Final positional and thermal parameters, with standard deviations in parentheses

(*a*) Non-hydrogen atom positions ($\times 10^4$)

	x/a	y/b	z/c
C(1)	2126(10)	−917(5)	2661(13)
C(2)	1461(8)	−106(5)	2046(11)
C(3)	−2(9)	1619(5)	3026(12)
C(4)	1509(8)	1456(5)	2181(11)
N	2338(6)	660(3)	2839(7)
C(5)	3955(7)	574(5)	2322(10)
C(6)	4890(7)	1345(5)	2815(9)
O(1)	4587(4)	1679(5)	4751(5)
C(7)	5266(7)	2390(5)	5458(9)
O(2)	6243(6)	2697(3)	4656(7)
C(8)	4580(7)	2741(3)	7314(8)
O(3)	4485(5)	2065(3)	8472(6)
C(11)	2978(8)	3112(4)	6819(9)
C(12)	2639(8)	3505(4)	5176(10)
C(13)	1178(10)	3836(6)	4806(14)
C(14)	41(9)	3786(6)	5911(14)
C(15)	347(9)	3401(6)	7573(16)
C(16)	1829(8)	3054(4)	8039(10)
C(21)	5607(7)	3395(4)	8416(9)
C(22)	5826(9)	4170(4)	7742(11)
C(23)	6726(10)	4770(4)	8757(13)
C(24)	7406(10)	4630(5)	10526(13)
C(25)	7206(10)	3850(5)	11192(12)
C(26)	6310(9)	3251(4)	10192(10)
Cl	2418(1)	543(1)	7221(2)

TABLE 1 (*Continued*)

(*b*) Anistropic thermal parameters ($\times 10^4$) *

	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	240(15)	61(4)	353(24)	−7(6)	50(15)	20(8)
C(2)	188(12)	57(3)	324(21)	−21(5)	54(13)	8(7)
C(3)	168(12)	60(4)	366(23)	4(5)	62(13)	7(7)
C(4)	171(12)	64(4)	288(19)	7(5)	44(12)	34(7)
N	141(8)	52(2)	168(10)	−12(5)	40(7)	7(4)
C(5)	140(11)	68(4)	232(16)	−16(5)	55(10)	−25(6)
C(6)	144(10)	64(3)	182(14)	−17(5)	29(10)	15(6)
O(1)	142(6)	51(2)	194(10)	−20(5)	62(6)	6(3)
C(7)	118(9)	48(3)	205(14)	−5(4)	28(9)	26(5)
O(2)	201(9)	75(3)	277(13)	−44(4)	96(8)	27(5)
C(8)	133(9)	41(2)	185(13)	−18(3)	53(9)	13(4)
O(3)	178(7)	42(2)	195(10)	−17(2)	37(6)	21(3)
C(11)	120(9)	40(2)	247(16)	−13(4)	34(10)	0(5)
C(12)	164(12)	58(3)	263(18)	0(5)	37(11)	35(6)
C(13)	207(15)	73(5)	381(26)	27(6)	0(16)	39(9)
C(14)	160(12)	64(4)	390(25)	4(5)	17(14)	14(8)
C(15)	181(14)	53(4)	550(34)	−6(5)	167(17)	−13(9)
C(16)	147(11)	46(3)	306(19)	−15(4)	83(11)	12(6)
C(21)	132(9)	43(3)	211(15)	−11(4)	54(9)	7(5)
C(22)	188(12)	49(3)	310(20)	−15(5)	37(12)	29(6)
C(23)	205(14)	44(3)	390(25)	−22(5)	50(15)	13(7)
C(24)	193(14)	61(4)	373(25)	−39(5)	64(15)	−19(8)
C(25)	214(15)	77(5)	307(22)	−33(6)	13(14)	1(8)
C(26)	213(13)	53(3)	247(18)	−30(5)	22(12)	22(6)
Cl	162(3)	49(1)	178(4)	−24(1)	46(2)	15(1)

(*c*) Hydrogen atom positions ($\times 10^3$)

	x/a	*y/b*	*z/c*
H(1)(C1)	235	−94	417
H(2)(C2)	320	−104	198
H(3)(C3)	154	−140	214
H(1)(C2)	37	−1	279
H(2)(C2)	161	−36	9
H(1)(C3)	12	153	417
H(2)(C3)	−55	224	249
H(3)(C3)	−88	118	233
H(1)(C4)	128	138	49
H(2)(C4)	218	200	273
H(N)	230	74	411
H(1)(C5)	460	−4	280
H(2)(C5)	413	28	97
H(1)(C6)	449	179	234
H(2)(C6)	631	109	232
H(03)	411	165	805
H(C12)	339	364	457
H(C13)	94	396	339
H(C14)	−105	380	661
H(C15)	−32	345	925
H(C16)	203	275	927
H(C22)	534	424	630
H(C23)	661	532	800
H(C24)	826	514	1075
H(C25)	781	364	1238
H(C26)	635	262	1068

* Anisotropic thermal parameters are coefficients in the expression exp $-(h^2b_{11} + \ldots + 2hkb_{12} + \ldots)$.

R 0·104 and *R'* 0·160 over all 2116 observations. Refinement of an isotropic correction for extinction [5] was included. Final positions, vibrations, and estimated standard deviations are in Table 1; structure factors are listed in Supplementary Publication No. SUP 21009 (13 pp., 1 microfiche).†

DISCUSSION OF THE STRUCTURE

A perspective drawing of the molecule, giving the numbering scheme, is shown in Figure 2. Figure 3 shows the intramolecular distances and angles, and Table 2 presents some non-bonded and hydrogen-bonded distances. Each nitrogen atom is surrounded by four chlorine ions, and is hydrogen bonded to one of them: O(3) is also hydrogen bonded to chlorine, as was the corresponding oxygen atom in hyoscyamine hydrobromide.[2]

The N–C–C–O torsion angle is *gauche*, as found in practically all molecules containing this grouping.[6] The principal contacts between the *N*-ethyl groups and the ester oxygen O(1) are given in Table 3. The ester group

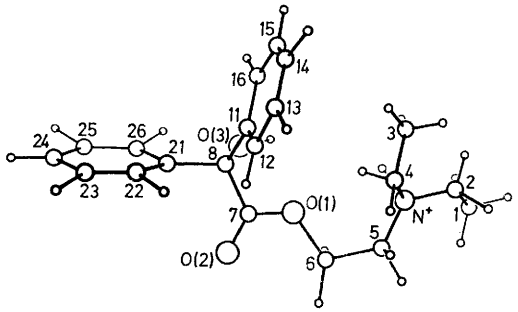


FIGURE 2 Perspective drawing of the benactyzine molecule, showing the numbering scheme

TABLE 2

Some non-bonded and hydrogen-bonded distances (pm)

N · · · O(1)	280
N · · · O(2)	484
N · · · O(3)	469
N · · · centre ring A	510
N · · · centre ring B	763
O(2) · · · O(3)	346
O(2) · · · H(03)	371
N · · · Cl	312
	398
	467
	492
H(N) · · · Cl	225
H(3) · · · Cl	236

TABLE 3

Non-bonded contacts (pm) between O(1) and N–Et groups

O(1) · · · C(1)	480
O(1) · · · C(2)	426
O(1) · · · C(3)	414
O(1) · · · C(4)	317
O(1) · · · H(1)(C1)	455
O(1) · · · H(2)(C1)	475
O(1) · · · H(3)(C1)	576
O(1) · · · H(1)(C2)	472
O(1) · · · H(2)(C2)	507
O(1) · · · H(1)C(3)	393
O(1) · · · H(2)(C3)	476
O(1) · · · H(3)(C3)	505
O(1) · · · H(1)(C4)	405
O(1) · · · H(2)(C4)	253

is planar, but the torsion angles about the C(7)–C(8) bond are different from those found in the closely related quinuclidinyl benzilate,[7] (QB) and quinuclidinyl diethienylglycolate (QT).[8] The O(2)–C(7)–C(8)–O(3)

† See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1973, Index issue.

[5] W. C. Hamilton, *Acta Cryst.*, 1971, **A26**, 71.

[6] R. W. Baker, C. H. Chothia, P. Pauling, and T. J. Petcher, *Nature*, 1971, **230**, 439, and references therein.

[7] D. Carlström and A. Meyerhöffer, *Acta Cryst.*, 1969, **B25**, 1119.

[8] A. Meyerhöffer, *Acta Cryst.*, 1970, **B26**, 341.

torsion angle is −135, compared with −7 and 15° respectively in the last two compounds. In benactyzine, C(21) occupies the position taken by O(3) in those two compounds. There, intramolecular hydrogen bonding pertains in solution.[9] To this extent, the conformation observed in this crystal structure is not directly pertinent to the conformation one may expect to find at the cholinergic receptor. The confirmation of the N–C–C–O

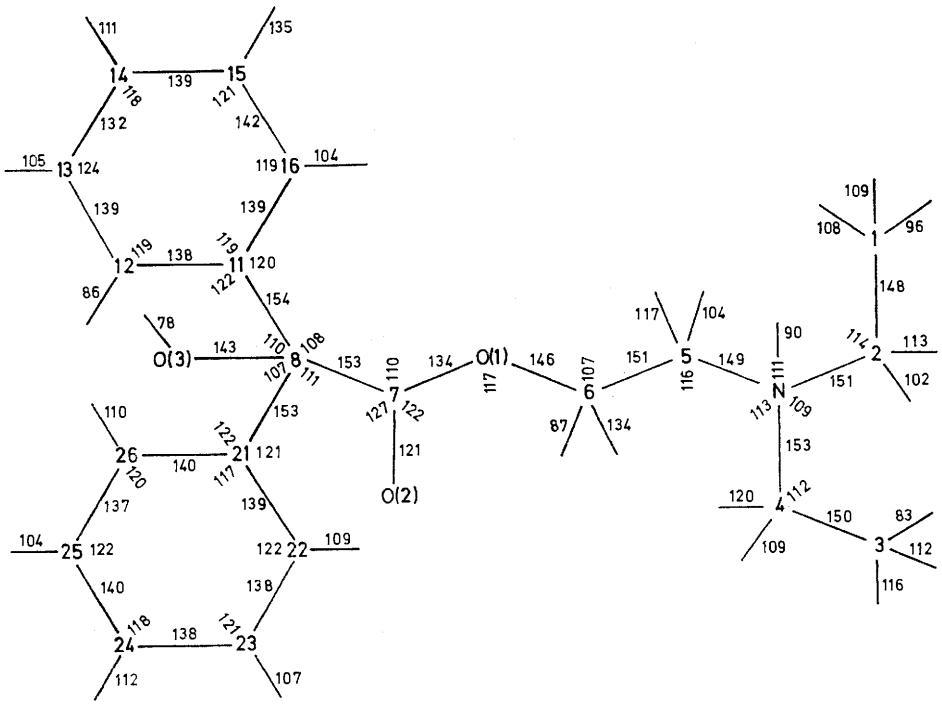


FIGURE 3 Geometry of the molecule: C(7)–C(8)–O(3) 108°, C(11)–C(8)–C(21) 112°; mean σ(C–C) 1 pm, mean σ (C–C–C) 0·6°

O(3)–H · · · O(2) is possible in the observed conformations whereas in benactyzine, the crystal packing is presumably more favourable if the intermolecular hydrogen bond O(3)–H · · · Cl forms (Figure 4), resulting

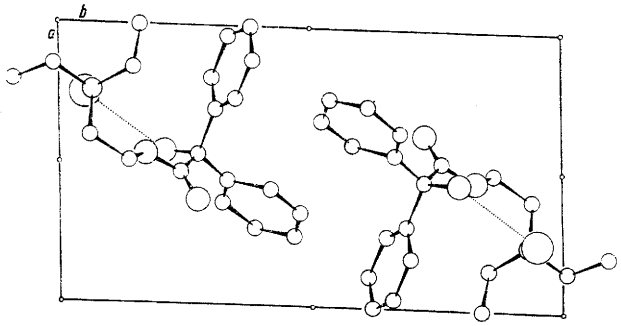


FIGURE 4 Packing diagram, *c* axis projection. Dotted lines indicate hydrogen bonds

in a rotation about the C(7)–C(8) bond. There is evidence for other similar glycolates that the species with an intramolecular hydrogen bond is that which *gauche* conformation in a compound where the basic group is $-\overset{+}{N}HEt_2$, rather than the $-\overset{+}{N}Me_3$ in most other cholinergic drugs studied,[6] is, however, useful. If the C(7)–C(8) bond is rotated so that O(2) and O(3) are *cis*, then the disposition of the nitrogen atom relative to the aromatic rings is very similar to that found in QB and QT, where the nitrogen atom is part of a rigid ring-system. That conformation would seem to be the one which the molecule is most likely to adopt when interacting with the cholinergic receptor. Further conformational studies are obviously required, in particular, the crystal structure of benactyzine as a base, in conjunction with n.m.r. studies in solution.

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[3/2206 *Received*, 26*th October*, 1973]

[9] S. G. Kuznetsov, *Zhur. obshchei Khim.*, 1960, **30**, 3353; 1961, **31**, 3360, 3366.