Polish J. Chem., **75**, 1361–1366 (2001)

Crystal and Molecular Structures of Two Antiarrythmic α-[(Diarylmethoxy)methyl]-1-piperidineethanols

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(Received February 26th, 2001; revised manuscript March 26th, 2001)

The crystal structures of two antiarrythmic piperidineethanols, α-{[(2-methylphenyl)phenylmethoxy]methyl}-2,6-dimethyl-1-piperidineethanol (**1**) and α-[(bis(2,6-dimethylphenyl)methoxy)methyl]-2,6-dimethyl-1-piperidineethanol (**2**) have been determined by X-ray structure analysis of single crystals. The piperidine rings are close to ideal chair conformations, the methyl substituents are in equatorial positions. Overall shapes of the molecules differ significantly: in compound **1** the oxygen atoms are in *anti* position, while in **2** their mutual disposition is *gauche*. Dihedral angles between the phenyl rings and C–O–C plane are close to 90° for the mono- or di-substituted phenyl rings, while for the unsubstituted phenyl ring in **1** this value is smaller, equals 27.8(3)°. The bond angles in phenyl rings are influenced by the presence of methyl substituents. In both crystal structures the molecules make centrosymmetric dimers connected by strong O–H···N hydrogen bonds (piperidine nitrogen atoms act as acceptors).

Key words: piperidineethanols, crystal and molecular structure, hydrogen bonds, conformation

A series of α-[(diarylmethoxy)methyl]-1-piperidineethanols was synthesized and evaluated for antiarrythmic activity [1]. The idea of these studies emerged from the observation that certain quaternary ammonium compounds had the long duration of antiarrythmic action (for example, methyl lidocaine – more than 6 h, as compared with lidocaine – less than 15 min). Further investigations proved that the structurally related tertiary amine, α-[(diphenylmethoxy)methyl]-2,6-dimethyl-1-piperidineethanol also exhibited an excellent antiarrythmic activity with relatively long duration of action, and it caused less tachycardia than the previously studied compounds. Structure-activity studies [1] of the series of similar compounds showed that the presence of 2,6-dimethylpiperidine group gives the best antiarrythmic action. Unfortunately, for greater doses the increased side effects, including central nervous system involvement, were observed. Therefore, as the anticipating therapeutic index was too small, the further studies were concentrated on the most promising group of 2,6-dimethyl α,α-diaryl-1-piperidinebutanols [2].

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Here we report the crystal and molecular structures of two piperidineethanols: α-{[(2-methylphenyl)phenylmethoxy]methyl}-2,6-dimethyl-1-piperidineethanol and α-[(bis(2,6-dimethylphenyl)methoxy)methyl]-2,6-dimethyl-1-piperidineethanol (hereinafter referred to as **1** and **2,** respectively). Compound **1** possessed the best activity profile in the series (activity rating, defined as the ratio of the effect due to test drug and the effect due to ideal drug, was equal to 0.68), and compound **2** was less active, still its activity rating was evaluated at 0.47 [1].

EXPERIMENTAL

The samples were provided by Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, MI, USA. Colorless crystals, suitable for X-ray structure analysis were grown from solutions in diisopropyl ether (**1**) and diisopropyl ether – ethyl acetate system (**2**) by slow evaporation.

X-ray diffraction data were collected on an Enraf-Nonius CAD4-F κ-geometry diffractometer [3], using Ni-filtered CuK_α (λ = 1.54178 Å) radiation. The unit cell dimensions were calculated from the least-squares fit of 25 automatically centered reflections (2Θ range: 12°–35° for **1**, 16°–42° for **2**). Relevant crystallographic data, together with data collection and structure refinement details, are listed in Table 1. The ω-2Θ scan method and a variable scan speed, depending on reflection intensity, were used. Three control reflections were measured after every 30 minutes of measurement; they showed only slight change during data collection. Intensity data were corrected for Lorentz and polarization effects [4]. All structures were solved by direct methods, using the SHELXS86 program [5]. Full-matrix least-squares refinement was done with the SHELXL93 program [6]. Scattering factors incorporated in SHELXL93 were used. The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized, with $w^{-1} = [\sigma^2(F_o)^2 + A \cdot P^2 + B \cdot P]$ ($P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$). Empirical extinction corrections were also applied according to the formula $F_c' = kF_c[1 + 0.001 \times F_c^2\lambda^3/\sin 2\Theta]^{-1/4}$ [6]. The final values for A, B, and x are listed in Table 1. At the final stages of refinement some reflections (12 for **1**, 14 for **2**) were excluded from the reflection files due to their large $|F_o|^2 - |F_c|^2$ differences. The non-hydrogen atoms were refined anisotropically. The coordinates of all hydrogen atoms were constrained to an appropriate parent side (as a riding model) and their U_{iso}'s were set as the multiplicity of the U_{eq} of their carrier atom (the multiplication factors of 1.2, 1.4 and 1.5 were used for CH, CH_2 and CH_3 groups, respectively).

Table 1. Crystal data, data collection and structure refinement.

Compound	**1**	**2**
Formula weight	367.51	409.59
Crystal system	monoclinic	triclinic
Space group	$P2_1/c$	$P\bar{1}$
a(Å)	8.3883(11)	15.589(1)
b(Å)	8.1163(11)	9.032(1)
c(Å)	31.749(3)	8.938(1)
α(°)	90	87.177(9)
β(°)	97.119(9)	75.289(7)
γ(°)	90	88.711(9)
V(Å^3)	2144.9(5)	1215.7(2)
Z	4	2
D_x(g cm^{-3})	1.14	1.12
F(000)	800	448
μ(mm^{-1})	0.55	0.53

Table 1 (continuation)

Crystal size (mm)	0.35×0.2×0.15	0.2×0.2×0.15
Θ range (°)	2–55	2–55
hkl range	$0 \le h \le 8$	$-15 \le h \le 16$
	$0 \le k \le 8$	$-9 \le k \le 9$
	$-32 \le l \le 32$	$0 \le l \le 9$
Decay of standards	3%	4%
Reflections:		
unique (R_{int})	2291	2573
observed ($I > 2\sigma(I)$)	1548	1955
Number of parameters	244	272
Weighting scheme:		
A	0.005	0.005
B	0.9	0.8
Extinction parameter x	0	0.0019(4)
$R(F)$	0.079	0.072
$wR(F^2)$	0.147	0.143
Goodness of fit	1.12	1.08
max/min Δρ (e Å^{-3})	0.25/–0.14	0.16/–0.15

Surprisingly high values of R-factors (without any traces of disorder or any other systematical errors) can be related to the small diffraction power of both compounds. Nevertheless, the quality of the results: very small residual electron densities on the difference Fourier maps and quite agreeable values of standard deviations of geometrical parameters justify the responsible discussion of the conformation, configuration and the crystal packing of the compounds.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 158425 (**1**) and CCDC 158426 (**2**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: +44(0)1223 336033; e-mail: deposit@ccdc.cam.ac.uk].

RESULTS AND DISCUSSION

Selected bond lengths, bond angles and torsion angles for both compounds are compared in Table 2. Anisotropic displacement ellipsoid representations of the molecules, together with atomic numbering schemes, are shown in Figures 1 and 2.

For both molecules the bond lengths values agree well with the standard values [7]; the endocyclic bond angles pattern within the phenyl rings is to some extent disturbed by the influence of methyl substituent, and the changes in bond angles are similar to those described by Domenicano and Murray-Rust [8]. These substituents influence also the exocyclic angles at C5 and C11 carbon atoms. In **1** the steric stress is negligible but in **2**, due to the presence of four methyl groups, the steric conditions are more severe. Consequently in **1** the above mentioned exocyclic angles are almost equal, within the experimental error, while in **2** they differ by as much as 10° (*cf.* Table 2).

Table 2. Selected bond lengths (Å), bond angles (deg) and torsion angles (deg) with e.s.d.'s in parentheses.

	1	**2**
C(1)–O(1)	1.381(4)	1.414(4)
C(2)–N(1′)	1.468(5)	1.474(4)
N(1′)–C(6′)	1.466(5)	1.492(4)
N(1′)–C(2′)	1.506(5)	1.502(4)
C(3)–O(3)	1.412(4)	1.406(4)
O(3)–C(4)	1.434(4)	1.441(4)
O(1)–C(1)–C(2)	112.2(4)	109.4(3)
O(1)–C(1)–C(3)	106.8(3)	110.6(3)
O(3)–C(3)–C(1)	109.6(3)	110.0(3)
C(3)–O(3)–C(4)	111.9(3)	112.6(2)
C(6)–C(5)–C(10)	118.6(5)	119.1(4)
C(6)–C(5)–C(4)	120.0(4)	125.4(3)
C(10)–C(5)–C(4)	121.5(4)	115.5(3)
C(5)–C(6)–C(7)	118.3(5)	119.5(4)
C(9)–C(10)–C(5)	123.1(6)	117.6(4)
C(12)–C(11)–C(16)	118.9(4)	119.9(4)
C(12)–C(11)–C(4)	120.9(4)	115.0(3)
C(16)–C(11)–C(4)	120.2(4)	125.1(3)
C(11)–C(12)–C(13)	121.0(5)	120.0(4)
C(11)–C(16)–C(15)	119.4(5)	117.6(4)
O(1)–C(1)–C(2)–N(1′)	64.6(5)	71.6(4)
C(3)–C(1)–C(2)–N(1′)	–176.3(3)	–167.4(3)
O(1)–C(1)–C(3)–O(3)	–176.0(3)	–64.8(4)
C(2)–C(1)–C(3)–O(3)	61.7(5)	175.0(3)
C(1)–C(3)–O(3)–C(4)	171.8(3)	178.3(3)
C(3)–O(3)–C(4)–C(5)	–166.4(3)	–151.0(3)
C(3)–O(3)–C(4)–C(11)	69.3(4)	77.2(4)
O(3)–C(4)–C(5)–C(6)	151.6(4)	–91.4(4)
O(3)–C(4)–C(11)–C(12)	–110.0(4)	–161.2(3)

The overall conformations of both compounds are essentially different. In **1** the oxygen atoms O1 and O3 are in position *anti* one to another, while in **2** their mutual position is *gauche* (O1–C1–C3–O3 torsion angle is –176.0(3)° in **1** and –64.8(4)° in **2**. Also the disposition of phenyl rings is different in both compounds. The dihedral angle between the phenyl rings is closer to 90° in **2** (89.39(11)°) than in **1** (71.50(14)°). In **1** their least-squares planes make dihedral angles of 82.0(3)° and

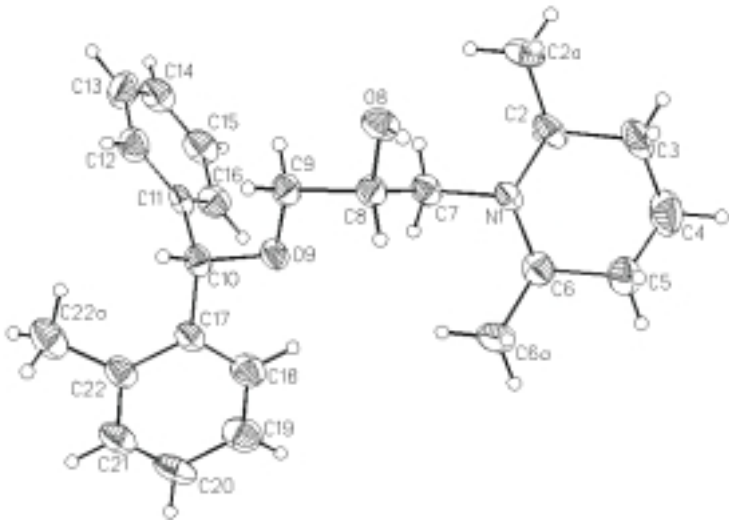

Figure 1. Displacement ellipsoid representation (at the 33% probability level) of the compound **1** [13], together with numbering scheme. The hydrogen atoms are drawn as spheres with arbitrary radii.

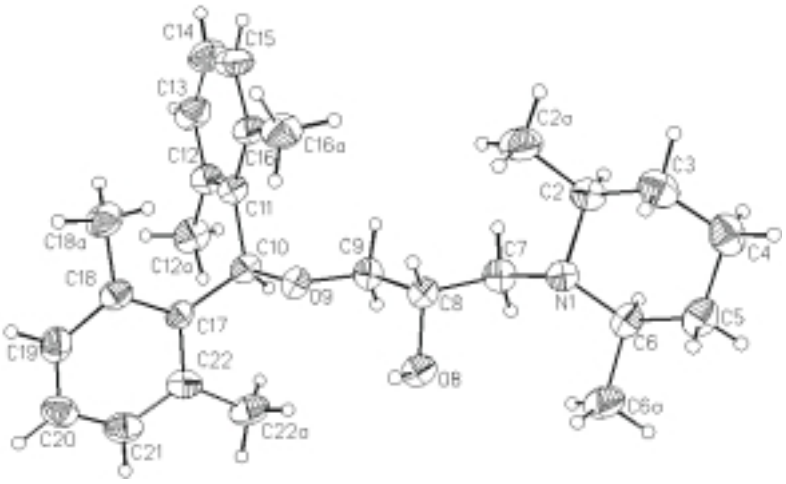

Figure 2. Displacement ellipsoid representation (at the 33% probability level) of the compound **2** [13], together with numbering scheme. The hydrogen atoms are drawn as spheres with arbitrary radii.

27.8(3)° with the C3–O3–C4 plane, for methyl-substituted and unsubstituted rings, respectively. In **2** both phenyl rings are 2,6-dimethyl substituted, and their least-squares planes make the dihedral angles of 82.3(2)° and 85.0(2)° with the C–O–C plane. Similar correlation between the presence of substituents and the disposition of

phenyl ring with respect to the C–O–C plane was observed in α-{[(2,6-dimethyl-phenyl)phenylmethoxy]methyl}-2,6-dimethyl-1-piperidineethanol [9], where the appropriate dihedral angles are 25.3° and 89.1° for unsubstituted and di-methyl-substituted phenyl rings, respectively.

Both piperidine rings are close to ideal chair conformation. The largest asymmetry parameters [10] are 3.3° and 5.7° for **1** and **2**, respectively (in both cases $\Delta C_2^{3,4}$ has the largest value). The methyl substituents at C2′ and C6′ are in equatorial positions.

In both structures the molecules make centrosymmetric dimers, connected by means of strong O–H···N hydrogen bonds (Table 3), with piperidine nitrogen atoms acting as acceptors. Using graph-set notation [11, 12] both dimeric rings can be noted as $R_2^2(10)$. Regardless of the substantial conformational differences, in both molecules the shapes of hydrogen bonded fragments are almost identical.

Table 3. Hydrogen bond data.

				Compound **1**		
D	H	A	D–H	H···A	D···A	D–H···A
O1	H1A	N1^{i}	0.82	2.14	2.881(4)	150
				Compound **2**		
D	H	A	D–H	H···A	D···A	D–H···A
O1	H1A	N1^{ii}	0.82	2.12	2.928(3)	168

Symmetry codes:
^{i}1 – x, –1 – y, 1 – z; ^{ii}–x, 2 – y, 1 – z.

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