Structural and Molecular Modeling Study of Mono(pyrrolidiniomethyl)phenylacetate Antiarrhythmic Agents

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Abstract

Crystal structures of three class I antiarrhythmic agents: (1) *iso*-butyl 3-(1-pyrrolidinylmethyl)-4-(hydroxy)-methylphenylacetate hydrochloride, (2) 1,4-benzo-dioxan-2-methyl-3-(1-pyrrolidinylmethyl)-4-(hydroxy)-methylphenylacetate hydrochloride and (3) 1,4-benzodioxan-2-methyl-3-(1-pyrrolidinylmethyl)methyl-phenylacetate oxalate were determined. All three compounds are protonated at the N atom of the pyrrolidine ring. The protonated amine forms strong N—H···Cl or N—H···O intermolecular hydrogen bonds with the anions (either the chloride ion or the O atom of the hydrogen oxalate). The pyrrolidine rings are found in a similar orientation relative to the phenyl ring in all these compounds. The separations between the N atom of the pyrrolidine ring and the carbonyl O atom are observed in a range close to the N···O distance for class Ic antiarrhythmic agents found by Glowka, Dargie & Codding [*J. Med. Chem.* (1991), **34**, 2678–2684]. Molecular mechanics calculations are used to identify the structural similarity of these antiarrhythmic agents, and to establish possible binding features required for class I agents.

Introduction

Sudden cardiac arrest is a leading cause of mortality in Western society and ventricular arrhythmias play a major role in these deaths. A cardiac arrhythmia alters the normal beat of the heart and is caused by localized changes in ionic currents across membranes; the ion channels that permit the flow of charged species are important to this effect. Antiarrhythmic drugs stabilize the nonconducting states of the channels, thereby increasing the time between channel openings. Class I drugs act predominantly by decreasing sodium channel conduction during the rapid depolarization phase of the action potential of the cardiac cell. Class I agents have been further subdivided to Ia, Ib and Ic based on their effect on action potential duration (Harrison, 1985) and on the rate of onset–offset of a frequency-dependent

block (Campbell, 1983a,b). They have been shown to bind to a saturable stereospecific site on the sodium channel (Sheldon, Cannon & Duff, 1987; Sheldon, Cannon, Nies & Duff, 1988). In 1989, the Cardiac Arrhythmia Suppression Trial (CAST study) was designed to test the hypothesis that suppression of premature ventricular depolarizations (PVD) in a population with prior myocardial infarction would reduce the incidence of sudden arrhythmic death. Two of the agents employed in the study were the class Ic agents, flecainide and encainide. While these two agents were effective in suppressing PVD's, they did not decrease mortality. The failure of these two class Ic agents in the CAST study has increased interest in understanding the mechanism of class I drugs and the binding features required for active compounds.

Recently, a new series of 3-(1-pyrrolidinylmethyl)-phenylacetates (*e.g.* 1–3) was found to have class I antiarrhythmic activity (Chorvat, 1992; Chorvat *et al.*, 1993). These compounds are chemically similar to the

(1)

(2)

(3)

(4)
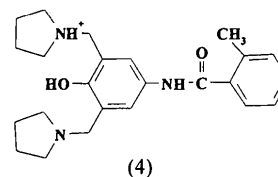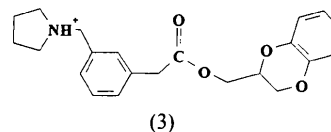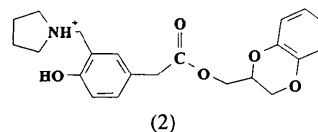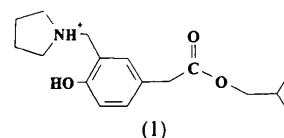
4-substituted 2,6-bis(1-pyrrolidinylmethyl)phenols studied by Glowka, Dargie & Codding (1991), *e.g.* (4). Glowka and co-workers identified several molecular features as important for activity: an intramolecular hydrogen bond between the phenol OH group and one pyrrolidine ring N-atom which restricts the orientation of this pyrrolidine ring, a preferred conformation for the benzanilide fragment, a preferred orientation of the free pyrrolidine ring and a restricted set of torsion angles that define the mutual orientation of the two pyrrolidine rings. In contrast, the title compounds have only one pyrrolidine ring connected to the phenyl ring, an ester group instead of the amide group in the central part of the molecule, and a longer interconnecting chain which joins the aliphatic main group to the lipophilic group. Therefore, to further understand the binding features required for class I antiarrhythmics, the crystal structures of three of these compounds have been determined and a full conformational search was performed using molecular mechanics calculations.

Results and discussion

The molecular conformations and atomic labeling schemes for (1–3) are shown in Figs. 2–4. Experimental details are given in Table 1 and the atomic coordinates of all three structures in Table 2. Table 3 contains selected geometric data, torsion angles and the geometries of intermolecular hydrogen bonds for these compounds.* Molecular mechanics calculations for important fragments of the title compounds, (*a*) 4-methyl-2-(1-pyrrolidinylmethyl)phenol and (*b*) methyl (3-methyl-4-hydroxy)phenylacetate (see Fig. 1), were performed using the *MacroModel* program (Mohamadi *et al.*, 1990) implemented on an IBM/RISC6000 computer. Extensions of the AMBER molecular mechanics force field provided in *MacroModel* were used; Monte Carlo conformational searches on these two fragments were carried out to identify all possible low-energy conformers and the relative populations of each conformer. In each calculation, the total number of conformers sought was determined by the number of variable torsion angles multiplied by 500, *i.e.* 500 Monte Carlo steps were performed for each variable torsion angle.

All three compounds, crystallized as hydrochloride or hydrogen oxalate salts, are protonated at the N atom of the pyrrolidine ring. The protonated amine forms a strong intermolecular hydrogen bond with the anion (either the chloride ion or an O atom of the hydrogen oxalate). The protonation of these compounds suggests a possible interaction between the drug and the sodium channel
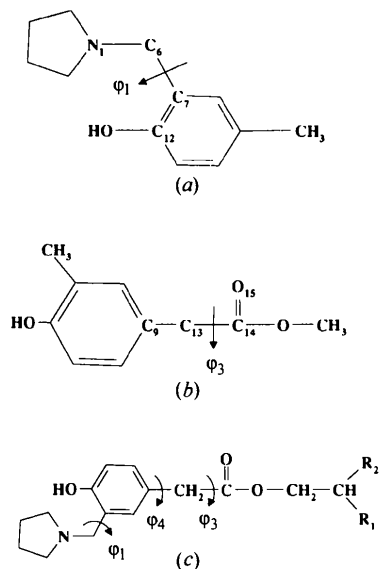
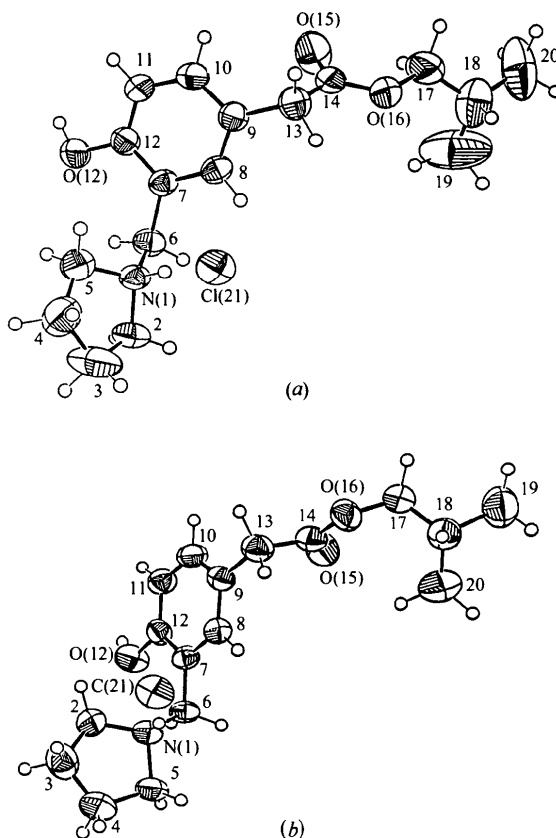Fig. 1. Fragments used for molecular mechanics calculations.

Fig. 2. A view of the two unique molecules of (1) showing the labeling of the non-H atoms. Thermal ellipsoids are drawn at 50% probability. Molecule 1 is labeled by adding 01 to the atom number and molecule 2 is labeled by adding 02. The figure was prepared using the program *ORTEP*II (Johnson, 1976).

Table 1. Experimental details

	(1)	(2)	(3)
Crystal data			
Chemical formula	$C_{17}H_{26}NO_3Cl$	$C_{22}H_{26}NO_5Cl$	$C_{22}H_{26}NO_4^+.C_2HO_4^-$
Chemical formula weight	327.8	419.9	457.5
Cell setting	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/n$	$P2_1/c$	$P\bar{1}$
a (Å)	16.763 (1)	15.684 (2)	8.3651 (3)
b (Å)	10.1619 (7)	6.4228 (7)	25.628 (1)
c (Å)	21.503 (2)	22.249 (2)	5.5890 (3)
α (°)	90	90	95.447 (4)
β (°)	97.758 (6)	109.656 (9)	106.614 (4)
γ (°)	90	90	82.653 (4)
V (Å^3)	3629.5 (4)	2110.7 (4)	1136.6 (1)
Z	8	4	2
D_x (Mg m^{-3})	1.200	1.321	1.336
Radiation type	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$
Wavelength (Å)	1.54178	1.54178	1.54178
No. of reflections for cell parameters	25	23	25
θ range (°)	33.03–44.73	17.28–27.30	21.37–29.02
μ (mm^{-1})	1.97	1.88	0.8
Temperature (K)	293	293	293
Crystal form	Cube	Needle	Plate
Crystal size (mm)	0.30 × 0.30 × 0.20	0.30 × 0.10 × 0.10	0.25 × 0.20 × 0.10
Crystal color	Colorless	Colorless	Colorless
Data collection			
Diffractometer	Enraf–Nonius CAD-4F	Enraf–Nonius CAD-4F	Enraf–Nonius CAD-4F
Data collection method	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
Absorption correction	None	Empirical (DIFABS; Walker & Stuart, 1983)	None
T_{min}		0.807	
T_{max}		1.194	
No. of measured reflections	6710	4544	4758
No. of independent reflections	6131	3994	4652
No. of observed reflections	3891	2575	3341
Criterion for observed reflections	$I > 2.5\sigma(I)$	$I > 2.5\sigma(I)$	$I > 2.5\sigma(I)$
R_{int}	0.054	0.0316	0.019
θ_{max} (°)	65	70	75
Range of h, k, l	$-18 \rightarrow h \rightarrow 18$	$0 \rightarrow h \rightarrow 17$	$-9 \rightarrow h \rightarrow 9$
	$0 \rightarrow k \rightarrow 18$	$0 \rightarrow k \rightarrow 7$	$0 \rightarrow k \rightarrow 28$
	$0 \rightarrow l \rightarrow 24$	$-24 \rightarrow l \rightarrow 24$	$-6 \rightarrow l \rightarrow 6$
No. of standard reflections	3	3	3
Frequency of standard reflections (s)	2000	3000	3000
Intensity decay (%)	<10	<10	<10
Refinement			
Refinement on	F	F	F
$R[F^2 > 2\sigma(F^2)]$	0.065	0.069	0.055
$wR(F^2)$	0.086	0.073	0.059
S	0.9770	1.0408	1.0886
No. of reflections used in refinement	3891	2575	3341
No. of parameters used	212	282	395
H-atom treatment	See text	See text	See text
Weighting scheme	$w = 1/[\sigma^2(F) + 0.0002F^2]$	$w = 1/[\sigma^2(F) + 0.00012F^2]$	$w = 1/[\sigma^2(F) + 0.00015F^2]$
$(\Delta/\sigma)_{max}$	0.0162	0.00454	0.00786
$\Delta\rho_{max}$ (e Å^{-3})	0.386	0.384	0.387
$\Delta\rho_{min}$ (e Å^{-3})	−0.31	−0.23	−0.32
Extinction correction method	Zachariasen (1967)	Zachariasen (1967)	Zachariasen (1967)
Extinction coefficient	2.9 (2) × 10^{-3}	1.1 (1) × 10^{-3}	1.37 (6) × 10^{-3}
Source of atomic scattering factors	Cromer & Mann (1968) for non-H atoms; Stewart, Davidson & Simpson (1965) for H atoms	Cromer & Mann (1968) for non-H atoms; Stewart, Davidson & Simpson (1965) for H atoms	Cromer & Mann (1968) for non-H atoms; Stewart, Davidson & Simpson (1965) for H atoms
Computer programs			
Data collection	CAD-4F	CAD-4F	CAD-4F
Cell refinement	XRAY76 (Stewart, 1976)	XRAY76 (Stewart, 1976)	XRAY76 (Stewart, 1976)
Data reduction	XRAY76 (Stewart, 1976)	XRAY76 (Stewart, 1976)	XRAY76 (Stewart, 1976)
Structure solution	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)	SHELXS86 (Sheldrick, 1985)
Structure refinement	XRAY76 (Stewart, 1976)	XRAY76 (Stewart, 1976)	XRAY76 (Stewart, 1976)

Table 2. *Fractional coordinates* $(\times 10^4)$ *and equivalent isotropic thermal parameters* $(\times 10^4)$ *for non-H atoms (e.s.d.'s in parentheses)*

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$$

	x	y	z	U_{eq}
(a) (1)				
N(101)	−1174 (2)	86 (4)	2040 (2)	500 (16)
C(201)	−881 (3)	192 (6)	1413 (2)	666 (22)
C(301)	−427 (5)	−1043 (8)	1354 (3)	1158 (38)
C(401)	−686 (4)	−1990 (7)	1810 (4)	1096 (37)
C(501)	−576 (3)	−1348 (6)	2129 (3)	675 (23)
C(601)	−1879 (3)	961 (5)	2099 (2)	546 (19)
C(701)	−2060 (3)	1042 (5)	2766 (2)	481 (18)
C(801)	−1579 (3)	1817 (5)	3199 (2)	489 (18)
C(901)	−1711 (3)	1947 (5)	3816 (2)	510 (18)
C(1001)	−2348 (3)	1252 (6)	3999 (2)	587 (20)
C(1101)	−2841 (3)	473 (6)	3590 (2)	589 (21)
C(1201)	−2704 (3)	379 (5)	2966 (2)	536 (19)
O(1201)	−3192 (2)	−356 (4)	2539 (2)	716 (16)
C(1301)	−1197 (3)	2845 (6)	4259 (2)	613 (21)
C(1401)	−1604 (3)	4126 (6)	4382 (2)	572 (21)
O(1501)	−2311 (2)	4267 (4)	4394 (2)	937 (19)
O(1601)	−1074 (2)	5081 (4)	4505 (2)	837 (18)
C(1701)	−1370 (5)	6354 (7)	4709 (3)	1087 (36)
C(1801)	−838 (4)	7409 (7)	4545 (4)	1020 (33)
C(1901)	−982 (7)	7639 (10)	3852 (5)	1877 (62)
C(2001)	−1029 (6)	8645 (8)	4913 (4)	1501 (47)
Cl(2101)	334 (1)	320 (2)	3047 (1)	668 (5)
N(102)	6187 (2)	1261 (4)	7820 (2)	479 (15)
C(202)	5896 (3)	1345 (6)	8451 (2)	626 (21)
C(302)	5572 (5)	7 (8)	8563 (3)	1158 (37)
C(402)	5713 (4)	−854 (6)	8020 (3)	826 (27)
C(502)	6360 (3)	−164 (6)	7728 (3)	658 (23)
C(602)	6867 (3)	2196 (5)	7752 (2)	484 (18)
C(702)	7061 (3)	2237 (5)	7086 (2)	452 (17)
C(802)	6596 (3)	3014 (5)	6642 (2)	484 (18)
C(902)	6789 (3)	3118 (5)	6036 (2)	496 (18)
C(1002)	7444 (3)	2427 (6)	5881 (2)	598 (22)
C(1102)	7909 (3)	1646 (6)	6313 (2)	602 (21)
C(1202)	7723 (3)	1558 (5)	6923 (2)	513 (19)
O(1202)	8166 (2)	830 (4)	7373 (2)	711 (16)
C(1302)	6294 (3)	3985 (6)	5562 (2)	645 (22)
C(1402)	6619 (2)	5352 (2)	5525 (2)	602 (21)
O(1502)	7264 (2)	5730 (4)	5784 (2)	804 (17)
O(1602)	6119 (2)	6106 (4)	5142 (2)	715 (15)
C(1702)	6377 (4)	7440 (6)	5005 (3)	752 (25)
C(1802)	5941 (3)	8448 (6)	5354 (3)	691 (24)
C(1902)	6094 (4)	9807 (7)	5072 (3)	1036 (34)
C(2002)	6202 (5)	8449 (8)	6048 (3)	1133 (36)
Cl(2102)	4611 (1)	1450 (2)	6863 (1)	701 (6)

Table 2 (cont.)

	x	y	z	U_{eq}
(b) (2)				
N(1)	−1436 (3)	−4844 (5)	9002 (2)	523 (14)
C(2)	−1440 (3)	−6942 (7)	9299 (2)	649 (20)
C(3)	−2171 (3)	−8118 (7)	8781 (2)	740 (23)
C(4)	−2830 (4)	−6467 (8)	8413 (3)	843 (24)
C(5)	−2415 (3)	−4380 (7)	8663 (2)	612 (19)
C(6)	−884 (3)	−4895 (6)	8566 (2)	545 (17)
C(7)	−824 (3)	−2853 (6)	−8257 (2)	485 (15)
C(8)	−1350 (3)	−2435 (6)	7634 (2)	538 (17)
C(9)	−1250 (3)	−622 (6)	7317 (2)	535 (16)
C(10)	−576 (3)	756 (7)	7656 (2)	535 (17)
C(11)	−40 (3)	390 (6)	8276 (2)	509 (17)
C(12)	−173 (3)	−1407 (6)	8589 (2)	481 (15)
O(12)	319 (2)	−1844 (4)	9198 (1)	665 (12)
C(13)	−1818 (3)	−208 (7)	6635 (2)	654 (19)
C(14)	−2285 (3)	1882 (7)	6529 (2)	645 (19)
O(15)	−2344 (3)	3028 (5)	6934 (2)	977 (18)
O(16)	−2650 (2)	2243 (5)	5913 (2)	810 (15)
C(17)	−3109 (4)	4233 (8)	5744 (3)	1055 (29)
C(18)	−3458 (4)	4320 (10)	5029 (3)	993 (28)
C(19)	−3776 (4)	6358 (10)	4767 (3)	1098 (33)
O(20)	−4094 (3)	6232 (8)	4092 (2)	1177 (24)
C(21)	−4634 (4)	4524 (12)	3844 (3)	931 (30)
C(22)	−4682 (4)	2843 (10)	4206 (3)	830 (25)
O(23)	−4198 (3)	2751 (6)	4852 (2)	944 (17)
C(24)	−5130 (5)	4562 (14)	3207 (3)	1212 (39)
C(25)	−5682 (6)	2906 (18)	2936 (3)	1346 (45)
C(26)	−5735 (5)	1202 (14)	3295 (4)	1284 (39)
C(27)	−5240 (6)	1187 (14)	3939 (4)	1066 (38)
Cl(28)	−1288 (1)	−2107 (2)	10174 (1)	744 (5)
(c) (3)				
N(1)	3107 (2)	3961 (1)	1406 (3)	314 (6)
C(2)	3060 (3)	4368 (1)	3494 (4)	412 (8)
C(3)	2957 (4)	4884 (1)	2332 (5)	560 (11)
C(4)	2187 (3)	4773 (1)	−485 (4)	438 (9)
C(5)	1849 (3)	4201 (1)	−801 (4)	373 (8)
C(6)	2809 (3)	3424 (1)	1906 (5)	451 (9)
C(7)	3011 (3)	3032 (1)	−179 (5)	453 (9)
C(8)	4604 (3)	2822 (1)	−283 (5)	474 (9)
C(9)	4841 (4)	2488 (1)	−2291 (5)	575 (11)
C(10)	3446 (5)	2357 (1)	−4176 (5)	726 (14)
C(11)	1862 (5)	2555 (1)	−4063 (6)	766 (14)
C(12)	1638 (4)	2892 (1)	−2096 (6)	629 (12)
C(13)	6609 (5)	2274 (1)	−2372 (8)	779 (17)
C(14)	7415 (4)	1913 (1)	−319 (7)	699 (14)
O(15)	8197 (4)	2043 (1)	1741 (5)	1130 (14)
O(16)	7083 (3)	1415 (1)	−1031 (4)	786 (10)
C(17)	7809 (7)	1041 (1)	863 (9)	911 (19)
C(18)	7400 (6)	521 (1)	−104 (8)	1248 (23)
C(19)	6823 (8)	329 (2)	−2346 (9)	1750 (32)
O(20)	6478 (3)	−188 (1)	−2987 (4)	981 (11)
C(21)	7214 (4)	−526 (1)	−1123 (6)	668 (13)
C(22)	8017 (4)	−343 (1)	1234 (6)	664 (13)
O(23)	8160 (3)	183 (1)	1864 (4)	917 (11)
C(24)	7118 (5)	−1061 (1)	−1657 (8)	878 (17)
C(25)	7816 (5)	−1408 (1)	166 (7)	872 (18)
C(26)	8634 (6)	−1230 (1)	2509 (7)	878 (18)
C(27)	8733 (6)	−697 (1)	3057 (7)	891 (18)
O(28)	6905 (2)	3752 (1)	4015 (3)	485 (6)
O(29)	9303 (2)	3997 (1)	3799 (3)	703 (9)
C(30)	7921 (3)	3876 (1)	2826 (4)	343 (7)
C(31)	7134 (3)	3869 (1)	−25 (4)	312 (7)
O(32)	5622 (2)	4006 (1)	−804 (3)	451 (6)
O(33)	8142 (2)	3736 (1)	−1315 (3)	497 (7)

binding site: a proton may transfer from the binding site to the drug. For (1) and (2), the same chloride ion also forms a strong hydrogen bond with the hydroxyl group of another molecule. Therefore, the chloride ion links two molecules through these two hydrogen bonds and stabilizes the crystal structure. For (3), stabilization is due to the two carbonyl O atoms of the oxalate ion; one O atom forms a hydrogen bond with the protonated N atom and the other forms a hydrogen bond with another oxalate ion.

The pyrrolidine ring is found in a similar orientation in all four unique molecules in the three crystals. The torsion angle $\varphi_1 = $ C(12)—C(7)—C(6)—N(1) (using the atomic labeling of 2), which defines the orientation, is approximately $\pm 100°$ for all four observed structures (see Table 3). Since the crystals are centrosymmetric, both the positive and negative values of these torsion angles are observed and are hence equivalent. Since the amine N atom of the pyrrolidine ring and the phenyl ring are common components of class-I antiarrhythmics, the relative orientation of these groups may be important for activity. Therefore, computational methods were used to identify all favored orientations. Molecular mechanics

Table 3. *Selected bond lengths, angles, torsion angles and intermolecular hydrogen-bond geometry for* (1), (2) *and* (3)

	(1a)	(1b)	(2)	(3)
Bond lengths (Å)				
N(1)—C(2)	1.500 (7)	1.507 (7)	1.501 (6)	1.495 (3)
N(1)—C(5)	1.494 (7)	1.494 (7)	1.496 (5)	1.498 (2)
N(1)—C(6)	1.498 (7)	1.506 (6)	1.504 (7)	1.496 (3)
C(6)—C(7)	1.508 (7)	1.510 (7)	1.498 (6)	1.498 (3)
C(9)—C(13)	1.503 (7)	1.508 (7)	1.503 (5)	1.522 (5)
O(12)—C(12)	1.365 (6)	1.357 (6)	1.344 (4)	—
C(13)—C(14)	1.510 (8)	1.498 (8)	1.509 (6)	1.493 (5)
C(14)—O(15)	1.198 (7)	1.210 (7)	1.191 (6)	1.190 (4)
C(14)—O(16)	1.319 (7)	1.335 (6)	1.316 (6)	1.340 (4)
O(16)—C(17)	1.473 (9)	1.465 (8)	1.453 (6)	1.444 (5)
Bond angles (°)				
C(2)—N(1)—C(6)	113.1 (4)	113.1 (4)	110.6 (3)	114.2 (2)
C(5)—N(1)—C(6)	115.1 (4)	115.9 (4)	113.2 (3)	114.9 (2)
N(1)—C(6)—C(7)	112.0 (4)	111.8 (4)	114.5 (3)	110.8 (2)
C(7)—C(12)—O(12)	118.5 (4)	117.9 (4)	117.7 (4)	—
C(13)—C(14)—O(15)	125.4 (5)	125.4 (5)	126.1 (4)	125.6 (6)
C(13)—C(14)—O(16)	111.2 (5)	111.3 (4)	109.8 (4)	111.5 (3)
C(14)—O(16)—C(17)	117.5 (5)	118.5 (4)	115.3 (4)	114.9 (3)
Torsion angles (°)				
C(7)—C(6)—N(1)—C(2)	−168.7 (4)	−171.4 (4)	178.8 (3)	−175.5 (2)
C(7)—C(6)—N(1)—C(5)	70.1 (5)	66.7 (5)	−64.7 (4)	65.6 (2)
C(12)—C(7)—C(6)—N(1)	−104.3 (5)	−101.8 (5)	−84.1 (5)	−96.7 (3)
C(14)—C(13)—C(9)—C(8)	103.2 (6)	93.5 (6)	−127.7 (5)	66.2 (4)
C(14)—C(13)—C(9)—C(10)	−74.6 (6)	−85.8 (6)	54.6 (6)	−113.8 (3)
O(15)—C(14)—C(13)—C(9)	32.5 (7)	8.6 (8)	11.4 (7)	−88.2 (5)
C(18)—C(17)—O(16)—C(14)	−153.9 (5)	−105.6 (5)	−179.3 (5)	−179.1 (4)
O(23)—C(18)—C(17)—O(16)	—	—	−70.2 (6)	179.9 (2)
O(23)—C(18)—C(19)—C(20)	—	—	62.5 (7)	17.3 (9)
Hydrogen-bond geometry	X—H (Å)	$X\cdots Y$ (Å)	H$\cdots Y$ (Å)	$\angle X$—H$\cdots Y$ (°)
(1)				
N(101)—H(101)$\cdots$Cl(2101)	0.95 (5)	3.109 (4)	2.18 (5)	164 (4)
N(102)—H(102)$\cdots$Cl(2102)	0.87 (4)	3.128 (4)	2.31 (4)	158 (4)
O(1201)—H(1201)$\cdots$Cl(2102^i)	0.94 (6)	3.062 (4)	2.13 (6)	171 (5)
O(1202)—H(1202)$\cdots$Cl(2101^{ii})	0.85 (5)	3.019 (4)	2.17 (5)	175 (5)
(2)				
N(1)—H(1)$\cdots$Cl(28)	0.88 (4)	3.088 (4)	2.30 (4)	149 (4)
O(12)—H(12)$\cdots$Cl(28^{iii})	0.887 (3)	3.046 (3)	2.17 (1)	171 (2)
(3)				
N(1)—H(1)$\cdots$O(32)	0.93 (3)	2.747 (3)	1.87 (3)	155 (2)
O(28)—H(28)$\cdots$O(33^{iv})	1.04 (3)	2.520 (2)	1.49 (3)	172 (3)

Symmetry codes: (i) $-x, -y, -z + 1$; (ii) $-x + 1, -y, -z + 1$; (iii) $-x, -y, -z + 2$; (iv) $x, y, z + 1$.

calculations were performed on the unprotonated form of fragment (*a*). The calculations identify three stable conformations. The lowest has $\varphi \approx 54°$ and an intramolecular hydrogen bond between the hydroxyl group of the phenyl ring and the pyrrolidine N atom. The other two conformations are: (1) a conformation at $\varphi_1 \approx \pm 100°$ which is *ca* 20.9 kJ mol^{-1} higher in energy, but is three times more populated than the low energy form; (2) a conformation at $\varphi_1 \approx 180°$ which is 29.3 kJ mol^{-1} higher in energy and 12 times less favored. Of these three conformations, only the $\varphi_1 \approx \pm 100°$ conformation is observed in the crystal structures reported here. The low-energy form is not observed because the N atom of the pyrrolidine ring is protonated and the intramolecular hydrogen bond cannot be formed. Similarly, structures of bis-(1-pyrrolidinylmethyl)phenol (Glowka, Dargie & Codding, 1991) displayed all three of these conformations for unprotonated rings and only the $\pm 100°$ conformation for protonated rings; for these.

Glowka *et al.* suggested that the coplanar (180°) conformation is disfavored for steric reasons due to the presence of H$^+$ on the N atom. Attempts to model the preferred conformation of the protonated pyrrolidine ring using an adaptation of the AMBER force field showed a low-energy conformation with $\varphi_1 \approx 53°$ and a higher-energy (*ca* 20.9 kJ mol^{-1}) conformation at $\varphi_1 \approx \pm 100°$. The conformation with $\varphi_1 \approx 53°$ has an intramolecular hydrogen bond between the protonated N—H group and the O atom of the hydroxyl group, which is the reverse of the hydrogen bond predicted for the unprotonated compound. Because the protonated N—H group forms an intermolecular hydrogen bond with an anion (Cl$^-$) in crystal structures, only the conformation with $\varphi_1 \approx \pm 100°$ is observed in the solid state. Given the difficulty inherent in including electrostatic effects in a force field, the crystallographic observation of $\pm 100°$ in four unique molecules may be a more reliable indication of the preferred conformation.

All three *gauche* orientations of the pyrrolidine ring relative to the phenyl ring were found in our molecular mechanics calculations, as was found in the previous work (Glowka, Dargie & Codding, 1991). The two conformations which separate the pyrrolidine ring from the phenyl ring [φ_2 = C(7)—C(6)—N(1)—C(5) $\approx$ 60 or 180°] are favored 3:1 over the conformation that places one ring over the other ($\varphi_2 \approx$ −60°). The two favored orientations avoid steric interactions between the two rings and are the only orientations observed in the solid state, either in this study or in the previous study.

In the crystal structures, the central carbonyl group and the pyrrolidine ring are found on opposite sides of the plane of the phenyl ring (one above and one below) in (1*a*), (1*b*) and (3), and on the same side for (2). The torsion angle C(14)—C(13)—C(9)—C(8), which defines the orientation of the ester plane to the phenyl ring plane, has two positions: one representing a *gauche* conformation [66.2 (4)° for 3 and −127.7 (5)° for 2] and one representing a perpendicular conformation [103.2 (6) and 93.5 (6)°, for 1*a* and 1*b*, respectively]. For (1) and (2), the hydroxyl group of the phenyl ring forms a strong O—H· · ·Cl intermolecular hydrogen bond with the chloride ion. Due to this hydrogen bond, the H atom of the hydroxyl group points away from the pyrrolidine ring. Therefore, the molecule can be considered to have two molecular edges, one which contains the pyrrolidine ring and one which contains the H atom of the hydroxyl group. The central carbonyl O atom was located on the same molecular edge as the pyrrolidine ring in (3) or on the same edge as the H atom of the hydroxyl group in (1*a*), and even within the middle of these two edges in (1*b*) and (2). The torsion angle φ_3 = O(15)—C(14)—C(13)—C(9), which indicates the orientation of the O atom relative to the phenyl ring, is −88.2 (5)° for (3), 32.5 (7)° for (1*a*), and 8.6 (8)° and

11.4 (7)° for (1*b*) and (2), respectively. Thus, the orientation of the carbonyl O atom relative to the pyrrolidine ring is quite variable. Molecular mechanics calculations of the conformation of fragment (*b*) found three positions for the carbonyl O atom; the O atom could be: (1) on the same side as the pyrrolidine ring ($\varphi_3 \approx$ −100°), as observed in (3); (2) on the same side as the H atom of the hydroxyl group ($\varphi_3 \approx$ 100°), as observed in (1*a*); (3) in the middle of these two positions ($\varphi_3 \approx$ 1°), as observed in (1*b*) and (2). The deviations between the observed conformations and the calculated conformations may be attributed to stabilization due to intermolecular interactions, particularly those accommodating the anion and the bulky pyrrolidinylmethyl group rather than the simple methyl group modeled in the fragment. In the bis(pyrrolidinylmethyl)phenol compounds (Glowka, Dargie & Codding, 1991), the carbonyl C=O bond was found to be antiparallel to the phenol O—H bond in each observation, thus the carbonyl O atom is on the same edge as the free pyrrolidine ring. Based on this finding, Glowka and coworkers proposed that the carbonyl group and its relative orientation to the free pyrrolidine ring are important for recognition and binding. They also found that the distances between the N atom of the amine group and the carbonyl O atom fall in distinct ranges for class I*a*, I*b* and I*c* agents. Class I*c* agents, which have the slowest recovery time constant, have the longest average N· · ·O distance of 5.2 Å; class I*b* agents, which have the fastest recovery time constant, have the shortest average N· · ·O distance of 3.2 Å; and class I*a* agents have an intermediate value of 4.0 Å. Glowka and coworkers suggested that this phenomenon may arise because the longer separation between the N and O would require the molecule to overcome many individual energy barriers as it folds to reach an optimal separation for binding. In this study, the average N· · ·O distance is 6.6 Å for the four unique molecules (7.1, 6.7, 6.7 and 6.1 Å for 1*a*, 1*b*, 2 and 3, respectively), which is longer than the average N· · ·O distance of any of these three different subclass I agents, but is relatively closer to the average N· · ·O distance for the class I*c* agents (*i.e.* 5.2 Å) than the distance in the two other subclasses. The
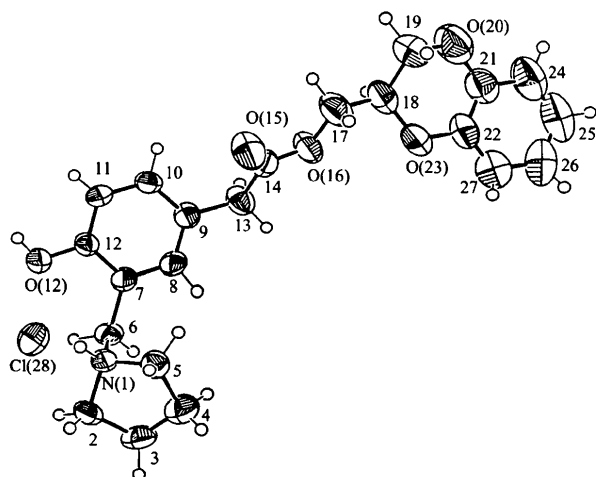

Fig. 3. A view of the unique molecule of (2) showing the labeling of the non-H atoms. Thermal ellipsoids are drawn at 50% probability. The figure was prepared using the program *ORTEP*II (Johnson, 1976).
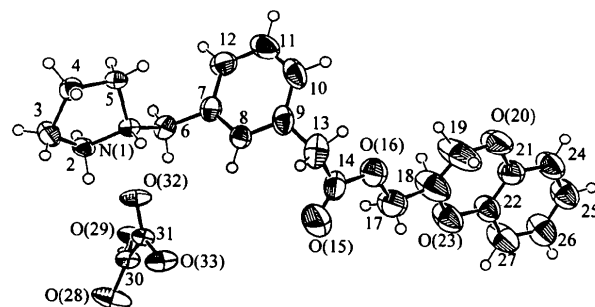

Fig. 4. A view of the unique molecule of (3) showing the labeling of the non-H atoms. Thermal ellipsoids are drawn at 50% probability. The figure was prepared using the program *ORTEP*II (Johnson, 1976).

N⋯O distances in the bis(pyrrolidinylmethyl)phenol compounds (Glowka, Dargie & Codding, 1991) are 5.0, 5.4, 4.5 and 5.5 Å for the four unique molecules, respectively. In order to understand how the molecules studied here may fold to reach an average N⋯O distance of *ca* 5.2 Å, the *MacroModel* program was used to model these molecules. The crystal structures were used, the torsion angle φ_1 was fixed at its observed value (*i.e.* ±100°), and the torsion angles φ_3 and φ_4 (see Fig. 1c) were varied to obtain a N⋯O distance of 5.2–5.6 Å and then fixed. The steric energy of each of the conformations obtained by folding the crystal structure was then minimized. The steric energy differences between the crystal structure and the folded conformation for (1a), (1b), (2) and (3) are all less than 1 kcal mol^{-1} (4.19 kJ mol^{-1}).

When the crystal structures of (1a), (1b), (2), (3) and one of the bis(pyrrolidinylmethyl)phenol compounds with the N⋯O distance 5.5 Å and (4) are superimposed, the O atoms of the carbonyl groups of each structure are in a different orientation. However, when the conformations obtained by folding crystal structures of (1), (2) and (3) are superimposed on the crystal structure of (4) (Fig. 5), the carbonyl O atoms of the modeled folded molecules point in the same direction as does that in (4), and the overall orientations of the molecules are rather similar. This comparison, which shows these molecules can easily adopt a N⋯O separation typical of class Ic agents, taken with the observation of different orientations for the carbonyl O atom relative to the pyrrolidine ring, suggests that the relative separation between the amine N atom and the carbonyl O atom is more important for recognition than the relative orientation of these two pharmacophoric groups. Thus, these drug molecules may undergo a stepwise conformational change until they adopt a specific conformation to fit the binding site.

Activity studies of (2) and (3) (Chorvat, 1992) show there is a sixfold decrease in potency if the hydroxyl group is removed from the phenyl ring. This finding suggests that either the hydroxyl group is involved in recognition and binding or, as suggested by Glowka and coworkers, the hydroxyl group serves to orient the unprotonated pyrrolidine ring by forming an intramolecular hydrogen bond.

Considerable variability was observed and calculated for the lipophilic side chains (isopropyl for 1 or benzodioxan for 2 and 3), preventing any definition of a preferred conformation for this portion of each molecule. Therefore, we examined the possibility that these groups are more important for their hydrophobicity than for their shape. Two of the common class I drugs, lidocaine and procainamide, have been shown to access the binding site on sodium channels *via* a direct hydrophobic pathway (Zamponi, Doyle & French, 1993; Zamponi, Sui, Codding & French, 1993), which suggests that hydrophobicity may play an important role in the *in vivo* action of class I antiarrhythmics. For apolar molecules, hydrophobicity has been shown to be linearly related to the van der Waals volume, and it has been shown that the volume contribution of the polar groups in different polar molecules bearing the same polar group can be separated from that of the apolar part (Moriguchi, Kanada & Komatsu, 1976). Therefore, we assumed that the hydrophobicity trend in these molecules could be calculated from the variation in volumes of these compounds. The *MacroModel* program was used to calculate the volumes of the crystallographically observed conformation. (1) differs from (2) only in the side chain, yet (2) is almost sevenfold more potent than (1). The volumes are: (1a) $V = 275.6$, (1b) $V = 278.7$ and (2) $V = 341.0$ Å^3. For comparison, the four observed conformations of the three equipotent bis(1-pyrrolidinylmethyl) compounds (Glowka, Dargie & Codding, 1991) had almost equal volumes of 345.2, 353.3, 344.5 and 358.8 Å^3. Thus, volume seems to predict relative activity for a series of molecules with the same polar groups. The difference in activity of (1) and (2) can be partially
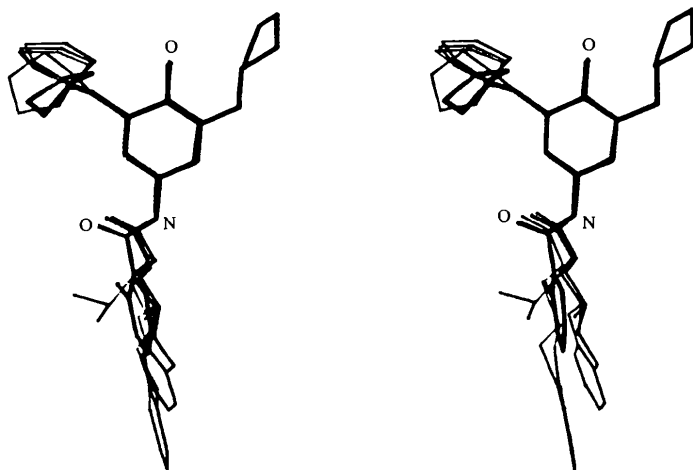

Fig. 5. The superposition of the crystal structure of (4) drawn with a thick line and the conformations obtained by folding crystal structures of (1), (2) and (3). The diagram was prepared using the program *MMS* (Dempsey, 1986).

attributed to a difference in hydrophobicity, suggesting that the lipophilic side chain is probably more important for its hydrophobicity than for its shape. It is noteworthy that (3), which differs from (1) and (2) in the polar region, has the same lipophilic side chain as in (2) and is more active than (1). The order of activity in this series is (2) > (3) > (1).

The observed molecular structures and modeled conformational preferences provide suggestions of what is important to the active shape of these compounds, which include: (1) the pyrrolidine ring oriented at $\varphi_1 \approx \pm 100°$ and separated from rather than stacked over the central phenyl ring, and (2) the relative separation between the amine N atom and the central carbonyl O atom (which is more important than the relative orientation of these two groups). The combination of a model interaction consisting of a strong intermolecular hydrogen bond between the protonated amine and the anions, and a conserved orientation for the pyrrolidine ring relative to the phenyl ring found in the structures reported here and in the bis(pyrrolidinylmethyl) compounds (Glowka, Dargie & Codding, 1991) suggests that the pyrrolidine ring is a pharmacophoric group and its orientation relative to the phenyl ring is important to the activity of these class I agents. The flexible side chain attached to the central carbonyl C atom serves to increase the hydrophobicity of the molecule and thus increase in biology activity. Class I antiarrhythmic agents appear to have a distinct recognition requirement for shape and for the relative separation of functional groups, and a hydrophobicity requirement for transport to the binding site.

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Tetramethylpyrazinium Polyiodides

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Abstract

(1): Tetramethylpyrazinium triiodide tetramethylpyrazine, $C_{12}H_{19}N_3I_3$, $M_r = 586.00$, triclinic, $P\bar{1}$, $a = 8.226 (3)$, $b = 8.393 (3)$, $c = 13.878 (6)$ Å, $\alpha = 85.28 (3)$, $\beta = 74.54 (3)$, $\gamma = 87.96 (3)°$, $V = 920.2 (6)$ Å^3, $Z = 2$, $D_x = 2.12$ g cm^{-3}, $\lambda(\text{Mo} K\alpha) = 0.71073$ Å, $\mu = 50.9$ cm^{-1}, $F(000) = 542$, $T = 293 \pm 1$ K, $R = 0.033$ for 2476 unique observed reflections. (2): Tetramethylpyrazinium triiodide.0.5-methylhydroquinone.0.5methylquinone, $C_{15}H_{20}N_2O_2I_3$, $M_r = 641.03$, monoclinic, $P2_1/n$, $a = 7.679 (2)$, $b = 12.520 (4)$, $c = 10.774 (3)$ Å, $\beta = 100.60 (2)°$, $V = 1019.9 (6)$ Å^3, $Z = 2$, $D_x = 2.09$ g cm^{-3}, $\lambda(\text{Mo} K\alpha) = 0.71073$ Å, $\mu = 46.0$ cm^{-1}, $F(000) = 598$, $T = 293 \pm 1$ K, $R = 0.086$ for 1267 unique observed reflections. (3): Tetramethylpyrazinium pentaiodide.hydrate, $C_8H_{15}N_2OI_5$, $M_r = 789.72$, triclinic, $P\bar{1}$,