Articles

Synthesis and Antiarrhythmic Activity of α-[(Diarylmethoxy)methyl]-1-piperidineethanols

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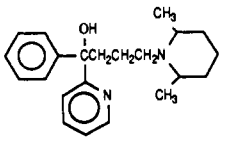
A series of α-[(diarylmethoxy)methyl]-1-piperidineethanols was evaluated for antiarrhythmic activity in the coronary artery ligated dog model. Structure–activity relationship studies indicated that the 2,6-dimethylpiperidine group afforded the best antiarrhythmic agents in this series and was essential for long duration of action. This investigation indicated that quaternary ammonium salts were not essential for a long duration of action. It was also shown that the antiarrhythmic activity could be separated from the tachycardia frequently caused by this type of agent.

The investigation of several series of quaternary ammonium salts and hindered tertiary amines in the coronary artery ligated (Harris) dog preparation led to the discovery of pirmenol[1] (I), a potent antiarrhythmic agent with a long



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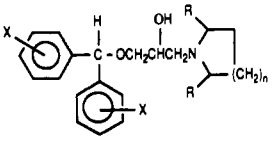
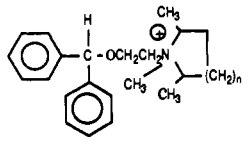
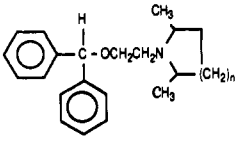


I: 6, X=H, R=CH_3, and n=2



2, n = 2
3, n = 1

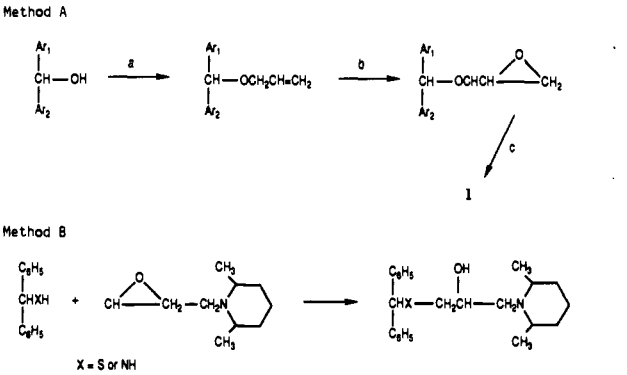


4, n = 2
5, n = 1

duration of action.[2] The work presented in this paper describes the investigation of a series of α-[(diarylmethoxy)methyl]-1-piperidineethanols (I). This work led directly to the investigation of the series of *cis*-2,6-dimethyl-α,α-diaryl-1-piperidinebutanols[3] from which pirmenol was chosen.

The impetus for these studies was the long duration of action reported for two quaternary ammonium compounds, methyl lidocaine[4] and UM272.[5] Both agents in our animal model showed antiarrhythmic activity lasting for more than 6 h compared to that of lidocaine, which had a duration of less than 15 min. A number of quaternary ammonium salts[6] derived from diphenhydramine was available from earlier work in this laboratory, and the initial investigation substantiated that selected compounds were potent and long-acting antiarrhythmic agents. In particular, it was found that the 2,6-dimethylpiperidinyl (**2**) and 2,5-dimethylpyrrolidinyl (**3**) analogues possessed the best

Scheme I[a]



[a] (a) Allyl alcohol, *p*-toluenesulfonic acid, toluene; (b) *m*-chloroperbenzoic acid; (c) substituted amine.

activity following oral administration. However, additional studies in normal dogs revealed that both agents caused a severe tachcardia even at doses where there was no demonstrable antiarrhythmic activity.

Further investigation showed that the corresponding tertiary amino compounds (**4**, **5**) were also potent antiarrhythmic agents with a relatively long duration of action, but these agents also caused a severe tachycardia. Examination of the structurally related tertiary amino compound α-[(diphenylmethoxy)methyl]-2,6-dimethyl-1-piperidineethanol (**6**) suggested that this agent caused less tachycardia while exhibiting excellent antiarrhythmic activity. Therefore, it was decided to investigate this series further.

Chemistry

The series of α-[(diarylmethoxy)methyl]-substituted-1-piperidineethanols (I) were prepared by method A described by Petrow[7] and shown below (Scheme I). Allyl bisarylmethyl ethers were obtained in good yields by the azeotropic removal of water from a mixture of the diarylbenzhydrol, allyl alcohol, and *p*-toluenesulfonic acid in toluene. Oxidationwith *m*-chloroperbenzoic acid in chloroform converted the double bond of the allyl group to an epoxide in moderate to good yields. Treatment of the 1-(diarylmethoxy)-2,3-epoxypropane with the amine at room temperature yielded the desired products (I).

(1) Fleming, R. W. U. S. Patent 4,112,103, 1978.
(2) Mertz, T. E.; Steffe, T. J. *J. Cardiovasc. Pharmacol.* **1980**, *2*, 527.
(3) Hoefle, M. L.; Blouin, L. T.; Fleming, R. W.; Hastings, S.; Hinkley, J. M.; Mertz, T. E.; Steffe, T. J.; Stratton, C. S. *J. Med. Chem.*, following paper in this issue.
(4) Gillis, R. A.; Levine, F. H.; Thibodeaux, H.; Raines, R.; Standaert, F. G. *Circulation* **1973**, *47*, 697.
(5) Kniffen, F. J.; Schuster, D. P.; Luchesi, B. R. *J. Pharmacol. Exp. Ther.* **1974**, *187*, 260.
(6) Rieveschl, G. U. S. Patent 2,508,422, 1950.
(7) (a) Petrow, V.; Stephenson, O.; Thomas, A. J. *J. Pharm. and Pharmacol.* **1956**, *8*, 666. (b) Jin, K. *Chem. Abstr.* **1966**, *65*, 5390.

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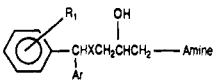
Table I. Structures and Physical Properties of 6–20



no.	Ar	R_1	X	amine	synth method	% yield[a]	mp, °C	recryst solvent	empirical formula	anal.
6	C_6H_5	H	O	2,6-dimethylpiperidine	A	69	95–96	i-Pr_2O	$C_{23}H_{31}NO_2$	C,H,N
7	C_6H_5	H	O	1,2,6-trimethylpiperidinium	A	46	171–174	*i*-PrOH–EtOAc 1:1	$C_{24}H_{34}NO_2Cl$	C,H,N
8	C_6H_5	H	O	2,5-dimethylpyrrolidine	A	71	57–59	pet. ether[b]	$C_{22}H_{29}NO_2$	C,H,N
9	C_6H_5	H	O	dimethyl amine	A		59–60[c]	*i*-PrOH–EtOAc 1:1	$C_{18}H_{23}NO_2$·HCl	
10	C_6H_5	H	O	trimethylammonium	A	89	128–130	*i*-PrOH	$C_{20}H_{29}NO_5S$	C,H,N
11	2′-$CH_3C_6H_4$	2-CH_3	O	2,6-dimethylpiperidine	A	60	119–120	EtOAc–*i*-Pr_2O 1:2	$C_{25}H_{35}NO_2$	C,H,N
12	2′-$CH_3C_6H_4$	2-CH_3	O	2-methylpiperidine	A	62	90–93	*i*-PrOH-EtOAc 1:1	$C_{24}H_{33}NO_2$·$C_2H_2O_4$	C,H,N
13	2′-$CH_3C_6H_4$	2-CH_3	O	piperidine	A	71	143–145	*i*-PrOH	$C_{23}H_{31}NO_2$·$C_2H_2O_4$	C,H,N
14	C_6H_5	2-CH_3	O	2,6-dimethylpiperidine	A	71	98–99	*i*-Pr_2O	$C_{24}H_{33}NO_2$	C,H,N
15	C_6H_5	2,6-$(CH_3)_2$	O	2,6-dimethylpiperidine	A	34	135–136	*i*-Pr_2O	$C_{25}H_{35}NO_2$	C,H,N
16	2′-$CH_3OC_6H_4$	2-CH_3O	O	2,6-dimethylppiperidine	A	60	127.5–129	EtOAc	$C_{25}H_{35}NO_4$	C,H,N
17	2′,6′-$(CH_3)_2$-C_6H_3	2,6-$(CH_3)_2$	O	2,6-dimethylpiperidine	A	56	128–129	*i*-PrOH–EtOAc 1:1	$C_{27}H_{39}NO_2$	C,H,N
18	CH_3	H	O	2,6-dimethylpiperidine	A	57	74–77	CH_3CN	$C_{18}H_{29}NO_2$	C,H,N
19	C_6H_5	H	S	2,6-dimethylpiperidine	B	36	91–91.5	benzene–pet. ether 1:1	$C_{23}H_{31}NO_5$	C,H,N
20	C_6H_5	H	NH	2,6-dimethylpiperidine	B	8.1	94–100	EtOAc	$C_{23}H_{32}N_2O$·2HCl·0.75CH_3CO_2Et	C,H,N

[a] Yield is based on final step of indicated synthetic method. [b] Pet. ether refers to low-boiling petroleum ether throughout this paper. [c] Literature[7] mp 61–61.5 °C.

A few compounds were prepared by method B, which utilized 2,6-dimethyl-1-(β,γ-epoxypropyl)piperidine which was obtained in poor yield from the reaction of 2,6-dimethylpiperidine with epichlorohydrin. The reaction of this epoxy compound with diphenylmethylamine or the sodium salt of the diarylmethanol or diphenylmethyl mercaptan proceeded in good yield.

The structure, physical properties, and method of synthesis of the compounds prepared are shown in Table I.

Biology

All of the compounds were evaluated for antiarrhythmic effects in the conscious coronary artery ligated dog model first described by Harris.[8] The dogs were utilized in the conscious state on the first day following ligation when the arrhythmia was severe. Details of the methodology have been described previously.[2,9]

An activity rating was utilized to compare the relative antiarrhythmic activities of the compounds described in this paper. With group data for each compound, the percent normal beats was plotted at the end of dose, at 20 min, and at 1 h. The activity of the test compound is proportional to the area under this curve minus the area of the control. This activity was compared to the assumed activity of the ideal compound, which in the same animals would effect 100% normal beats for the entire hour.

$$\text{activity rating} = \frac{\text{effect of test compound}}{\text{effect of ideal compound}} \times 100 = \frac{\text{area under test curve minus control area}}{\text{area under ideal curve minus control area}} \times 100$$

The ideal compound would have an activity rating of 100, and a compound with no effect would have a rating of zero. The activity rating for each compound in this series dosed at 5 mg/kg administered over 5 min is shown in Table II. For comparison, lidocaine when dosed at 10 mg/kg over 5 min followed immediately by 5 mg/kg over 20 min had an activity rating of 20, and procainamide hydrochloride at 30 mg/kg over 5 min had an activity rating of 52.

The tendency for compounds to cause tachycardia could not be determined from efficacy studies in the coronary artery ligated dogs since their heart rates were usually already higher than 170 beats/min. Consequently, compounds were tested for tachycardia in conscious normal dogs trained to sit quietly while sling restrained. For ease in interpretation, the degree and duration of tachycardia has been rated according to the definitions given as a footnote to Table III.

Results and Discussion

The original objective of this work was to identify compounds that were as efficacious as lidocaine in converting ectopic heart beats to a normal sinus rhythm and, in addition, possessed a long duration of action. Procainamide, a widely used antiarrhythmic agent, was reasonably long acting in our test when administered iv at 30 mg/kg but had only moderate efficacy as shown in Figure 1. The investigation of quaternary ammonium salts of diphenhydramine had shown that certain compounds such as **2** possessed potent and long-acting antiarrhythmic activity that almost met the original objective. However, the severe tachycardia associated with **2** made it necessary to expand the objective to require a lesser effect on heart rate.

The use of 2,6-dimethylpiperidine in the diphenhydramine series was found to enhance the efficacy and duration of action (compounds **2** and **4**), and a similar beneficial effect has been reported in other antiarrhythmic series.[10,11] Consequently, this amino substituent was incorporated into all new types of tertiary amino compounds

(8) Harris, A. S. *Circulation* **1950**, *1*, 1318.
(9) Kaplan, H. R.; Mertz, T. E.; Steffe, T. J.; Toole, J. H. *New Drugs Annual: Cardiovascular Drugs*; Scriabine, A., Ed.; Academic Press: New York, 1983; p 133.
(10) Nordin, I. C.; Parcell, R. F. U. S. Patent 3,446,811, 1969.
(11) Yonan, P. K.; Novotney, R. L.; Wo, C. M.; Pradau, K. A.; Hershenson, F. M. *J. Med. Chem.* **1980**, *23*, 1102.

Table II. Antiarrhythmic Effect in Coronary Ligated Dogs at 5 mg/kg Iv

no.	no. of animals	% normal beats[a]				activity rating[c]
		control	end of dose[b]	20 min	1 h	
6	6	12 ± 5	88 ± 8	67 ± 12	53 ± 13	56
7	2	16 ± 8	15 ± 4	33 ± 6	28 ± 4	15
8	2	3 ± 2	96 ± 2	39 ± 7	12 ± 3	36
9	2	7 ± 2	61 ± 7	25 ± 3	15 ± 0	19
10	2	0 ± 0	52 ± 5	1 ± 1	0 ± 0	9
11	4	30 ± 17	87 ± 8	68 ± 14	50 ± 12	51
12	2	5 ± 2	49 ± 26	44 ± 6	24 ± 10	36
13	3	14 ± 5	79 ± 18	31 ± 7	16 ± 3	21
14	6	28 ± 7	87 ± 10	71 ± 14	81 ± 8	68
15	2	18 ± 17	60 ± 35	19 ± 7	16 ± 12	8
16	1	0	100	62	33	57
17	2	35 ± 24	49 ± 32	76 ± 14	54 ± 37	47
18	2	9 ± 8	62 ± 39	16 ± 15	11 ± 10	13
19	3	12 ± 3	95 ± 6	49 ± 18	42 ± 24	51
20	4	5 ± 2	92 ± 2	47 ± 13	30 ± 15	44
lidocaine HCl[d]	6	4 ± 3	86 ± 6	23 ± 7	9 ± 5	20
procainamide HCl[e]	6	10 ± 3	72 ± 9	66 ± 10	34 ± 9	52

[a] Values as mean ± SEM if three or more animals, values mean ± SD if two animals. [b] Dosed iv over a 5-min period. [c] Activity rating = effect due to test drug/effect due to ideal drug × 100; see the text for details. [d] Dosed iv at 10 mg/kg over 5 min, then 5 mg/kg over 20 min. [e] Dosed iv at 30 mg/kg over 5 min.

Table III. Heart Rate Effect in Normal Dogs at 5 mg/kg Iv

no.	no. of dogs	heart rate, beats/min[a]				rating	
		control	end dose	20 min	1 h	degree[b]	duration[c]
6	2	128 ± 33	172 ± 99	171 ± 66	150 ± 60	moderate	moderate
7	2	110 ± 1	167 ± 0	152 ± 25	101 ± 10	moderate	short
8	2	78 ± 22	140 ± 29	117 ± 33	102 ± 27	slight	moderate
9	2	119 ± 12	121 ± 1	115 ± 1	110 ± 18	none	
10	2	124 ± 5	242 ± 15	135 ± 6	118 ± 9	severe	moderate
11	2	118 ± 12	153 ± 13	113 ± 20	142 ± 6	slight	short
14	2	119 ± 17	153 ± 28	153 ± 33	134 ± 29	moderate	moderate
16	2	149 ± 2	234 ± 19	232 ± 20	232 ± 10	severe	long
18	2	119 ± 14	156 ± 1	101 ± 2	144 ± 5	slight	long
19	2	135 ± 4	185 ± 14	148 ± 23	148 ± 4	moderate	short
20	2	109 ± 15	141 ± 7	132 ± 4	122 ± 1	slight	short

[a] Values as mean ± SD. [b] Degree of tachycardia: severe—heart rate ≥200 beats/min, moderate—heart rate 160–199 beats/min, slight—heart rate less than 160 beats/min after an increase of ≥20 beats/min, none—no change greater than 20 beats/min. [c] Duration (effect sustained for): long—greater than 2 h, moderate—0.5–2 h, short—less than 0.5 h.

synthesized for screening as potential antiarrhythmic compounds. Compound **6** was the first example tested from the series of α-[(diarylmethoxy)methyl]-1-piperidineethanols (I), and the initial structure–activity studies on this series involved variation of the amino substituent.

On the basis of earlier experiences, it was not surprising that the preferred amino group in this series was again 2,6-dimethylpiperidine. The high activity rating for compounds **6**, **11**, and **14** was primarily due to their long duration of action as shown by the percentage of normal beats after 1 h. This appeared to be a major contribution of the 2,6-dimethylpiperidine group. Thus, comparison of compounds **11–13** indicated that the 2,6-dimethyl substitution on the piperidine ring was required for the longer duration of action. Replacement by 2,5-dimethylpyrrolidine as in **8** resulted in a decreased duration of action, while replacement by dimethylamino as in **9** resulted in decreased efficacy of conversion to normal beats as well as a decreased duration of action. Finally, the formation of quaternary ammonium salts **7** and **10** resulted in the loss of antiarrhythmic activity and an increase in tachycardia. Although compounds **6**, **11**, and **14** caused some degree of tachycardia, the range was from moderate to slight, indicating that it was not directly related to the antiarrhythmic activity.

The effect of substitution in the ortho positions of the phenyl groups was briefly examined. The introduction of one *o*-methyl group in **14** had little effect on efficacy but improved duration of action and yielded the best activity rating for the series. The introduction of another *o*-methyl group on the second phenyl ring (**11**) again had no effect on efficacy, but now the duration of action is again comparable to that of **6**. Shifting a methyl group to yield 2,6-dimethylphenyl (**15**) decreased both efficacy and duration, but replacing the phenyl group in **15** with another 2,6-dimethylphenyl group, giving **17**, reversed the deleterious effect. Methoxy substituents as in **16** appeared to actually improve efficacy but decreased the duration of action, which was somewhat surprising because a methoxy group is more metabolically stable than a methyl group. However, the most unexpected finding was that **16** caused the most severe and long-lasting tachycardia in this limited series. Finally, the replacement of phenyl by a methyl group in compound **18** greatly decreased the antiarrhythmic activity.

The remaining structural variation examined was the replacement of the oxygen atom in the ether linkage of compound **6** by sulfur (**19**) and nitrogen (**20**). Both compounds possessed excellent efficacy and a moderate duration of action.

Compound **14** possessed the best activity profile as shown in Figure 1, so it was chosen for additional studies. However, at doses greater than 10 mg/kg, increased side effects including central nervous system involvement were observed, and this appeared to be typical for this series. Thus, the anticipated therapeutic index was considered to be too small, and work on this series was discontinued in order to concentrate on the development of the more promising series of 2,6-dimethyl-α,α-diaryl-1-piperidine-

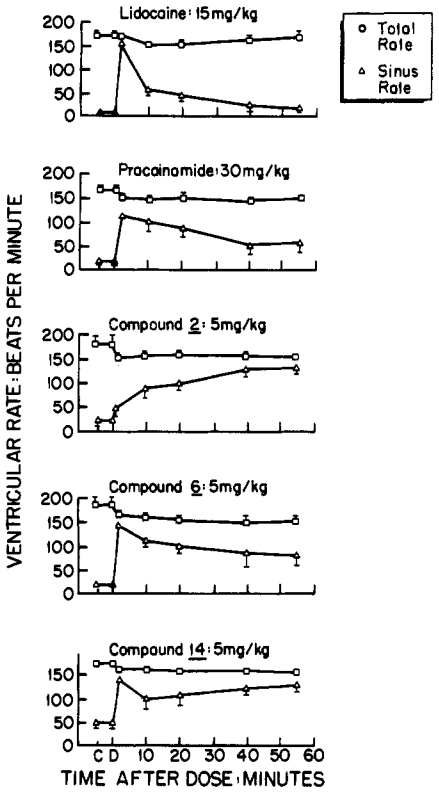


Figure 1. Antiarrhythmic activity in coronary artery ligated dogs. Total rate denotes all ventricular beats (ventricular ectopic beats plus ventricular beats of normal sinus origin); sinus rate denotes the ventricular beats of normal sinus origin. For complete conversion to normal sinus rhythm the two lines become superimposable. There were six dogs in each treatment group. Lidocaine was administered iv at 10 mg/kg over 5 min followed immediately by 5 mg/kg over 20 min. Procainamide (30 mg/kg) and compounds **2**, **6**, and **14** (5 mg/kg) were administered iv over 5 min. Values are expressed as mean ± SEM.

butanols.[3] Although the number of compounds in this series was small, this work indicated that a quaternary ammonium salt was not required for long duration of action and that the antiarrhythmic activity could be separated from the tachycardia found in this series of compounds.

Experimental Section

Chemistry. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were determined on a Varian EM 360 or EM 390 spectrometer using Me_4Si as the internal standard. Only spectral data of representative compounds are included, but where not reported, the data agreed with the proposed structures. Analytical results are within ±0.4% unless otherwise noted.

***cis*-1-[2-(Diphenylmethoxy)ethyl]-2,6-dimethylpiperidine Monohydrochloride (4).** A mixture of 45.3 g (0.4 mol) of 2,6-dimethylpiperidine and 25.0 g (0.2 mol) of 2-bromoethanol was heated on a stream bath for 2 h. After cooling, 500 mL of ether was added to the crystalline mass and the mixture was filtered. The precipitate was washed with ether, and the combined ether filtrates were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled, yielding 2,6-dimethyl-1-piperidineethanol: 13.15 g (42%); bp 101–102 °C (0.1 mmHg). Anal. ($C_9H_{19}NO$) C, H, N.

2,6-Dimethyl-1-piperidineethanol (19.27 g, 0.12 mol) was dissolved in 20 mL of toluene. The resulting solution was heated at reflux and 14.8 g (0.06 mol) of benzhydryl bromide was added in small portions over a period of 40 min. A solid separated out near the end of the addition, but the mixture was heated at reflux with stirring for an additional 17 h. After cooling, the mixture was filtered and washed with ether. The filtrate was concentrated under reduced pressure, and the residue was distilled to yield 14.5 g of an oil; bp 153–157 °C (0.17 mmHg). This product was dissolved in 200 mL of Et_2O and a saturated solution of hydrogen chloride in ether was added dropwise until no additional precipitate was formed. The precipitate was collected by filtration and dried in a vacuum oven at 60 °C; mp 135–139 °C. The product (4) was purified by dissolving in 20 mL of *i*-PrOH, diluting with 200 mL of Et_2O, and chilling: 11.2 g (51.3%); mp 141–142 °C. Anal. ($C_{22}H_{29}NO{\cdot}HCl$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-1,2,6-trimethylpiperidinium Methanesulfonate (2). A solution of 3.47 g (10.7 mmol) of *cis*-1-[2-(diphenylmethoxy)ethyl]-2,6-dimethylpiperidine and 2.36 g (21.4 mmol) of methyl methanesulfonate in 20 mL of CH_3CN was stirred at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and 200 mL of anhydrous Et_2O was added. Upon cooling, a precipitate separated which was removed by filtration and transferred rapidly to a vacuum dessicator and dried because it was very hygroscopic: 4.2 g; mp 126.5–131 °C. The product was purified by dissolving in 10 mL of *i*-PrOH and diluting with 200 mL of anhydrous Et_2O. Upon cooling and seeding, the product crystallized out and was removed by filtration. This recrystallization was repeated twice to yield **2**: 1.33 g (29%); mp 138.5–141 °C. Anal. ($C_{24}H_{35}NO_4S$) C, H, N.

***cis*-1-[2-(Diphenylmethoxy)ethyl]-2,5-dimethylpyrrolidine Monohydrochloride (5).** Following the procedure described for compound **4**, but using 2,5-dimethyl-1-pyrrolidineethanol,[12] yielded the free base of **5**: 57%; bp 132–136 °C (0.12 mmHg). Conversion to the monohydrochloride gave **5**: mp 148–150 °C. Anal. ($C_{21}H_{28}NOCl$) C, H, N.

1-[2-(Diphenylmethoxy)ethyl]-1,2,5-trimethylpyrrolidinium Methanesulfonate (3). Following the procedure described for compound **2** but utilizing the free base of **5** from above yielded compound **3**: 59%; mp 146–147 °C; ^1H NMR (D_2O) γ 1.42 (d, 6, J = 7 Hz, CH_3), 1.65–2.50 (m, 4, aliphatics), 2.75–3.10 (m, 5, CH_3N(cycl CH)), 3.30–4.20 (m, 4, OCH_2CH_2N), 5.62 (s, 1, Ar_2CHO), 7.20–7.70 (m, 10, aromatics). Anal. ($C_{23}H_{30}NO_4S$) C, H, N.

***cis*-α-[(Diphenylmethoxy)methyl]-2,6-dimethyl-1-piperidineethanol (6).** A mixture of 14.42 (0.06 mol) of [(diphenylmethoxy)methyl]oxirane[7] and 7.47 g (0.066 mol) of cis-2,6-dimethylpiperidine was heated on a steam bath for 18 h. The reaction mixture was warmed with 100 mL of hexane and filtered to remove insoluble material. Diisopropyl ether (75 mL) was added and the resulting solution was treated with charcoal. Upon cooling the crystalline product was collected by filtration and purified by recrystallizing twice from *i*-Pr_2O: 16.2 g, mp 94–95 °C. Since TLC indicated a spot at the origin along with another impurity, the product was dissolved in EtOAc and washed with water (2 × 100 mL). The solution was dried over anhydrous $MgSO_4$ and the EtOAc was removed under reduced pressure. The residue was recrystallized from *i*-Pr_2O to yield **6**: 14.6 g (69%); mp 94.5–95.5 °C; ^1H NMR ($CDCl_3$) δ 1.03 (d, 3, J = 7 Hz, CH_3), 1.10 (d, 3, J = 7 Hz, CH_3), 1.15–1.82 (m, 6, aliphatics), 2.20–2.80 (m, 4, CH_2N(cycl CH)), 3.32–4.00 (m, 4, $OCH_2CH(OH)$), 5.38 (s, 1, Ar_2CHO), 7.10–7.50 (m, 10, aromatics). Anal. ($C_{23}H_{31}NO_2$) C, H, N.

1-[3-(Diphenylmethoxy)-2-hydroxypropyl]-1,2,6-trimethylpiperidinium Chloride (7). Compound **6** (8.0 g) was combined with 25 mL of a solution of CH_3Cl (20% by weight) in CH_3CN. The resulting solution was heated in a small autoclave on a steam bath for 16 h. After cooling, 75 mL of CH_3CN was added to the reaction mixture which was then treated with charcoal. After removal of the solvent, the residue was dissolved in 25 mL of *i*-PrOH and 250 mL of EtOAc was added and the mixture was chilled for 4 h. The product was removed by filtration and further purified by repeating the above recrystallization two additional times. After drying over toluene in a drying pistol, pure compound **7** was obtained: 4.2 g (46%); mp 171–174 °C; ^1H NMR (D_2O) δ 1.27 (d, 3, J = 7 Hz, CH_3), 1.54 (d, 3, J = 7 Hz, CH_3), 1.70–2.15 (m, 6, aliphatics), 2.80 (s, 3, NCH_3), 3.10–4.30 (m, 8), 5.67 (s, 1, Ar_2CHO), 7.15–7.80 (m, 10, aromatics). Anal. ($C_{24}H_{34}NO_2Cl$) C, H, N.

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cis-α-[(Diphenylmethoxy)methyl]-2,5-dimethyl-1-pyrrolidineethanol (8). Following the procedure described for compound 6 but using 2,5-dimethylpyrrolidine gave compound 8: 71%; mp 57–59 °C. Anal. ($C_{22}H_{29}NO_2$) C, H, N.

3-(Diphenylmethoxy)-2-hydroxy-*N*,*N*,*N*-trimethyl-1-propaniminium Methanesulfonate (10). A solution of compound 9 (4.57 g, 0.016 mol) and 1.85 g (0.0168 mol) of methyl methanesulfonate in 25 mL of CH_3CN was heated at reflux for 3 h with stirring. After cooling, 200 mL of anhydrous Et_2O was added and a solid separated which was removed by filtration. The product was dissolved in 60 mL of *i*-PrOH and 95 mL of Et_2O was added and the mixture was chilled for 1.5 h. The product was collected by filtration and purified by recrystallizing as described above to yield compound 10: 5.6 g (89%); mp 128–130 °C. Anal. ($C_{20}H_{29}NO_5S$) C, H, N.

cis-α-[[Bis(2-methylphenyl)methoxy]methyl]-2,6-dimethyl-1-piperidineethanol (11). A solution of 42.5 (0.2 mol) of 2,2′-dimethylbenzhydrol,[13] 13.9 g (0.24 mol) of allyl alcohol, and 8.0 g of *p*-toluenesulfonic acid monohydrate in 100 mL of benzene was heated at reflux for 16 h while the H_2O was removed with a Dean–Stark water separator. The resulting solution was washed with H_2O and then aqueous $NaHCO_3$ solution. After drying over anhydrous $MgSO_4$, the solvent was removed under reduced pressure on a rotary evaporator, and the residue was distilled to yield 1,1′-[(2-propenyloxy)methylene]bis(1-methylbenzene): 44.3 g (88%); bp 103–106 °C (0.1 mmHg).

1,1′-[(2-propenyloxy)methylene]bis(2-methylbenzene) (44.1 g, 0.174 mol) was dissolved in 115 mL of $CHCl_3$ and then added to a suspension of 39 g (0.192 mol) of *m*-chloroperoxybenzoic acid (85%) in 525 mL of $CHCl_3$ which had been swirled to dissolve the bulk of the acid. After mixing thoroughly, the flask was stoppered and the reaction mixture was allowed to stand at room temperature for 4 days. After filtering to remove a small amount of insoluble material, the chloroform solution was washed with 5% NaOH solution (3 × 100 mL) and then water (2 × 100 mL) and finally dried over anhydrous $MgSO_4$. The chloroform was removed under reduced pressure on a rotary evaporator to yield 46.9 g of [[bis(2-methylphenyl)methoxy]methyl]oxirane as an oil which solidified on standing. Vapor-phase chromatography indicated that this material was 95.5% pure.

A mixture of 10.75 g (0.04 mol) of [[bis(2-methylphenyl)-methoxy]methyl]oxirane described above and 5.45 g (0.048 mol) of 2,6-dimethylpiperidine was heated overnight on the steam bath. *n*-Hexane (100 mL) was added, and the mixture was warmed until all was in solution. After chilling overnight, filtration yielded 11.4 g of crude product; mp 117–119 °C. Three recrystallizations from EtOAc–*i*-Pr_2O (1:2) yielded 9.05 g (60%) of pure compound 11: mp 118.5–119.5 °C; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3, J = 7 Hz, CH_3), 1.06 (d, 3, J = 7 Hz, CH_3), 1.25–1.90 (m, 6, aliphatics), 2.27 (br s, 6, ArCH_3), 2.37–2.85 (m, 4, CH_2N(cyclo CH)), 3.30–4.15 (m, 4, OCH_2CH(OH)), 5.71 (s, 1, Ar_2CHO), 7.00–7.90 (m, 8, aromatics). Anal. ($C_{25}H_{35}NO_2$) C, H, N.

α-[[Bis(2-methylphenyl)methoxy]methyl]-2-methyl-1-piperidineethanol Ethanedioate (12). Following the procedure described for compound 11 but using 2-methylpiperidine yielded compound 12 isolated as the oxalic acid salt: 62%; mp 90–93 °C. Anal. ($C_{24}H_{33}NO_2 \cdot C_2H_2O_4$) C, H, N.

α-[[Bis(2-methylphenyl)methoxy]methyl]-1-piperidineethanol Ethanedioate (13). Following the procedure described for compound 11 but using piperidine yielded compound 13 isolated as the oxalic acid salt: 71%; mp 143–145 °C. Anal. ($C_{23}H_{31}NO_2 \cdot C_2H_2O_4$) C, H, N.

cis-2,6-Dimethyl-α-[[(2-methylphenyl)phenylmethoxy]-methyl]-1-piperidineethanol (14). Starting with 2-methyl-α-phenylbenzenemethanol[14] and following the procedures used in the preparation of compound 11 yielded 1-methyl-2-[phenyl(2-propenyloxy)methyl]benzene (81.3%; bp 95–97 °C at 0.1 mmHg), [[(2-methylphenyl)phenylmethoxy]methyl]oxirane (91%; bp 138–139 °C at 0.2 mmHg), and compound 14 (71%; mp 98–99 °C. Anal. ($C_{24}H_{33}NO_2$) C, H, N).

cis-α-[[(2,6-Dimethylphenyl)phenylmethoxy]methyl]-2,6-dimethyl-1-piperidineethanol (15). Starting with 2,6-dimethyl-α-phenylbenzenemethanol[15] and following the procedures utilized in the preparation of compound 11 yielded 2,6-dimethyl-1-[phenyl(2-propenyloxy)methyl]benzene (79%; bp 100–108 °C at 0.15 mmHg), [[(2,6-dimethylphenyl)phenylmethoxy]methyl]oxirane (79%; mp 134–136 °C), and compound 15 (34%; mp 135–136 °C. Anal. ($C_{25}H_{35}NO_2$) C, H, N).

cis-α-[[Bis(2-methoxyphenyl)methoxy]methyl]-2,6-dimethyl-1-piperidineethanol (16). Starting with 2-methoxy-α-(2-methoxyphenyl)benzenemethanol[16] and following the procedures described for the preparation of compound 11 yielded 1,1′-[(2-propenyloxy)methylene]bis(2-methoxybenzene) (77%; mp 70–72 °C), [[bis(2-methoxyphenyl)methoxy]methyl]oxirane (49%; mp 101–103 °C), and compound 16 (60%; mp 128–129 °C. Anal. ($C_{25}H_{35}NO_4$) C, H, N).

cis-α-[[Bis(2,6-dimethylphenyl)methoxy]methyl]-2,6-dimethyl-1-piperidineethanol (17). Starting with α-(2,6-dimethylphenyl)-2,6-dimethylbenzenemethanol[17] and utilizing the procedures described for the preparation of 11 yielded 1,1′-[(2-propenyloxy)methylene]bis(2,6-dimethylbenzene) (90%; bp 126–128 °C at 0.1 mmHg), [[bis(2,6-dimethylphenyl)methoxy]-methyl]oxirane (85%; bp 144–148 °C at 0.1 mmHg), and compound 17 (56%; mp 128–129 °C. Anal. ($C_{27}H_{39}NO_2$) C, H, N).

cis-2,6-Dimethyl-α-[(1-phenylethoxy)methyl]-1-piperidineethanol (18). To 122 g (1.0 mol) of α-methylbenzenemethanol in 1 L of toluene was added 42 g (1.0 mol) of a NaH dispersion (57%) in portions over 0.5 h. Reaction mixture was stirred at room temperature for 1 h and then under reflux for 1 h. The reaction mixture was cooled to 7 °C and 92.5 g (1.0 mol) of (chloromethyl)oxirane was added dropwise over 1 h. At the end of the addition the pot temperature was 45 °C. The reaction mixture was stirred at 60 °C for 3 h and then at 80 °C for an additional 3 h. After cooling, the solution was washed with H_2O and dried over Na_2SO_4. The toluene was removed and the residue was distilled under reduced pressure: 38.1 g; bp 62 °C (0.1 mmHg). NMR indicated a mixture of α-methylbenzenemethanol and product which was used in the next step.

A mixture of 14.8 g (0.05 mol calculated as 60% pure based on VPC) of [(1-phenylethoxy)methyl]oxirane from above and 5.6 g (0.05 mol) of 2,6-dimethylpiperidine in 40 mL of toluene was heated at reflux for 48 h. The solvent was removed under reduced pressure on a rotary evaporator to yield a liquid. This material was dissolved in benzene, and the solution was washed with water and then extracted with 1 N HCl (3 × 100 mL). The acidic extract was made basic with 5 N NaOH to yield a brown oil which was dissolved in benzene, and this solution was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue solidified on standing. Two recrystallizations from CH_3CN yielded compound 18: 5.3 g (37%); mp 74–77 °C; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3, J = 7 Hz, CH_3), 1.03 (d, 3, J = 7 Hz, CH_3), 1.15–1.65 (m, 9, aliphatics), 2.15–2.88 (m, 4, CH_2N(cyclo CH)), 3.10–3.90 (m, 4, OCH_2CH(OH)), 4.45 (q, 1, ArCHO), 7.10–7.40 (m, 5, aromatics). Anal. ($C_{18}H_{29}NO_2$) C, H, N.

cis-α-[[(Diphenylmethyl)thio]methyl]-2,6-dimethyl-1-piperidineethanol (19). A mixture of 339.39 (3.0 mol) of 2,6-dimethylpiperidine and 310 mL of H_2O was stirred at room temperature and 277.6 g (3.0 mol) of (chloromethyl)oxirane was added in portions over 0.5 h. The reaction temperature was slowly raised to 50 °C and held at this point for 7.5 h by external heating. The mixture was allowed to stand at room temperature overnight and after cooling 150 g of NaOH dissolved in 300 mL of H_2O was added with stirring over 10 min. After stirring at room temperature for 1 h the organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined and dried over KOH. The low-boiling fractions were removed on a rotary evaporator with a bath at 35 °C. The residue was fractionally distilled with a short Vigeroux column yielding 132 g of a fraction boiling at 87–90 °C (9.0 mmHg) and checked by NMR.

2,6-Dimethyl-1-(oxiranylmethyl)piperidine from above (16.9 g, 0.1 mol) was added dropwise to a solution of 18.0 g (0.09 mol)

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of α-phenylbenzenemethanethiol[18] in 250 mL of EtOH containing 6.0 g (0.105 mol) of $NaOCH_3$. The resulting solution was stirred at reflux for 4 h. The solvent was removed under reduced pressure on a rotary evaporator, and water (100 mL) was added to the residue. The oil was extracted with 200 mL of benzene and the organic layer was washed with 2 N NaOH and H_2O. After treating with charcoal and drying over anhydrous $MgSO_4$, the benzene solution was concentrated to 100 mL on a steam bath and 300 mL of petroleum ether was added. Upon cooling, 28.6 g of compound **19** was collected by filtration; mp 89–91 °C. The product was further purified by dissolving in 100 mL of benzene and diluting with 400 mL of petroleum ether: 13.0 g (36%); mp 89–91 °C; ^1H NMR ($CDCl_3$) δ 1.01 (d, 6, J = 7 Hz, CH_3), 1.15–1.85 (m, 6, aliphatics), 2.10–2.35 (m, 6), 3.10–3.75 (m, 2), 5.25 (s, 1, Ar_2CHS), 7.10–7.40 (m, 10, aromatics). Anal. ($C_{23}H_{31}NOS$) C, H, N.

***cis*-α-[[(Diphenylmethyl)amino]methyl]-2,6-dimethyl-1-piperidineethanol Dihydrochloride (20).** A mixture of 8.5 g (0.05 mol) of 2,6-dimethyl-1-(oxiranylmethyl)piperidine from above and 9.2 g (0.5 mol) of α-phenylbenzenamine was heated in an oil bath at 100–110 °C for 41 h. After cooling, the resulting orange gum was dissolved in 200 mL of benzene, washed with H_2O, and dried over anhydrous $MgSO_4$. The benzene was removed under reduced pressure and the residue was dissolved in ether and filtered, and HCl gas was bubbled through the solution, yielding a gummy brown mass. The ether layer was decanted and treated with additional HCl to yield a beige solid which was collected by filtration and dried in vacuo. A portion of this product was boiled in EtOAc for 0.5 h and then filtered and dried in vacuo to yield compound **20**: 2.0 g melting over a range of 94–100 °C. Anal. ($C_{23}H_{32}N_2O\cdot 2HCl\cdot 0.75C_4H_8O_2$) C, H, N.

Biological Methods. All of the compounds were evaluated in conscious mongrel dogs on the first day following ligation of the left anterior descending coronary artery.[8] A minimum of two dogs was used for each test compound and it was required that the arrhythmia be severe with >50% ventricular ectopic beats during the predose control period. The animals were dosed with 5 mg/kg of test drug as a solution in 10–20 mL of isotonic saline administered by iv infusion over 5 min. The animals' ECGs were monitored continuously from limb lead II for up to 6 h or until antiarrhythmic activity was no longer evident. The conversion of ventricular arrhythmias to normal sinus rhythm and the duration of the antiarrhythmic effect were quantitated throughout the monitor period.[2,9]

Selected compounds were evaluated for their liability to cause tachycardia in conscious normal dogs trained to sit quietly while sling restrained. The animals were dosed with iv injections identical with those used in the ligated dog studies, and effects on heart rate was determined by continuous monitoring of limb lead II ECG. The heart rate was determined during a control period, at the end of dosing, after 20 min, and after 1 h. Animals showing a heart rate greater than 140 beats/min were monitored until the rate decreased to 140 beats/min. Both the normal dogs and the coronary-ligated dogs were monitored for overt side effects, including mydriasis, tremors, agitation, and convulsions. The occurrence of these side effects is noted at several places in the text but was not included in the tables.

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Synthesis and Antiarrhythmic Activity of *cis*-2,6-Dimethyl-α,α-diaryl-1-piperidinebutanols

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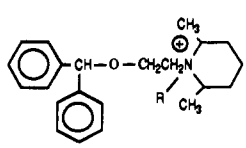
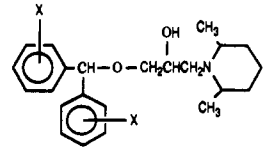
A series of α,α-diaryl-1-piperidinebutanols was evaluated for antiarrhythmic activity in the coronary ligated dog model. Structure–activity relationship studies indicated that the 2,6-dimethylpiperidine group yielded compounds with the best antiarrythmic profiles in this series. The length of the methylene chain separating the diarylcarbinol and the amino group was not crucial. Substitution of a hydrogen or a number of functional groups for the hydroxyl group had little effect on efficacy or duration but yielded compounds that produced severe tachycardias. Replacement of one of the aryl groups by hydrogen or a pyridinyl or cyclohexyl group had little effect on efficacy but decreased the duration of action. Compound 18 (pirmenol) was ultimately chosen for further studies and is now being investigated in man.

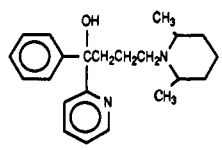
In the preceding paper it was reported that quaternary ammonium salts of diphenhydramine (I) and α-[(diaryl-



I



II



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methoxy)methyl]-2,6-dimethyl-1-piperidineethanols (II) were potent antiarrhythmic agents in the coronary artery ligated (Harris) dog model.[1] These agents were notable for their long duration of action, but the associated tachycardia and other side effects discouraged further development of either series. However, structural modifications of II ultimately led to the discovery of pirmenol[2] (18, cis-(±)-α-[3-(2,6-dimethyl-1-piperidinyl)propyl]-α-phenyl-2-pyridinemethanol monohydrochloride). This compound is a potent, orally effective antiarrhythmic agent with a long duration of action and a favorable therapeutic index relative to the other drugs of this class.[3] The work presented here describes the synthesis and the biological evaluation of the key compounds in the series from which pirmenol was chosen.

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