Journal of Crystallographic and Spectroscopic Research, Vol. 22, No. 4, 1992

Relationship of the crystal structure of γ-N,N-dimethylaminopropyl 2,2-diphenylpropionate hydrochloride to antimuscarinic activity

Jean M. Karle,[1] Isabella L. Karle,[2] Haim Leader,[3,4] Eli Breuer,[3,5] Amy H. Newman,[3] Richard K. Gordon,[3] and Peter K. Chiang[3]

Received November 8, 1991

The title compound was synthesized, characterized by ^{1}H nmr, and crystallized for x-ray crystallography. The antimuscarinic potency of the title compound was about equipotent to aprophen or atropine in inhibiting acetylcholine-induced contraction of guinea pig ileum (K_B = 4.5 nM) and in inhibiting carbachol-stimulated release of α-amylase from rat pancreatic acinar cells (K_i = 1.4 nM), and in inhibiting the binding of [N-methyl-^{3}H]scopolamine to cerebral cortex (K_i = 6.6 nM). In the crystal, the O—C—C—C—N^+ segment adopted a gauche–gauche configuration resulting in an $N^+ \cdots O$ (carbonyl) distance of 5.001(9) Å, a distance comparable to that in aprophen. The ether oxygen atom is buried rendering it inaccessible for interaction with the muscarinic receptor. The carbonyl oxygen atom is exposed to the surface of the molecule and is readily accessible for intermolecular interactions. The similarity in biological activities of the title compound and aprophen is congruous with their similar $N^+ \cdots O$ (carbonyl) distances.

Introduction

The title compound was prepared in the continuing search for potent antimuscarinic agents to serve as anticholinergic and antispasmodic agents. The title compound, $Ph_2C(CH_3)COOCH_2CH_2CH_2N(CH_3)_2$, was designed to contain an additional methylene group between the nitrogen and oxygen atoms than contained in aprophen, a potent antimuscarinic agent (Leader *et al.*, 1989). The title compound also contains a terminal dimethylamine group in place of the diethylamine group in aprophen. However, while the aminoalcohol portion of aprophen was modified, neither the hydrophobic (the 2,2-diphenylpropionate) nor the ester moieties were altered. The effect of changing the aminoalcohol moiety of aprophen was assessed by determining whether the pharmacological properties of the title compound at muscarinic receptors were diminished or increased.

An estimation of the $N^+ \cdots O$ (carbonyl) distance by molecular modeling in α-substituted 2,2-diphenylpropionate antimuscarinic agents in which the cationic nitrogen atom is part of a ring system led the authors to predict an optimal $N^+ \cdots O$ distance of 4.9 to 5.4 Å for antimuscarinic activity (Gordon *et al.*, 1989). The crystal structure of the title compound was determined to measure the $N^+ \cdots O$ (carbonyl) distance of the title compound and to compare its overall conformation to aprophen.

[1] Department of Pharmacology, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100.
[2] Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375-5000.
[3] Applied Biochemistry Branch, Division of Biochemistry, Walter Reed Army Institute of Research, Washington, DC 20307-5100.
[4] National Research Council Senior Associate, on leave from the Department of Organic Chemistry, Israel Institute for Biological Research, Ness Ziona, Israel.
[5] National Research Council Senior Associate, on leave from the Department of Pharmaceutical Chemistry, Hebrew University of Jerusalem, Jerusalem, Israel.

0277-8068/92/0800-0485$06.50/0

Experimental

Preparation of γ-N,N-dimethylaminopropyl 2,2-diphenylpropionate hydrochloride

A solution of 2,2-diphenylpropionic acid (2.26 g, 0.01 mol) and thionyl chloride (10 ml) in dry benzene (70 ml) was stirred at reflux for 4 hr. After cooling to room temperature, the benzene and excess thionyl chloride were removed under reduced pressure, and the residue was dissolved in dry benzene (50 ml). The benzene solution was added dropwise to a stirred solution of 3-N,N-dimethylaminopropan-1-ol (1.23 g, 0.012 mol) and triethylamine (1.20 g, 0.012 mol) in dry benzene (100 ml). The reaction mixture was refluxed for 4 hr. After cooling, the solid was filtered, and the filtrate evaporated to leave a viscous oil. The crude ester was dissolved in 1 N HCl (50 ml), the acidic aqueous solution was extracted with ether (2 × 50 ml), and then basified with solid Na_2CO_3. Extraction of the basic aqueous solution with ether (3 × 100 ml), drying ($MgSO_4$), and evaporation of the ether afforded 2.2 g of the crude ester as a pale yellow oil. The crude product was chromatographed on a silica gel column ($CHCl_3$/MeOH, 98:2) to give 1.8 g of colorless viscous oil. The product showed a single spot on thin layer chromatography at an R_f of 0.3 (silica, $CHCl_3$/MeOH, 95:5). The ^{1}H nmr spectrum in $CDCl_3$ gave δ 7.30–7.23 (m, 10H), 4.18 (t, 2H, J = 6.27 Hz), 2.14–2.08 (m, 2H) 2.12 (s, 6H, $N(CH_3)_2$), 1.92 (s, 3H, CCH_3), 1.71, (m, 5 lines, 2H).

The HCl salt was prepared by adding an HCl–ether solution to an ethereal solution of the aminoester and recrystallization of the white salt from ethyl acetate, mp 120–121°C. Elemental analysis on C,H,N was correct for $C_{20}H_{26}NO_2Cl$. The ^{1}H nmr spectrum in $CDCl_3$ gave δ 7.40-7.20 (m, 10H), 4.35 (t, 2H), 2.55 (s, 6H, $N^+(CH_3)_2$), 2.50 (t, 2H), 2.20 (m, 2H), 1.92 (s, 3H, CCH_3).

Crystal data for γ-N,N-dimethylaminopropyl 2,2-diphenylpropionate hydrochloride

$C_{20}H_{26}NO_2^+ \cdot Cl^-$, M_r = 347.9, monoclinic, $P2_1/n$, a = 7.049(10) Å, b = 9.518(12) Å, c = 29.397(37) Å, β = 90.39(11)°, V = 1972.6(44) Å^3, Z = 4, D_X = 1.171 g cm^{-3}, Cu $K\alpha$, λ = 1.54178 Å, μ = 18.01 cm^{-1}, F(000) = 744, room temperature, final R = 8.2% for 1624 reflections with $|F_o| > 3\sigma(F)$.

Data collection and solution

Diffraction data were collected from a colorless plate containing small occlusions, 0.6 × 0.16 mm, 0.06 mm thick, in the θ-2θ mode to a maximum 2θ value of 112° on a R3m/micro Nicolet four-circle diffractometer (Siemens Analytical X-ray Instruments, Inc., Madison, WI) with a graphite monochromator. Range of indices: h −8 → 0, k 0 → 11, and l −32 → 32. The total number of independent reflections was 2578. The standard reflections 109, 025, and 210, were monitored after every 100 intensity measurements. The standards varied by up to 4.9%. The lattice parameters were based on 25 centered reflections with 2θ values between 18 and 35°. No correction for absorption or extinction was used. The structure was solved routinely by direct phase determination (Karle *et al.*, 1966). All of the nonhydrogen atoms were found in the first E map. Eighteen of the hydrogen atoms were found in the difference maps. Least-squares refinement was performed using 1624 reflections with $|F_o| > 3\sigma(F)$ (R_{merge} = 0.030). Coordinates for all atoms except the hydrogen atoms were refined (on F) by a blocked cascade program in the SHELXTL system (Sheldrick, 1985). Coordinates for the hydrogen atoms were kept in idealized positions. Anisotropic thermal parameters for the C, N, O, and Cl atoms and isotropic thermal parameters for the hydrogen atoms were refined on a total of 218 parameters. Final R = 8.2% and wR = 7.9%, $w = 1/[\sigma^2(|F|) + 0.0005(F_o)^2]$. Final difference electron density $|\rho|_{max}$ = 0.59 and $|\rho|_{min}$ = −0.30 e Å^{-3}. $(\Delta/\sigma)_{max}$ = 0.009. S = 2.05. Atomic scattering factors were those incorporated in SHELXTL (Sheldrick, 1985).

Biological assays

The biological assays were performed as previously described (Gordon *et al.*, 1989). This research was conducted in compliance with the Animal Welfare Act and adheres to the principles stated in the Guide for the Care and Use of Laboratory Animals, NIH Publication 85-23 (1985).

Results and discussion

Table 1 lists the coordinates and U_{eq} values for the non-hydrogen atoms. Table 2 lists bond lengths, bond angles, and torsion angles. The bond length of the hydrogen atoms attached to the carbon and nitrogen atoms was kept fixed at 0.96 Å throughout the refinement procedure.

The conformation and numbering scheme of the title compound is shown in Fig. 1. The $N^+ \cdots O$ (carbonyl) interatomic distance is 5.001(9) Å, and the $N^+ \cdots O$ (ether) distance is 3.586(9) Å. The $N^+ \cdots O$

Table 1. Fractional atomic coordinates ($\times 10^4$) and thermal parameters ($Å^2 \times 10^3$) with esd's in parentheses.
$U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$

	x	y	z	U_{eq}
O(1)	10107(7)	6107(5)	1314(2)	86(2)
O(2)	7039(6)	6721(4)	1296(2)	70(2)
N	4935(7)	7580(5)	2368(2)	69(2)
C(1)	4412(10)	6633(8)	2753(3)	84(3)
C(2)	4434(10)	9068(7)	2498(3)	95(3)
C(3)	4024(9)	7210(7)	1931(2)	70(3)
C(4)	4609(10)	5753(7)	1750(3)	78(3)
C(5)	6628(10)	5623(7)	1627(3)	76(3)
C(6)	8835(10)	6849(7)	1174(2)	68(3)
C(7)	9115(9)	8072(7)	832(2)	65(3)
C(8)	11129(9)	8629(9)	923(3)	97(3)
C(9)	7693(9)	9268(7)	916(2)	61(3)
C(10)	6547(11)	9812(8)	584(3)	81(3)
C(11)	5334(11)	10942(9)	668(3)	96(4)
C(12)	5282(11)	11539(8)	1092(3)	88(3)
C(13)	6418(10)	11011(7)	1432(2)	83(3)
C(14)	7592(10)	9866(7)	1344(2)	75(3)
C(15)	8920(11)	7428(7)	357(3)	68(3)
C(16)	7582(11)	6431(9)	254(3)	103(4)
C(17)	7451(13)	5870(10)	−179(3)	116(4)
C(18)	8623(11)	6255(8)	−511(3)	105(4)
C(19)	9906(14)	7292(9)	−420(3)	119(4)
C(20)	10048(13)	7799(9)	13(3)	100(3)
Cl	9245(2)	7870(2)	2444(1)	67(1)

Table 2. Bond lengths (Å), bond angles (°), and torsion angles (°) with esd's in parentheses

O(1)−C(6)	1.211(8)	O(2)−C(5)	1.458(8)
O(2)−C(6)	1.323(8)	N−C(1)	1.494(9)
N−C(2)	1.509(8)	N−C(3)	1.470(8)
C(3)−C(4)	1.539(9)	C(4)−C(5)	1.476(10)
C(6)−C(7)	1.551(10)	C(7)−C(8)	1.537(9)
C(7)−C(9)	1.537(9)	C(7)−C(15)	1.532(10)
C(9)−C(10)	1.364(10)	C(9)−C(14)	1.384(10)
C(10)−C(11)	1.397(11)	C(11)−C(12)	1.370(12)
C(12)−C(13)	1.372(11)	C(13)−C(14)	1.393(10)
C(15)−C(16)	1.370(11)	C(15)−C(20)	1.337(11)
C(16)−C(17)	1.382(12)	C(17)−C(18)	1.335(12)
C(18)−C(19)	1.365(12)	C(19)−C(20)	1.365(12)
C(5)−O(2)−C(6)	116.2(5)	C(1)−N−C(2)	108.4(5)
C(1)−N−C(3)	114.3(5)	C(2)−N−C(3)	110.2(5)
N−C(3)−C(4)	114.0(5)	C(3)−C(4)−C(5)	114.4(5)
O(2)−C(5)−C(4)	107.5(5)	O(1)−C(6)−O(2)	124.2(6)
O(1)−C(6)−C(7)	124.1(6)	O(2)−C(6)−C(7)	111.8(5)
C(6)−C(7)−C(8)	105.5(5)	C(6)−C(7)−C(9)	111.5(5)
C(8)−C(7)−C(9)	108.6(5)	C(6)−C(7)−C(15)	106.3(5)
C(8)−C(7)−C(15)	112.0(3)	C(9)−C(7)−C(15)	112.8(5)
C(7)−C(9)−C(10)	123.4(6)	C(7)−C(9)−C(14)	119.2(6)
C(10)−C(9)−C(14)	117.4(6)	C(9)−C(10)−C(11)	121.8(7)
C(10)−C(11)−C(12)	119.9(7)	C(11)−C(12)−C(13)	119.5(7)
C(12)−C(13)−C(14)	119.7(7)	C(9)−C(14)−C(13)	121.6(6)
C(7)−C(15)−C(16)	122.4(7)	C(7)−C(15)−C(20)	122.2(7)
C(16)−C(15)−C(20)	115.7(7)	C(15)−C(16)−C(17)	120.8(8)

Table 2. Continued

C(16)—C(17)—C(18)	122.0(8)	C(17)—C(18)—C(19)	117.9(8)
C(18)—C(19)—C(20)	118.9(8)	C(15)—C(20)—C(19)	124.9(8)
C(6)—O(2)—C(5)—C(4)	174.3(6)	C(5)—O(2)—C(6)—O(1)	1.2(9)
C(5)—O(2)—C(6)—C(7)	−178.5(5)	C(1)—N—C(3)—C(4)	−62.6(7)
C(2)—N—C(3)—C(4)	175.0(5)	N—C(3)—C(4)—C(5)	−65.7(8)
C(3)—C(4)—C(5)—O(2)	−56.0(7)	O(1)—C(6)—C(7)—C(8)	−30.4(9)
O(1)—C(6)—C(7)—C(9)	−148.1(7)	O(1)—C(6)—C(7)—C(15)	88.6(8)
O(2)—C(6)—C(7)—C(8)	149.3(6)	O(2)—C(6)—C(7)—C(9)	31.6(7)
O(2)—C(6)—C(7)—C(15)	−91.7(6)	C(6)—C(7)—C(9)—C(10)	−127.1(7)
C(6)—C(7)—C(9)—C(14)	55.0(8)	C(8)—C(7)—C(9)—C(10)	117.0(7)
C(8)—C(7)—C(9)—C(14)	−60.9(8)	C(15)—C(7)—C(9)—C(10)	−7.7(9)
C(15)—C(7)—C(9)—C(14)	174.4(6)	C(6)—C(7)—C(15)—C(16)	40.4(9)
C(6)—C(7)—C(15)—C(20)	−139.4(7)	C(8)—C(7)—C(15)—C(16)	155.1(7)
C(8)—C(7)—C(15)—C(20)	−24.7(10)	C(9)—C(7)—C(15)—C(16)	−82.0(9)
C(9)—C(7)—C(15)—C(20)	98.1(8)	C(7)—C(9)—C(10)—C(11)	−177.0(7)
C(14)—C(9)—C(10)—C(11)	0.9(11)	C(7)—C(9)—C(14)—C(13)	175.9(6)
C(9)—C(10)—C(11)—C(12)	0.4(12)	C(10)—C(11)—C(12)—C(13)	−0.5(12)
C(11)—C(12)—C(13)—C(14)	−0.7(11)	C(12)—C(13)—C(14)—C(9)	2.1(11)
C(7)—C(15)—C(16)—C(17)	−179.9(7)	C(20)—C(15)—C(16)—C(17)	0.0(12)
C(7)—C(15)—C(20)—C(19)	−178.0(8)	C(16)—C(15)—C(20)—C(19)	2.1(13)
C(15)—C(16)—C(17)—C(18)	0.9(14)	C(16)—C(17)—C(18)—C(19)	−3.7(13)
C(17)—C(18)—C(19)—C(20)	5.6(13)	C(18)—C(19)—C(20)—C(15)	−5.1(14)

(carbonyl) interatomic distance is very close to the corresponding distance of 5.072(9)Å in the crystal structure of aprophen hydrochloride (Karle *et al.*, 1990) despite the additional methylene group in the title compound. The torsion angles of −65.7(8)° for N^+—C(3)—C(4)—C(5) and −56.0(7)° for C(3)—C(4)—C(5)—O(2) demonstrate the gauche-gauche character of the N^+—CH_2—CH_2—CH_2—O segment. A gauche conformation is typical of ester-containing antimuscarinic agents with two methylene groups between the ether oxygen and the cationic nitrogen atom (Guy *et al.*, 1973; Petcher, 1974) as illustrated by the N^+—C—C—O torsion angle of −81.3(5)° in aprophen (Karle *et al.*, 1990). The orientation of the diphenylmethyl group is almost the same in both the title compound and aprophen. The O(2)—C(6)—C(7)—C(8) torsion angle of 149.3(6)° is similar to the corresponding torsion angle of 142.3(5)° in aprophen. The angle between the average plane of the aromatic rings is 87.5° in the title compound and is 86.2° in aprophen. Like the ester-containing aprophen-like compounds in which the ether oxygen atom is buried inside the molecule, the ether atom of the title compound is also buried making it inaccessible to interatomic interaction (Fig. 2). If the title compound is viewed perpendicular to the plane of the acyloxy group, one phenyl group is on the same side of the plane defined by atoms O(1), C(6), and O(2) as the nitrogen atom. This geometric feature is common to antimuscarinic agents containing an ester or a thioester group (Guy *et al.*, 1974; Karle *et al.*, 1990).

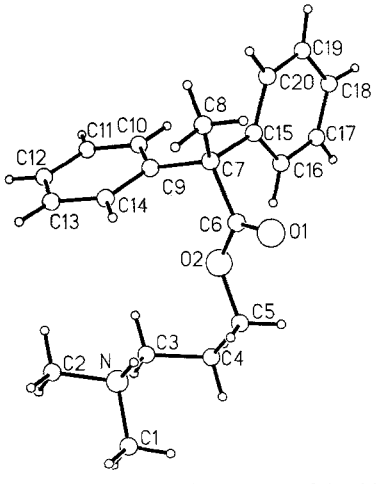

Fig. 1. Conformation and numbering scheme of the title compound. The size of the circles was arbitrarily chosen to correspond to the atomic weight of the atom. The figure was drawn using the SHELXTL program package.

A superposition of the crystal structures of thiodeacylaprophen hydrochloride and aprophen hydrochloride illustrates the common features of the two structures and their differences (Figs. 3a and b). When the acyloxy group of both structures is superimposed (Fig. 3a), the diphenylmethyl groups of both structures are nearly in the same orientation. However, the cationic nitrogen

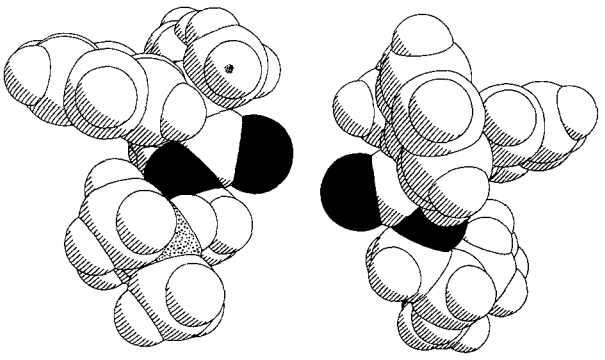

Fig. 2. Space-fill diagrams of the title compound depicting front and backsides. The oxygen atoms are colored black, and the nitrogen atom is dotted. The nitrogen atom is visible only in the left diagram. The radii of the spheres is 75% of the van der Waals radii. The figure was drawn using the SHELXTL program package.

atoms are 2.36 Å apart even though the intramolecular $N^+ \cdots O$ distances for both molecules differ by only 0.07 Å. In addition, the hydrogen atoms attached to the nitrogen atoms point in nearly opposite directions as shown by the $H-N^+ \cdots N^+-H$ torsion angle of 163.5°. When the O(1), O(2), and N^+ atoms of each structure are superimposed (Fig. 3b), the remainder of the molecules do not superimpose as well as in Fig. 3a even though the nitrogen atoms of the two molecules are only 0.19 Å apart. Again, the hydrogen atoms attached to the nitrogen atoms point in opposite directions with a $H-N^+ \cdots N^+-H$ torsion angle of 153.9°. The direction in which the nitrogen atoms of the title compound and aprophen can form a hydrogen bond may not be as important to antimuscarinic activity as the physical location of the positively charged group since compounds (Tollenaere *et al.*, 1979) that contain positively charged quaternary nitrogen or positively charged sulfur atoms cannot form a similar hydrogen bond, but are also potent antimuscarinic agents.

The packing of the title compound is illustrated in Fig. 4 with a view down the *b* axis. The cationic nitrogen atom is hydrogen bonded to the chloride ion with a $N^+ \cdots Cl$ distance of 3.057(10) Å, an $H \cdots Cl$ distance of 2.156(10) Å, and a $N^+-H \cdots Cl$ angle of 156.0(7)°. The hydrogen bond is almost parallel to the *a* axis. The phenyl rings from two neighboring molecules reside in parallel planes with the closest approach being the hydrogen atoms of C(17) of both rings at 2.567(10) Å. Although the title compound does not contain an asymmetric carbon atom, its mirror images are not superimposable due to the twist of the backbone and the phenyl rings. The crystal contains both mirror images.

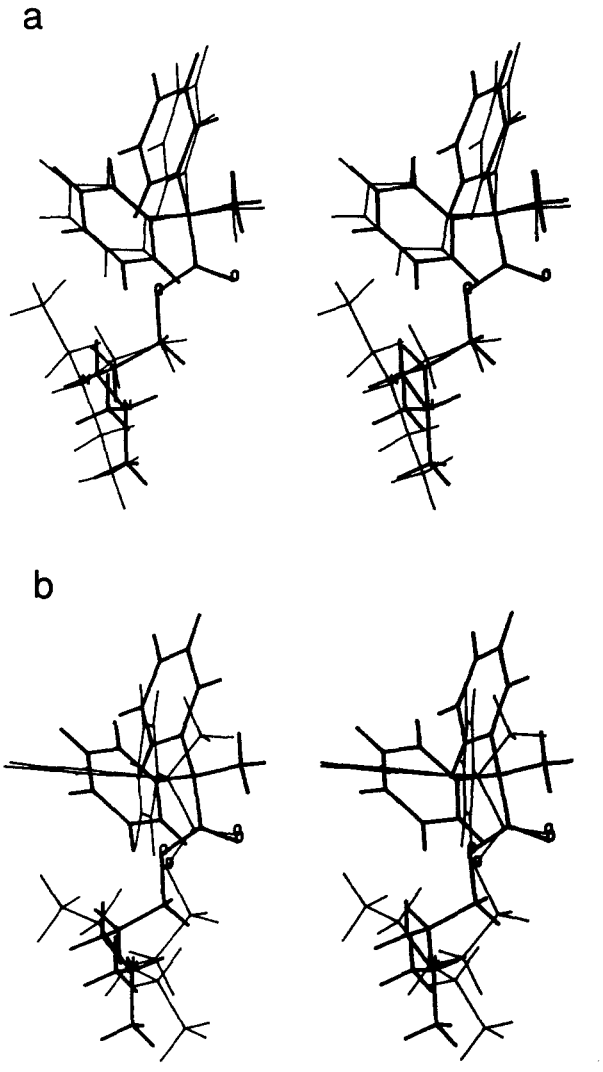

Fig. 3. Stereodiagrams of the superposition of the title compound (thick lines) with aprophen (thin lines). The heteroatoms of both structures are labeled. (a) Atoms O(1), O(2), C(6), and C(7) of both molecules were subjected to a least-squares fit. (b) Atoms O(1), O(2), and N of both molecules were subjected to a least-squares fit. Both figures were drawn using the SYBYL program from Tripos Associates (St. Louis, MO).

The results obtained from the biological assays (Table 3) showed the title compound to be about equipotent to aprophen or atropine in inhibiting acetylcholine-induced contraction of guinea pig ileum and in inhibiting carbachol-stimulated release of α-amylase from Sprague–Dawley rat pancreatic acinar cells, and in inhibiting the binding of [N-*methyl*-^{3}H]scopolamine to cerebral cortex. While the three biological assays contain different muscarinic receptor subtypes based on both pharmacological and genetic analysis (Peralta *et al.*, 1987), the title compound's potency in each assay var-

Table 3. Antimuscarinic activity[a] of title compound and standard compounds

Compound	Ileum contraction[b] K_B (M)	Pancreatic acini α-amylase release[c] K_i (M)	[*N-Methyl*-^{3}H]scopolamine binding[d] K_i (M)
Title	4.5×10^{-9}	1.4×10^{-9}	6.6×10^{-9}
Aprophen	3.1×10^{-9}[e]	1.7×10^{-9}[e]	3.6×10^{-8}
Atropine	2.0×10^{-9}[e]	1.6×10^{-9}[e]	1.6×10^{-9}

[a] Values represent mean ± standard error of three to six separate determinations. The standard errors were less than 10%.

[b] The ability of the test compound to block acetylcholine-induced contraction of male albino guinea pig ileum. Schild plots of the dose-dependent inhibition curves yielded the K_B values (Tallarida *et al.*, 1979).

[c] K_i, the equilibrium dissociation constant. The K_i values were derived from the IC_{50} values, the concentration of the test compound required for 50% inhibition of carbachol-stimulated release of α-amylase from Sprague–Dawley rat pancreatic acinar cells, according to the procedure of Munson and Robard (1979) and Cheng and Prusoff (1973).

[d] K_i, is the equilibrium displacement constant. The K_i values were derived from the IC_{50} values, the value required for 50% inhibition of binding [*N-methyl*-^{3}H]scopolamine to Sprague–Dawley rat cerebral cortex, according to the procedure of Munson and Robard (1979) and Cheng and Prusoff (1973).

[e] Values from Karle *et al.*, 1992.

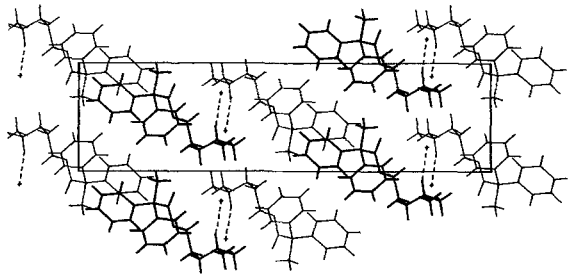

Fig. 4. Packing diagram of the title compound viewed down the *b* axis. The *c* axis is horizontal, and the *a* axis is vertical. The hydrogen bonds are depicted by the dotted lines. The small crosses represent the location of the chloride ions. The heavier and lighter lines were used to visually distinguish separate molecules. The figure was drawn using the SYBYL program from Tripos Associates (St. Louis, MO).

ied by less than 10-fold. Thus, like atropine, which is a nonselective muscarinic antagonist (Gordon *et al.*, 1989), the title compound displayed no selectivity for each of the three muscarinic receptor subtypes present in the biological assays. In this case, the additional flexibility afforded the title compound by the extra methylene group or the substitution of methyl groups for aprophen's ethyl groups was not sufficient to allow a conformation which discriminates muscarinic receptor subtypes (Flavin *et al.*, 1987). Since the $N^+ \cdots O$ (carbonyl) interatomic distances in the crystal structure of the title compound and aprophen (5.001 versus 5.072 Å, respectively) were comparable, it is not surprising that the inhibition constants were similar.

In summary, the gauche–gauche conformation of the $O-C-C-C-N^+$ segment of the title compound causes the title compound to have a folded conformation and a $N^+ \cdots O$ (carbonyl) distance similar to potent antimuscarinic agents containing an $O-C-C-N^+$ segment. The folded conformation also causes the ether oxygen atom of the title compound to be buried inside the molecule. The title compound and aprophen can be superimposed such that the diphenylmethyl and acyloxy groups of both compounds are in essentially identical conformations or such that the oxygen and nitrogen atoms of both molecules are in close proximity to each other. Similar to atropine, the title compound was not selective for any of the assayed muscarinic receptor subtypes.

References

Cheng, Y.-C., and Prusoff, W. H. (1973) *Biochem. Pharmacol.* **22,** 3099.

Flavin, M. T., Lu, C. M., Thompson, E. B., and Bhargava, H. N. (1987) *J. Med. Chem.* **30,** 278.

Gordon, R. K., Breuer, E., Padilla, F. N., Smejkal, R. M., and Chiang, P. K. (1989) *Mol. Pharmacol.* **36,** 766.

Guy, J. J., and Hamor, T. A. (1973) *J.C.S. Perkin II*, 942.

Guy, J. J., and Hamor, T. A. (1974) *Acta Crystallogr. B***30,** 2277.

Karle, J., and Karle, I. L. (1966) *Acta Crystallogr.* **21,** 849.

Karle, J. M., Karle, I. L., and Chiang, P. K. (1990) *Acta Crystallogr. B***46,** 215.

Karle, J. M., Karle, I. L., Gordon, R. K., and Chiang, P. K. (1992) *Acta Crystallogr.* in press.

Leader, H., Smejkal, R. M., Payne, C. S., Padilla, F. N., Doctor, B. P., Gordon, R. K., and Chiang, P. K. (1989) *J. Med. Chem.* **32,** 1522.

Munson, P. J., and Rodbard D. (1979) *Endocrinology* **105,** 1377.

Peralta, E. G., Ashkenazi, A., Winslow, J. W., Smith, D. H., Ramchandran, J., and Capon, D. J. (1987) *EMBO J.* **6,** 3923.

Petcher, T. J. (1974) *J.C.S. Perkin II*, 1151.

Sheldrick, G. M. (1985) in *Crystallographic Computing* 3, G. M. Sheldrick, C. Krüger and R. Goddard (eds.) (Oxford Univ. Press), p. 175.

Tallarida, R. J., Cowan, A., and Adler, M. W., (1979) *Life Sci.* **25,** 537.

Tollenaere, J. P., Moereels, H., and Raymaekers, L. A. *Atlas of the three-dimensional structure of drugs* (Elsevier/North-Holland Biomedical Press, Amsterdam, 1979).

Structure factor data, anisotropic thermal parameters of non-hydrogen atoms and hydrogen coordinates have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK, as supplementary publication No. 67092 (19 pages).