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.

(18) Klenk, M. M., Suter, C. M., Archer, S. *J. Am. Chem. Soc.* **1948**, *70*, 3846.

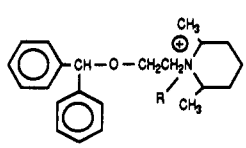
# Synthesis and Antiarrhythmic Activity of *cis*-2,6-Dimethyl-α,α-diaryl-1-piperidinebutanols

M. L. Hoefle,* L. T. Blouin, R. W. Fleming, S. Hastings, J. M. Hinkley, T. E. Mertz, T. J. Steffe, and C. S. Stratton

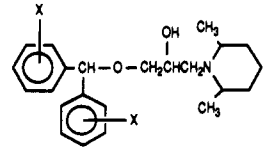
*Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48015.*
*Received November 24, 1987*

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.

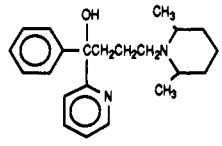
In the preceding paper it was reported that quaternary ammonium salts of diphenhydramine (I) and α-[(diaryl-



I



II



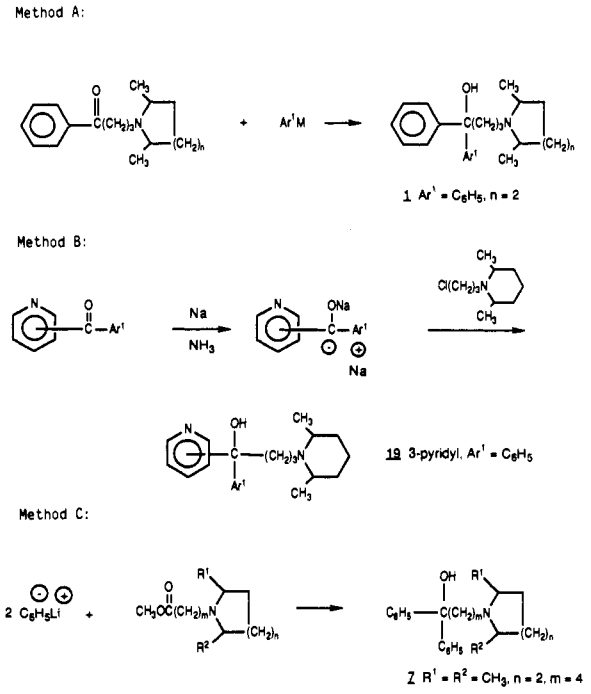
18

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.

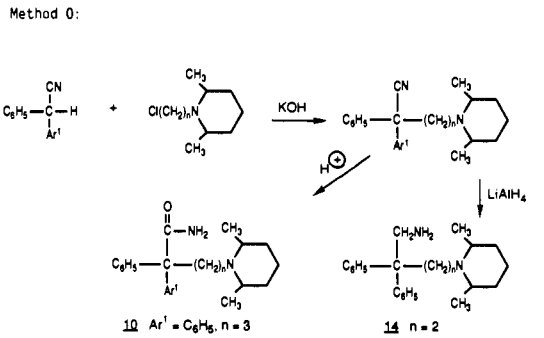
(1) Hoefle, M. L.; Blouin, L. T.; Fleming, R. W.; Hastings, S.; Hinkley, J. M.; Mertz, T. E.; Steffe, T. J.; Stratton, C. S.; Werble, L. M. *J. Med. Chem.*, preceeding paper in this issue.
(2) Fleming, R. W. U.S. Patent 4,112,103, 1978.
(3) Kaplan, H. R.; Mertz, T. E.; Steffe, T. J.; Toole, J. H. *New Drugs Annual: Cardiovascular Drugs*; Scriabine, A., Ed.; Academic Press: New York, 1983; p 133.

0022-2623/91/1834-0012$02.50/0 © 1991 American Chemical Society

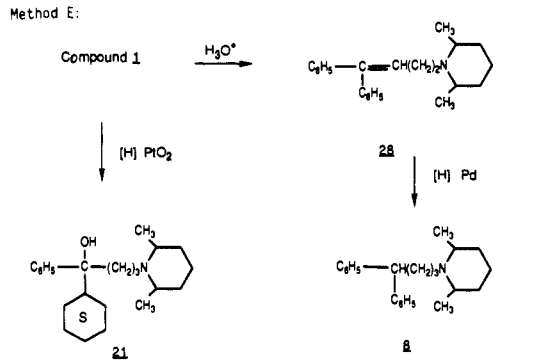
**Scheme I**




**Scheme II**




**Scheme III**




## Chemistry

The synthesis of the various α,α-diaryl-1-piperidinebutanol derivatives was straightforward. Three general routes were utilized (Scheme I). Method A was employed to introduce different aryl groups (**1**, **17**, **18**) by the addition of an aryl organometallic agent to 4-(2,6-dimethyl-1-piperidinyl)-1-phenyl-1-butanone. The use of other 4-substituted aminobutanones yielded the correspondingly substituted products (**3**, **23**, **24**). In those cases where the desired aryl group was pyridinyl (**19**, **20**, **22**) it was found to be more satisfactory to generate the disodium salts[4] of the available benzoylpyridines and alkylate with 1-(3-chloropropyl)-2,6-dimethylpiperidine (method B). In method C 2 equiv of phenyl lithium or phenyl magnesium bromide were added to the corresponding methyl aminoalkanoate to give the desired products in good yield (**2**, **4–7**). The synthesis of **2** by a different method has been described previously.[5]

The nitriles (**9**, **12**, **26**) were prepared by the alkylation of the corresponding acetonitriles with 1-(chloroalkyl)-2,6-dimethylpiperidine, and these compounds were utilized as starting materials for subsequent reactions (method D, Scheme II). Acid hydrolysis afforded the corresponding carboxamides **10**, **13**, and **27**. Reduction with lithium aluminum hydride gave amino compounds which were then acetylated with acetic anhydride (**11**, **15**).

Compound **1** was also utilized as the starting material as shown in method E (Scheme III). Dehydration under acidic conditions[6] afforded **28**, which was reduced at low pressure with palladium on charcoal as the catalyst to yield **8**. Reduction of **1** in glacial acetic acid with a catalytic amount of platinum oxide[7] gave cyclohexyl derivative **21**.

## Biology

All of the compounds were evaluated for antiarrhythmic activity in the conscious coronary artery ligated dog model described by Harris.[8] Selected compounds were tested in conscious, normal dogs to determine their tendency to cause tachycardia. Details of the methodology have been described previously.[1,9]

An activity rating was utilized to compare the relative antiarrhythmic activities of the test compounds. 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 dosed at 10 mg/kg over 5 min immediately followed by 5 mg/kg over 20 min had an activity rating of 20, and procainamide hydrochloride dosed at 30 mg/kg over 5 min had an activity rating of 52. All biological data are summarized in Table II. For ease in interpretation, the degree and duration of the tachycardia has been rated according to the definitions given as a footnote to Table II.

## Results and Discussion

The search for an antiarrhythmic agent that was an efficacious as lidocaine and, in addition, possessed a long duration of action led to the investigation of two series of compounds represented by formulas I and II. However,

(4) Hamrick, P. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1959**, *81*, 493.
(5) Libman, N. M.; Kuznetsov, S. G. *Zh. Obshch. Khim.* **1963**, *33*, 8.
(6) British Patent 682,160, 1952.
(7) Adamson, D. W.; Barrett, P. A.; Wilkinson, S. *J. Chem. Soc.* **1951**, 52.
(8) Harris, A. S. *Circulation* **1950**, *1*, 1318.
(9) Mertz, T. E.; Steffe, T. J. *J. Cardiovasc. Pharmacol.* **1980**, *2*, 527.

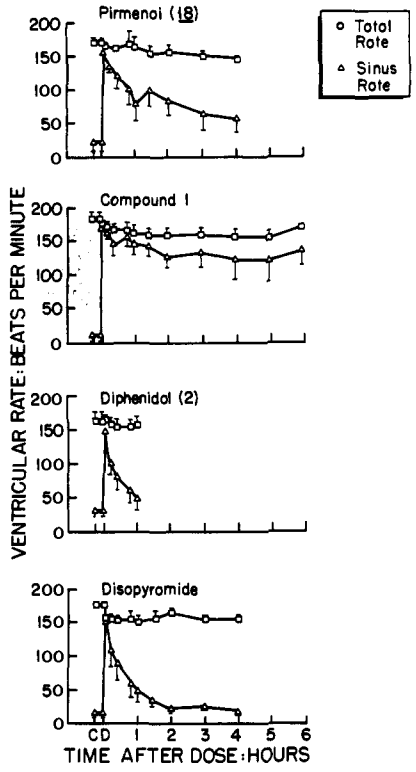
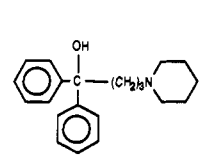



**Figure 1.** Antiarrhythmic effects of 5 mg/kg iv doses in coronary artery ligated conscious dogs. Total rate denotes all ventricular beats (ventricular ectopic beats plus ventricular beats of normal sinus origin); sinus rate denotes the ventricular beats of normal sinus origin. Pirmenol and disopyramide were tested in six animals each, compound 1 and diphenidol (2) in four animals each. C denotes control, D denotes dose administration of 5 mg/kg iv. Values are expressed as mean ± SEM.

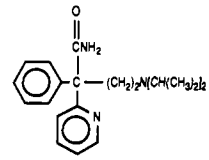
the potent antiarrhythmic activity shown by both types was accompanied by an increase in heart rate that was considered to be unacceptable for this type of agent.[1] Thus, the objective of the present investigation was to identify agents with less associated tachycardia as well as increased efficacy and duration of action.

One of the early structural modifications of II was to remove the ether linkage and shift the hydroxyl group to the carbon atom bearing two phenyl groups to yield *cis*-2,6-dimethyl-$\alpha,\alpha$-diphenyl-1-piperidinebutanol (1). The antiarrhythmic activity displayed by compound 1 was very encouraging because this agent possessed the activity profile which we had set out to find. As seen in Figure 1, compound 1 was very effective in converting ventricular arrhythmias of the first day Harris dog model to a normal sinus rhythm. In addition, this conversion was maintained over the 6-h period tested. However, the similarity of the structure of 1 to that of other known antiarrhythmic agents necessitated establishing the novelty and advantages of 1 before proceeding with the development of the series.

Previous experience had shown that the 2,6-dimethyl-1-piperidinyl substituent was beneficial in improving the antiarrhythmic activity in a number of diverse structural types.[1] It was particularly important that these findings extend to the present series because the analogue with the 1-piperidinyl substituent is diphenidol (2), which had been reported to have antiarrhythmic activity.[10] Diphenidol



2



III

was tested and was found to be less effective and to have a shorter duration of action than 1 (see Figure 1), and it caused tremors and convulsions in some animals.

Similarly, it was recognized that 18 shared a number of structural features with the antiarrhythmic agent disopyramide (III). In addition, it had been shown that the carboxamide group in III could be replaced by hydroxyl and the antiarrhythmic activity was retained.[11] Thus, disopyramide phosphate was also tested and compared with 1 (Figure 1), confirming the longer duration of action in the pirmenol series.

The structure–activity relationships within this series of compounds were examined by considering four major structural features indicated in Table I: (a) variation of the amine substituent, A; (b) variation of the chain length, *n*; (c) replacement of the hydroxyl group, x; and (d) variation of the aryl groups, $Ar_1$ and $Ar_2$. The results are shown in Table II.

**Variation of the Amine Group.** Earlier work had indicated that the 2,6-dimethyl-1-piperidinyl substituent afforded close to maximum efficacy and duration of action in related antiarrhythmic series.[1] This was checked by comparing the 1-piperidinyl (**2** and **23**), 2,5-dimethyl-1-pyrrolidinyl (**3** and **24**), and 2-ethyl-1-piperidinyl (**4**) analogues with **1** and **18**, respectively. Although good conversion of arrhythmias was observed for all except **3**, only **1** and **18** had the desired long duration of action. The effect on heart rate in normal dogs was determined for the 1,1-diphenyl compounds (**1–3**) only. Although there was unusually wide variation between animals, there is a suggestion that the tachycardia is both of lesser magnitude and of shorter duration for compound **1** with the 2,6-dimethyl-1-piperidinyl substituent.

**Variation of the Chain Length.** The chain length (*n*) was varied from 1 to 4 (compounds **5**, **6**, **1**, and **7**) and, except for **5**, all possessed an excellent antiarrhythmic profile. In fact, compounds **6** and **7** showed less tachycardia than **1**. However, compound **6** caused tremors and compound **7** caused agitation, which eliminated them from consideration for development. The compounds where $n = 2$ were of particular interest because of their relationship to the known antiarrhythmic agent disopyramide (III), and their activity is discussed below.

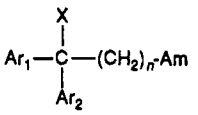
**Replacement of the Hydroxyl Group.** Since it has been reported that the carboxamide group in disopyramide can be replaced by a variety of functional groups with the retention of antiarrhythmic activity,[11] the hydroxyl group in the present series was replaced by H, CN, $CONH_2$, $CH_2NH_2$, and $CH_2NHAc$ (compounds **8–15**). Replacement by hydrogen (**8**) and carboxamide (**10**) yielded compounds with the highest activity ratings, but both produced a severe and long-lasting tachycardia which was an unusual finding in this series.

There was little difference in activity between the respective compounds where $n = 2$ and 3 except for carboxamides **10** and **13**, where the longer chain length afforded the more active compound. Nitriles **9**, **12**, and **26**

(10) (a) Leonard, C. A.; Fujita, T.; Tedeschi, D. H.; Zirkle, C. L.; Fellows, E. J. *J. Pharmacol. Exp. Ther.* **1966**, *154*, 339. (b) Mandel, W. J.; Hayakawa, H.; Vyden, J. K.; Carvalho, M.; Parmley, W. W.; Corday, E. *Am. J. Cardiol.* **1972**, *30*, 67. (c) Hayakawa, H.; Mandel, W. J. *J. Pharmacol. Exp. Ther.* **1972**, *185*, 447.

(11) Yen, C. H.; Lowrie, H. S.; Dean, R. R. *J. Med. Chem.* **1974**, *17*, 1131.

**Table I.** Structures and Physical Properties of 1–27




| no. | $Ar_1$ | $Ar_2$ | Am | n | x | synth method | % yield[a] | mp, °C | recryst solvent | empirical formula | anal. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | OH | A | 62 | 231–232 | EtOH | $C_{23}H_{31}NO\cdot HCl$ | C,H,N |
| 2 | $C_6H_5$ | $C_6H_5$ | 1-piperidinyl | 3 | OH | C | 74 | 213–214 | *i*-PrOH | $C_{21}H_{27}NO\cdot HCl$ | C,H,N |
| 3 | $C_6H_5$ | $C_6H_5$ | 2,5-dimethyl-1-pyrrolidinyl | 3 | OH | A | 42 | 186–187 | EtOH | $C_{22}H_{29}NO\cdot HCl$ | C,H,N |
| 4 | $C_6H_5$ | $C_6H_5$ | 2-ethyl-1-piperidinyl | 3 | OH | C | 68 | 127–129 | *i*-PrOH | $C_{23}H_{31}NO\cdot HCl$ | C,H,N |
| 5 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 1 | OH | C | 23 | 139–141 | pet. ether[b] | $C_{21}H_{27}NO$ | C,H,N |
| 6 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 2 | OH | C | 70 | 227–228 | *i*-PrOH | $C_{22}H_{29}NO\cdot HCl$ | C,H,N |
| 7 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 4 | OH | C | 59 | 125–126 | pet. ether | $C_{24}H_{33}NO$ | C,H,N |
| 8 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | H | E | 63.5 | 177–178 | *i*-PrOH–$Et_2O$ | $C_{23}H_{31}N\cdot HCl$ | C,N,N |
| 9 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | CN | D | 68 | 181–181.5 | *i*-PrOH | $C_{24}H_{30}N_2\cdot HCl\cdot 0.5H_2O$ | C,H,N |
| 10 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | $CONH_2$ | D | 65 | 216–218 | EtOH | $C_{24}H_{32}N_2O\cdot HCl$ | C,H,N |
| 11 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | $CH_2NHAc$ | D | 50 | 248–249 | *i*-PrOH | $C_{26}H_{36}N_2O\cdot HCl$ | C,H,N |
| 12 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 2 | CN | D | 64.2 | 229–230 | EtOAc | $C_{23}H_{28}N_2\cdot HCl\cdot 0.25H_2O$ | C,H,N |
| 13 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 2 | $CONH_2$ | D | 85.8 | 143–146 | *i*-PrOH | $C_{23}H_{30}N_2O\cdot HCl\cdot 0.50H_2O$ | C,H,N |
| 14 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 2 | $CH_2NH_2$ | D | 89 | 73–74 | $Et_2O$ | $C_{23}H_{32}N_2\cdot 0.25H_2O$ | C,H,N |
| 15 | $C_6H_5$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 2 | $CH_2NHAc$ | D | 91.5 | 174–175 | cyclohexane | $C_{25}H_{34}N_2O$ | C,H,N |
| 16 | $C_6H_5$ | H | 2,6-dimethyl-1-piperidinyl | 3 | OH | E | 44.5 | 149–150 | *n*-PrOH–$Et_2O$ | $C_{17}H_{27}NO\cdot HCl$ | C,H,N |
| 17 | 2-$CH_3C_6H_4$ | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | OH | A | 4.3 | 229–230 | EtOH–$Et_2O$ | $C_{24}H_{33}NO\cdot HCl\cdot 0.25H_2O$ | C,H,N |
| 18 | 2-pyridinyl | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | OH | A | 82 | 70–71 | pet. ether | $C_{22}H_{30}N_2O$ | C,H,N |
| 19 | 3-pyridinyl | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | OH | B | 72 | 226–228 | *i*-PrOH | $C_{22}H_{30}N_2O\cdot HCl$ | C,H,N |
| 20 | 4-pyridinyl | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | OH | B | 77 | 132–133.5 | benzene–hexane | $C_{22}H_{30}N_2O$ | C,H,N |
| 21 | cyclohexyl | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | OH | E | 33.5 | 205–206 | acetone | $C_{23}H_{37}NO\cdot HCl\cdot 0.25H_2O$ | C,H,N |
| 22 | 2-pyridinyl | 2-pyridinyl | 2,6-dimethyl-1-piperidinyl | 3 | OH | B | 70.7 | 191–192 | *i*-PrOH–$Et_2O$ | $C_{21}H_{29}N_3O\cdot HCl$ | C,H,N |
| 23 | 2-pyridinyl | $C_6H_5$ | 1-piperidinyl | 3 | OH | A | 72 | 207–208 | *i*-PrOH | $C_{20}H_{26}N_2O\cdot HCl$ | C,H,N |
| 24 | 2-pyridinyl | $C_6H_5$ | 2,5-dimethyl-1-pyrrolidinyl | 4 | OH | A | 72.3 | 66–67 | $CH_3CN$ | $C_{22}H_{30}N_2O\cdot H_2O$ | C,H,N |
| 25 | 2-pyridinyl | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | H | D | 57.5 | 173–173.5 | *i*-PrOH–$Et_2O$ | $C_{22}H_{30}N_2\cdot HCl\cdot 0.1H_2O$ | C,H,N |
| 26 | 2-pyridinyl | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | CN | D | 67.4 | 72–74 | hexane | $C_{23}H_{29}N_3$ | C,H,N |
| 27 | 2-pyridinyl | $C_6H_5$ | 2,6-dimethyl-1-piperidinyl | 3 | $CONH_2$ | D | 20.0 | 107–108 | benzene–pet. ether | $C_{23}H_{31}N_3O$ | C,H,N |

[a] Yield based on final step of indicated synthetic method. [b] Pet. ether refers to low-boiling petroleum ether throughout this paper.

demonstrated more severe central nervous system toxicity (tremors and convulsions) than compounds with any other functional groups.

**Variation of the Phenyl Group.** A comparison of the compounds obtained by varying one or both of the phenyl groups in **1** suggested that the major effect was on the duration of action. Replacement of one phenyl group by hydrogen (**16**) retained the efficacy but the long duration of action was lost. The introduction of a methyl substituent on one of the phenyl groups (**17**) similarly shortened the duration of action. Substituting a 2-pyridinyl group for phenyl yielded **18**, whose antiarrhythmic properties were very similar to those of compound **1**. However, comparison of compounds **1** with **18**, **2** with **23**, and **3** with **24** indicates that the introduction of the 2-pyridinyl as one of the aryl groups had little effect on efficacy but consistently decreased the duration of action. Replacement with 3- or 4-pyridinyl (**19**, **20**) decreased both efficacy and duration of action. Similarly, replacement of phenyl by cyclohexyl (**21**) had minimal effect on efficacy but decreased the duration of action.

Compound **1** was initially chosen for additional studies but was dropped when it was found to cause intestinal irritation in the dog after several days of oral administration at 15 mg/kg b.i.d. Compound **18** (pirmenol) was then chosen as the clinical candidate primarily because of the lack of side effects, and indeed, it was found to be free of any intestinal irritation when administered orally at 15

**Table II.** Pharmacological Data

| | antiarrhythmic effect in coronary ligated dogs at 5 mg/kg iv:[a] % normal beats[b] | | | | | heart rate effect in normal dogs at 5 mg/kg iv[a] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | heart rates, beats/min[b] | | | | | | |
| no. | no. of animals | control | end dose | 20 min | 1 h | activity rating | no. of dogs | control | end dose | 20 min | 1 h | degree[c] | duration[d] |
| 1 | 5 | 12 ± 5 | 96 ± 4 | 86 ± 8 | 76 ± 17 | 81 | 2 | 106 ± 6 | 187 ± 9 | 155 ± 5 | 165 ± 16 | mod. | long |
| 2 | 4 | 18 ± 5 | 90 ± 6 | 54 ± 16 | 34 ± 14 | 39 | 2 | 121 ± 4 | 200 ± 32 | 155 ± 24 | 142 ± 18 | mod. | long |
| 3 | 2 | 15 ± 1 | 69 ± 41 | 39 ± 39 | 35 ± 35 | 29 | 2 | 134 ± 21 | 243 ± 0 | 218 ± 7 | 193 ± 19 | severe | long |
| 4 | 2 | 3 ± 1 | 87 ± 13 | 48 ± 30 | 37 ± 8 | 46 | | | | | | NT[e] | NT |
| 5 | 2 | 7 ± 0 | 56 ± 34 | 16 ± 8 | 16 ± 6 | 15 | 2 | 106 ± 1 | 115 ± 9 | 92 ± 7 | 96 ± 4 | none | |
| 6 | 4 | 9 ± 5 | 97 ± 1 | 96 ± 3 | 74 ± 10 | 86 | 2[h] | 113 ± 9 | 137 ± 9 | 117 ± 3 | 130 ± 19 | none | |
| 7 | 3 | 12 ± 6 | 99 ± 1 | 84 ± 13 | 51 ± 13 | 72 | 2[h] | 122 ± 12 | 137 ± 7 | 139 ± 7 | 140 ± 5 | slight | mod. |
| 8 | 2 | 15 ± 9 | 95 ± 0 | 97 ± 1 | 92 ± 6 | 94 | 2[h] | 114 ± 21 | 255 ± 3 | 218 ± 7 | 179 ± 23 | severe | long |
| 9 | 2 | 14 ± 3 | 90 ± 9 | 88 ± 7 | 65 ± 35 | 82 | 2[h] | 111 ± 24 | 168 ± 4 | 147 ± 6 | 137 ± 16 | mod. | long |
| 10 | 3 | 14 ± 0 | 98 ± 2 | 90 ± 3 | 94 ± 4 | 91 | 2 | 101 ± 8 | 235 ± 0 | 223 ± 4 | 215 ± 4 | severe | long |
| 11 | 2 | 18 ± 4 | 95 ± 6 | 71 ± 1 | 53 ± 7 | 62 | | | | | | NT | NT |
| 12 | 2 | 7 ± 1 | 91 ± 8 | 72 ± 6 | 65 ± 4 | 70 | | | | | | NT | NT |
| 13 | 2 | 35 ± 23 | 64 ± 36 | 51 ± 50 | 83 ± 17 | 39 | | | | | | NT | NT |
| 14 | 2 | 14 ± 8 | 100 ± 0 | 61 ± 5 | 39 ± 16 | 50 | | | | | | NT | NT |
| 15 | 2 | 20 ± 5 | 82 ± 17 | 62 ± 15 | 49 ± 16 | 53 | 2 | 104 ± 1 | 141 ± 2 | 119 ± 2 | 103 ± 11 | slight | short |
| 16 | 2 | 6 ± 4 | 99 ± 1 | 45 ± 14 | 10 ± 9 | 35 | | | | | | NT | NT |
| 17 | 3 | 6 ± 7 | 92 ± 6 | 61 ± 29 | 61 ± 32 | 60 | 2 | 123 ± 13 | 155 ± 1 | 149 ± 16 | 151 ± 1 | slight | long |
| 18[f] | 6 | 13 ± 7 | 94 ± 2 | 80 ± 11 | 59 ± 14 | 71 | 4 | 110 ± 24 | 194 ± 26 | 172 ± 26 | 157 ± 17 | moderate | long |
| 19 | 3 | 1 ± 1 | 43 ± 24 | 16 ± 8 | 6 ± 4 | 13 | | | | | | NT | NT |
| 20 | 3 | 2 ± 2 | 51 ± 27 | 11 ± 6 | 7 ± 7 | 13 | | | | | | NT | NT |
| 21 | 4 | 11 ± 3 | 98 ± 2 | 65 ± 12 | 68 ± 7 | 66 | 2 | 111 ± 17 | 176 ± 19 | 152 ± 4 | 121 ± 11 | mod. | mod. |
| 22 | 2 | 5 ± 2 | 90 ± 7 | 68 ± 5 | 32 ± 5 | 53 | | | | | | NT | NT |
| 23 | 2 | 8 ± 8 | 97 ± 1 | 21 ± 3 | 8 ± 8 | 17 | | | | | | NT | NT |
| 24 | 2 | 21 ± 10 | 88 ± 6 | 52 ± 8 | 43 ± 8 | 42 | | | | | | NT | NT |
| 25 | 3 | 7 ± 7 | 62 ± 9 | 37 ± 31 | 67 ± 29 | 47 | | | | | | | |
| 26 | 2 | 32 ± 28 | 100 ± 0 | 50 ± 50 | 97[g] | 36 | 2[h] | 129 ± 10 | 154 ± 4 | 154 ± 36 | 131 ± 21 | slight | short |
| 27 | 4 | 14 ± 15 | 96 ± 5 | 87 ± 16 | 62 ± 44 | 80 | 2 | 84 ± 13 | 197 ± 3 | 145 ± 18 | 129 ± 6 | mod. | mod. |
| III[i] | 6 | 9 ± 3 | 89 ± 9 | 60 ± 16 | 16 ± 12 | 49 | | | | | | | |

[a] All doses administered over 5 min. [b] Values as mean ± SEM if three or more animals, values as mean ± SD if two animals. [c] Degree of tachycardia: severe—heart rate ≥200 beats/min, moderate (mod.)—heart rate 160–199 beats/min, slight—heart rate less than 160 beats/min after an increase of ≥20 beats/min, none—change in heart rate less than 20 beats/min. [d] Duration (effect sustained for): long—greater than 2 h, moderate (mod.)—0.5–2 h, short—less than 0.5 h. [e] NT denotes not tested. [f] Pirmenol. [g] One died. [h] Dosed at 2.5 mg/kg over 5 min. [i] Disopyramide.

mg/kg b.i.d. for 3 weeks in the dog.

Pirmenol is currently in phase 3 clinical trials. Electrophysiological studies[12] in isolated dog Purkinje fiber preparation demonstrated that at therapeutic concentrations pirmenol decreased action potential amplitude and upstroke velocity, accelerated repolarization, prolonged the effective refractory period, and decreased automaticity. It was of interest that the first two effects mentioned were independent of potassium concentration, which sets pirmenol apart from other common antiarrhythmic agents such as disopyramide, procainamide, and lidocaine. Pirmenol has a plasma half-life of about 8 h in man.[13] It is effective in refractory ventricular tachycardia, it terminates paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation, and it abolishes high frequency ventricular premature beats. In addition, pirmenol is well-tolerated and has a favorable safety profile, so it promises to be a useful agent for the treatment and prevention of a variety of cardiac arrhythmias.[14]

## 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 even where not reported the data agreed with the proposed structures. Analytical results are within ±0.4% unless otherwise noted.

***cis*-2,6-Dimethyl-α,α-diphenyl-1-piperidinebutanol Monohydrochloride (1).[15] Method A.** A mixture of 500 g of 4-chlorobutyrophenone, 225 g of ethylene glycol, 10 g of *p*-toluenesulfonic acid, and 1.5 L of benzene was heated at reflux under a water separator until water collection ceased. The resulting solution was cooled, neutralized with 10 mL of trimethylamine, and evaporated at reduced pressure to give 4-chlorobutyrophenone ethylene ketal suitable for use without further purification. The pure material boiled at 100–118 °C (0.1 mmHg) and melted at 57–59 °C.

4-Chlorobutyrophenone ethylene ketal (619 g), 700 g of *cis*-2,6-dimethylpiperidine, and 16 g of sodium iodide were stirred and heated at reflux for 48 h. The mixture was cooled, diluted with 1 L of anhydrous ether, and filtered to remove *cis*-2,6-dimethylpiperidine hydrochloride. The filter cake was washed with 1 L of ether, and the filtrate and washings were combined. The resulting ether solution was washed five times with 500-mL portions of water and then extracted with a solution of 300 mL of concentrated hydrochloric acid in 3 L of water. The acid extract was washed with 500 mL of ether and then heated to 70–80 °C and allowed to cool to room temperature over a period of 16 h. The resulting solution was made basic with 50% aqueous sodium hydroxide and the organic layer was separated. The aqueous layer was extracted with 500 mL of ether and the extract was combined with the organic layer. The combined extracts were washed several times with water, dried, and evaporated. The oily residue was distilled at reduced pressure to give 4-(2,6-dimethyl-1-piperidinyl)-1-phenyl-1-butanone; bp 138–141 °C (0.1 mmHg).

By the same procedure 1-phenyl-4-piperidinyl-1-butanone (72% yield; bp 100–117 °C at 0.05 mmHg) and 4-(2,5-dimethyl-1-pyrrolidinyl)-1-phenyl-1-butanone (68% yield; bp 125–130 °C at 0.05 mmHg) were obtained.

To 70 mL of THF was added with stirring under a nitrogen atmosphere 70 mL of a 2 M solution of phenyllithium in benzene–ether (70:30). The mixture was stirred while a solution of

(12) Reder, R. F.; Danilo, P.; Rosen, M. R. *Eur. J. Pharm.* **1980**, *61*, 321.
(13) Hammill, S. C.; Shand, D. G.; Routledge, P. A.; Hindman, M. C.; Baker, J. T.; Pritchett, E. L. C. *Circulation* **1982**, *65* (2), 369.
(14) Frick, M. H. *Am. J. Cardiol.* **1987**, *59*, No. 16, 56H.
(15) Fleming, R. W. U.S. Patent 4,031,101, 1977.

25.9 g of 4-(2,6-dimethyl-1-piperidinyl)-1-phenyl-1-butanone in 100 mL of THF was added dropwise over a period of 75 min. After the addition was complete, the mixture was stirred an additional 45 min, and then 15 mL of $H_2O$ was added slowly. The supernatant liquid was decanted from the precipitated solid and evaporated at reduced pressure. The residual oil was dissolved in 100 mL of petroleum ether and the solution was cooled to 0–5 °C to crystallize *cis*-2,6-dimethyl-α,α-diphenyl-1-piperidinebutanol, which was removed by filtration and recrystallized from petroleum ether: 20.9 g (62%); mp 90–91 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 1.28 (d, 6, $J$ = 7 Hz, $CH_3$) 1.4–2.1 (m, 8, aliphatics), 2.3–3.6 (m, 6, $CH_2$N(cycl CH)), 5.80 (s, 1, OH), 7.1–7.8 (m, 10, aromatics). The hydrochloride salt was prepared by dissolving 0.5 g of the free base in 5 mL of absolute EtOH, and 0.5 mL of *i*-PrOH saturated with HCl was added dropwise. Upon cooling, the product crystallized: mp 231–232 °C. Anal. ($C_{23}H_{31}NO$·HCl) C, H, N.

***cis*-2,6-Dimethyl-α-(2-methylphenyl)-α-phenyl-1-piperidinebutanol Monohydrochloride (17).** The Grignard reagent was prepared by warming 26.6 g (0.22 mol) of *o*-bromotoluene and 4.8 g (0.2 g atom) of magnesium turnings in 100 mL of anhydrous $Et_2O$ for 3 h. A solution of 34.8 g (0.13 mol) of 4-(2,6-dimethyl-1-piperidinyl)-1-phenyl-1-butanone in 100 mL of THF was added dropwise over 0.5 h. Internal reflux was maintained by gentle heating during the later part of the addition and continued for 16 h. After cooling, 20 mL of saturated $NH_4Cl$ solution was added and the solid inorganic material was removed by filtration and washed with 2 × 50 mL of $Et_2O$. The filtrates were combined and concentrated under reduced pressure. The residue was dissolved in 200 mL of 2 N HOAc and the resulting solution was extracted with 100 mL of $Et_2O$. The acidic solution was made strongly basic with 2 N NaOH solution, and the gummy free base which separated was dissolved in 400 mL of $Et_2O$, washed with $H_2O$, and dried over anhydrous $K_2CO_3$. After filtration, an excess of *i*-PrOH saturated with HCl was added to the filtrate and the solid hydrochloride salt separated. The solid was dissolved in 30 mL of absolute EtOH and diluted with 300 mL of $Et_2O$ and the product slowly precipitated on standing: 2.2 g (4.3%); mp 229–230 °C. The analytical sample was recrystallized from EtOH–$Et_2O$: mp 233–235 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 1.15 (d, 3, $J$ = 7 Hz, $CH_3$), 1.28 (d, 3, $J$ = 7 Hz, $CH_3$), 1.4–2.7 (m, 13, aliphatics), 2.8–3.5 (m, 4, $CH_2$N(cycl CH)), 5.6 (s, 1, OH), 7.0–7.5 (m, 9, aromatics). Anal. ($C_{24}H_{33}NO$·HCl·0.25$H_2O$) C, H, N.

***cis*-α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-phenyl-2-pyridinemethanol (18).** At −78 °C a solution of butyllithium (180 mL, 1.5 M) in heptane was added to 200 mL of THF. The mixture was stirred under $N_2$ while a solution of 43.0 g of 2-bromopyridine in 50 mL of THF was added over 2 h while the reaction temperature was maintained below −65 °C. After stirring for 1 h a solution of 65 g of 4-(2,6-dimethyl-1-piperidinyl)-1-phenyl-1-butanone in 70 mL of THF was added over a period of 20 min. The resulting reaction mixture was stirred at −65 to −75 °C for an additional 2 h and then allowed to warm to 0 °C, and then 10 mL of $H_2O$ was added dropwise. The supernatant organic layer was decanted from the precipitated solid and evaporated under reduced pressure to $^1/_3$ the original volume. The residue was poured into 2.5 L of cold water. The resulting precipitate was removed by filtration, washed with $H_2O$, and dried. Recrystallization from petroleum ether yielded 18: 79.9 g (82%); mp 70–71 °C. Anal. ($C_{22}H_{30}N_2O$) C, H, N.

The monohydrochloride salt of 18 was prepared by dissolving the free base in *i*-PrOH and adding an equivalent amount of a 10% solution of anhydrous hydrogen chloride in *i*-PrOH, followed by dilution with ether and filtration of the precipitated salt; mp 171–172 °C. Anal. ($C_{22}H_{30}N_2O$·HCl) C, H, N.

***cis*-2,5-Dimethyl-α,α-diphenyl-1-pyrrolidinebutanol Monohydrochloride (3).** Following the procedure used for 17 and starting with phenyl magnesium bromide and 4-(2,5-dimethyl-1-pyrrolidinyl)-1-phenyl-1-butanone yielded compound 3: 42% yield; mp 186–187 °C. Anal. ($C_{22}H_{29}NO$·HCl) C, H, N.

**α-[3-(1-Piperidinyl)propyl]-α-phenyl-2-pyridinemethanol Monohydrochloride (23).** Following the procedure used for preparing 18 and starting with 1-phenyl-4-(1-piperidinyl)-1-butanone gave compound 23: 72% yield; mp 207–208 °C. Anal. ($C_{20}H_{26}N_2O$·HCl) C, H, N.

***cis*-α-[3-(2,5-Dimethyl-1-pyrrolidinyl)propyl]-α-phenyl-2-pyridinemethanol (24).** Following the procedure used for preparing 18 and starting with 4-(2,5-dimethyl-1-pyrrolidinyl)-1-phenyl-1-butanone yielded compound 24: 72% yield; mp 66–67 °C. Anal. ($C_{21}H_{28}N_2O$·$H_2O$) C, H, N.

***cis*-α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-phenyl-4-pyridinemethanol (20). Method B.** To a stirred solution of 460 g of *cis*-2,6-dimethylpiperidine in 300 mL of xylene was added 278 g of 3-bromopropanol over a period of 15 min. The mixture was stirred and heated at reflux for 2 h and then allowed to cool while being stirred for 16 h. The mixture was filtered and the filtrate was evaporated at reduced pressure. The residue was distilled at reduced pressure to give *cis*-2,6-dimethyl-1-piperidinepropanol; bp 147–149 °C (25 mmHg).

*cis*-2,6-Dimethyl-1-piperidinepropanol (171 g) in 400 mL of benzene was cooled to 0–5 °C and 143 g of thionyl chloride was added dropwise over a period of 30 min. The mixture was then heated at reflux for 2 h, cooled, and diluted with 1 L of ether. The resulting precipitate was collected by filtration and melted at 173–174 °C after crystallization from *i*-$Pr_2O$. The free base was prepared by dissolving the hydrochloride in a minimum amount of water, cooled, and adding a slight excess of 50% aqueous sodium hydroxide. The liberated base was immediately extracted with several portions of benzene. The extracts were combined, dried, and evaporated to give the free base, *cis*-1-(3-chloropropyl)-2,6-dimethylpiperidine, which was used directly in the next step.

Sodium spheres (6.9 g, 0.3 g-atom) were dissolved in 250 mL of liquid $NH_3$. Then, a solution of 27.5 g (0.15 mol) of 4-benzoylpyridine in 100 mL of THF was added dropwise over 0.5 h, and the dark solution of the dianion was stirred for an additional 2 h. A solution of 28.5 g (0.15 mol) of 1-(3-chloropropyl)-2,6-dimethylpiperidine in 80 mL of THF was then added dropwise over 1 h and the reaction mixture was stirred for an additional 0.5 h. THF (125 mL) was added dropwise, the exterior cooling was removed, and the ammonia was allowed to evaporate. After stirring overnight, a light green solution with some solid material present was obtained which was poured into 300 mL of THF containing 50 mL of glacial acetic acid, and this was added to 500 mL of cold $H_2O$ with vigorous stirring. The aqueous layer was separated and extracted with 2 × 200 mL of $Et_2O$, and it was then made basic with 5 N $NH_4OH$ to yield a brown oil. This was dissolved in $Et_2O$ and the aqueous layer was extracted with 2 × 100 mL of $Et_2O$. The combined ether extracts were washed with water until neutral and dried over anhydrous $Na_2SO_4$. After concentrating under reduced pressure the resulting yellow gum was dissolved in hexane and a white solid (20) separated on cooling: yield 77%; mp 131.5–133.5 °C. The analytical sample was prepared by recrystallization from benzene–hexane (1:1): mp 132–133.5 °C; $^1$H NMR ($CDCl_3$) δ 1.10 (d, 6, $J$ = 7 Hz, $CH_3$), 1.2–1.8 (m, 8, aliphatics), 2.2–2.7 (m, 6, aliphatics), 7.1–7.6 (m, 7, aromatics and OH), 8.2–8.6 (m, 3, aromatics). Anal. ($C_{22}H_{30}N_2O$) C, H, N.

***cis*-α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-phenyl-3-pyridinemethanol Monohydrochloride (19).** The use of 3-benzoylpyridine in the above reaction sequence yielded 19 as a viscous yellow oil (yield 92%). The oil was dissolved in $Et_2O$ and an excess of 1 N HCl in *i*-PrOH was added and the solid hydrochloride salt separated and was purified by recrystallization from *i*-PrOH: yield 72%, mp 226–228 °C. Anal. ($C_{22}H_{30}N_2O$·HCl) C, H, N.

***cis*-α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-2-pyridinyl-2-pyridinemethanol Monohydrochloride (22).** Following the procedure used for 20 and starting with di-2-pyridinylmethanone gave compound 22: 70.7% yield; mp 191–192 °C. Anal. ($C_{21}H_{29}N_3O$·HCl) C, H, N.

***cis*-2,6-Dimethyl-α,α-diphenyl-1-piperidinepentanol (7). Method C.** Methyl 5-bromopentanoate (50 g, 0.256 mol) and 29.0 g (0.256 mol) of 2,6-dimethylpiperidine in 50 mL of xylene was heated at reflux for 5 h. The mixture was cooled and filtered and the precipitate was washed with $Et_2O$. The filtrate was concentrated under reduced pressure and the resulting brown oil was distilled, yielding methyl 5-(2,6-dimethyl-1-piperidinyl)pentanoate: 41.8 g (72%); bp 78–80 °C (0.2 mmHg).

Methyl 4-(2,6-dimethyl-1-piperidinyl)butanoate [64% yield; bp 79–81 °C (0.05 mmHg)], methyl 4-(2-ethyl-1-piperidinyl)butanoate [54% yield; bp 90–94 °C (5.0 mmHg)], methyl 3-(2,6-dimethyl-1-piperidinyl)propanoate [53% yield; bp 86–87 °C (2.2

mmHg)], and methyl (2,6-dimethyl-1-piperidinyl)acetate [75% yield; bp 91–94 °C (9 mmHg)] were also obtained by the method described above.

Phenyllithium was prepared by adding a solution of 31.6 g (0.2 mol) of bromobenzene in 85 mL of $Et_2O$ dropwise to a suspension of 2.94 g (0.42 g atom) of lithium ribbon in 60 mL of $Et_2O$ at room temperature. The solution was stirred for 0.5 h following the addition and cooled to 0 °C, and 20.9 g (0.09 mol) of methyl 5-(2,6-dimethyl-1-piperidinyl)pentanoate was added dropwise. The resulting mixture was poured into 600 mL of $H_2O$ and acidified to pH 6 with 3 N HOAc. The hydrobromide salt slowly separated from solution and was collected by filtration and dried: 31.6 g (82%); mp 233–234 °C from *i*-PrOH. The free base was obtained by suspending 12.0 g of the hydrobromide salt in 100 mL of $CHCL_3$ and adding 5 N $NH_4OH$. The chloroform solution was concentrated and the solid product was recrystallized from $Et_2O$ and then petroleum ether: 5.5 g (58.5%); mp 125–126 °C. Anal. ($C_{24}H_{33}NO$) C, H, N.

**α,α-Diphenyl-1-piperidinebutanol Monohydrochloride (2).** Following the procedure described for **7** and starting with methyl 4-(1-piperidinyl)butanoate, compound **2** was obtained: 74% yield; mp 90–91 °C (lit.[2] mp 104–105). The monohydrochloride was recrystallized from *i*-PrOH: mp 213–214 °C. Anal. ($C_{21}H_{27}NO$·HCl) C, H, N.

**2-Ethyl-α,α-diphenyl-1-piperidinebutanol Monohydrochloride (4).** Following the procedure described for **7** and starting with methyl 4-(2-ethyl-1-piperidinyl)butanoate yielded compound **4**: 66% yield; mp 127–129 °C. Anal. ($C_{23}H_{31}NO$·HCl) C, H,N.

***cis*-2,6-Dimethyl-α,α-diphenyl-1-piperidineethanol (5).** Following the method described for **7** and adding a solution of phenylmagnesium bromide to methyl 2,6-dimethyl-1-piperidineacetate yielded compound **5**: 23% yield; mp 139–141 °C. Anal. ($C_{21}H_{27}NO$) C, H, N.

***cis*-2,6-Dimethyl-α,α-diphenyl-1-piperidinepropanol Monohydrochloride (6).** Following the procedure used for **7** and starting with methyl 3-(2,6-dimethyl-1-piperidinyl)propanoate yielded compound **6**: 70% yield; mp 227–228 °C. Anal. ($C_{22}H_{29}NO$·HCl) C, H, N.

***cis*-2,6-Dimethyl-α,α-diphenyl-1-piperidinepentanenitrile Monohydrochloride Hemihydrate (9). Method D.** 3-Bromopropanol (278 g) was added to a stirred solution of 460 g of *cis*-2,6-dimethylpiperidine in 300 mL of xylene over a period of 15 min. The reaction mixture was heated at reflux for 2 h and allowed to cool with stirring for 16 h. The mixture was filtered, and the filtrate was washed with $H_2O$ and evaporated under reduced pressure. The residue was distilled, yielding *cis*-2,6-dimethyl-1-piperidinepropanol: bp 147–149 °C (25 mmHg).

A stirred solution of 171 g of *cis*-2,6-dimethyl-1-piperidinepropanol in 400 mL of benzene was cooled to 0–5 °C and 143 g of thionyl chloride was added dropwise over a period of 0.5 h. The mixture was heated at reflux for 2 h, cooled, and diluted with 1 L of ether. The resulting precipitate of *cis*-1-(3-chloropropyl)-2,6-dimethylpiperidine hydrochloride was collected by filtration and recrystallized from *i*-PrOH–$Et_2O$ (1:3): mp 173–174 °C. The free base was prepared as needed by dissolving the hydrochloride salt in $H_2O$ and adding a slight excess of 50% aqueous sodium hydroxide. The free base was extracted with several portions of benzene. The extracts were combined, dried, and evaporated to yield the free base.

A mixture of 90.0 g (0.47 mol) of diphenylacetonitrile, 98 g (0.48 mol) of 1-(3-chloropropyl)-2,6-dimethylpiperidine hydrochloride, and 100 g of KOH in 500 mL of 2-butanone was stirred at reflux for 24 h. After cooling, the brown solution was diluted with 500 mL of $Et_2O$ and filtered. The filtrate was extracted with 300 mL of 3 N acetic acid. The aqueous layer was made basic with aqueous NaOH, the oil which separated was extracted with $Et_2O$, and the organic layer was dried over anhydrous potassium carbonate. The solution was then treated with Norite, filtered, and saturated with hydrogen chloride gas. The product was removed by filtration, washed with $Et_2O$, and then triturated with hot ethyl acetate for 1 h and allowed to stand at room temperature overnight. The mixture was chilled and filtered to yield a beige powder which was dried in a vacuum oven: 122 g (68%); mp 178–179 °C. The analytic sample was recrystallized from *i*-PrOH to yield colorless crystals: mp 181–181.5 °C; $^1H$ NMR ($CDCl_3$) δ 1.40 (d, 6, $J$ = 7 Hz, $CH_3$), 1.5–3.5 (m, 14, aliphatics), 7.2–7.6 (m, 10, aromatics). Anal. ($C_{24}H_{30}N_2$·HCl·0.5$H_2O$) C, H, N.

***cis*-2,6-Dimethyl-α,α-diphenyl-1-piperidinepentanamide Monohydrochloride (10).** Compound **9** (12.0 g) was dissolved in 100 mL of 90% $H_2SO_4$ and warmed on a steam bath for 2 h. The resulting solution was chilled, diluted with 400 mL of $H_2O$, and made basic with 5 N NaOH. The gum which separated was taken up in $Et_2O$, washed with $H_2O$, and dried over $K_2CO_3$. A saturated solution of HCl in *i*-PrOH was added dropwise until no further precipitate was formed. The resulting gum was crystallized from *i*-PrOH, yielding 7.6 g of recovered starting material (mp 195–196 °C). The filtrate was concentrated and the second crop of crystals was recrystallized from EtOAc to yield **10**: 3.4 g (28%); mp 216–218 °C. Anal. ($C_{24}H_{32}N_2O$·HCl) C, H, N.

***cis*-2,6-Dimethyl-α,α-diphenyl-1-piperidinebutanenitrile Monohydrochloride (12).** Following the same procedure described for compound **9** and alkylating with 1-(2-chloroethyl)-2,6-dimethylpiperidine monohydrochloride yielded **12**: 64% yield; mp 229–230 °C. Anal. ($C_{23}H_{28}N_2$·HCl·0.25$H_2O$) C, H, N.

***cis*-2,6-Dimethyl-α,α-diphenyl-1-piperidinebutanamide Monohydrochloride (13).** Compound **12** (10.0 g) was dissolved in 100 mL of 90% $H_2SO_4$, and the solution was heated on a steam bath for 4 h. Water (400 mL) was added with cooling, and the resulting solution was made basic with 5 N NaOH. The gum which separated was taken up in $Et_2O$ and dried. Then a slight excess of HCl in *i*-PrOH was added and the gummy product was crystallized from *i*-PrOH–$Et_2O$ (1:2): 9.2 g (96%); mp 143–146 °C. Anal. ($C_{23}H_{30}N_2O$·HCl·0.5$H_2O$) C, H, N.

***cis*-2,6-Dimethyl-β,β-diphenyl-1-piperidinebutanamine (14).** Compound **12** (30.0 g, 0.09 mol) was dissolved in 200 mL of $Et_2O$ and the resulting solution was added dropwise to a stirred suspension of 76 g (0.2 mol) of lithium aluminum hydride in 50 mL of $Et_2O$ at a rate sufficient to maintain a gentle reflux. The reaction mixture was stirred at room temperature overnight and then refluxed for 8 h. The reaction mixture was then neutralized with aqueous NaOH. Removal of inorganic salts by filtration gave a colorless solution which was dried over $Na_2SO_4$. Removal of the solvent under reduced pressure yielded a yellowish solid: 27.2 g (89%); mp 73–77 °C. This was further purified by vacuum distillation to yield a viscous oil: bp 183–188 °C (0.5 mmHg). This was dissolved in ether and the solvent was slowly removed under reduced pressure to yield a white solid: 24.3 g; mp 73–74 °C; $^1H$ NMR ($CDCl_3$) δ 0.87 (d, 6, $J$ = 7 Hz, $CH_3$), 1.0–1.9 (m, 8, aliphatics), 2.0–3.0 (m, 8, $CH_2NH_2$ and $CH_2N$(cycl $CH$)), 7.1–7.4 (m, 10, aromatics and $NH_2$). Anal. ($C_{23}H_{32}N_2$·0.25$H_2O$) C, H, N.

***N*-[4-(2,6-Dimethyl-1-piperidinyl)-2,2-diphenylbutyl]-acetamide (15).** Compound **14** (8.4 g) and 2.5 g of acetic anhydride were mixed with 10 mL of benzene and heated on the steam bath for 1 h. The solution was cooled and 50 mL of petroleum ether was added. The resulting precipitate was collected by filtration and then dissolved in $H_2O$. The pH of the solution was adjusted to 10 and the solid which separated was removed by filtration and dried in a vacuum oven: 8.6 g (92%); mp 174–175 °C. Anal. ($C_{25}H_{34}N_2O$) C, H, N.

***N*-[5-(2,6-Dimethyl-1-piperidinyl)-2,2-diphenylpentyl]-acetamide Monohydrochloride (11).** By following the procedure described for **14** compound **9** was reduced and then acetylated and converted to the hydrochloride: 50% yield; mp 248–249 °C. Anal. ($C_{26}H_{36}N_2O$·HCl) C, H, N.

***cis*-2-[4-(2,6-Dimethyl-1-piperidinyl)-1-phenylbutyl]-pyridine Monohydrochloride (25).** Following the procedure described for **9** and starting with 2-benzylpyridine and *n*-butyllithium gave compound **25**: 58% yield; mp 173–173.5 °C. Anal. ($C_{22}H_{30}N_2$·HCl·0.1$H_2O$) C, H, N.

**α-[3-(2,6-Dimethyl-1-piperidinyl)propyl]-α-phenyl-2-pyridineacetonitrile (26).** Following the procedure described for **9** and starting with α-phenyl-2-pyridineacetonitrile gave compound **26**: 67% yield; mp 72–74 °C. Anal. ($C_{23}H_{29}N_3$) C, H, N.

***cis*-α-Cyclohexyl-2,6-dimethyl-α-phenyl-1-piperidinebutanol Monohydrochloride (21).** To a solution of 4.86 g of the hydrochloride salt of compound **1** in 100 mL of glacial HOAc was added 0.5 g of $PtO_2$ and the mixture was shaken in an atmosphere of $H_2$ until the theoretical amount had been taken up (2.5 h). The mixture was filtered and the filtrate was concentrated to 50 mL, and 150 mL of $H_2O$ was added. The resulting solution

was made basic with NaOH, and the gummy product which separated was taken up in $Et_2O$. This solution was washed with $H_2O$ and after drying over $K_2CO_3$ an excess of 2 N HCl in *i*-PrOH was added. The solid product (**21**) was removed by filtration and purified by recrystallization from acetone: 1.7 g (34%); mp 205–206 °C. Anal. ($C_{23}H_{37}NO\cdot HCl\cdot 0.25H_2O$) C, H, N.

***cis*-1-(4,4-Diphenylbutyl)-2,6-dimethylpiperidine Monohydrochloride (8). Method E.** Compound 1 (12.0 g) was dissolved in 200 mL of 2 N HCl and warmed on a hot plate for 36 h. The solution was cooled and made strongly basic with NaOH and the viscous product that separated was taken up in $Et_2O$ and dried over $K_2CO_3$. The addition of 2 N HCl in *i*-PrOH yielded the gummy hydrochloride. The supernatent was decanted and the insoluble salts were recrystallized from absolute EtOH, yielding two fractions. The second crop (6.3 g) was primarily starting material. The first crop (3.8 g; mp 190–202 °C) was purified by three recrystallizations from EtOH to yield pure 1-(4,4-diphenyl-3-butenyl)-2,6-dimethylpiperidine monohydrochloride (**28**): 2.0 g (18%); mp 220–221 °C. Anal. ($C_{23}H_{29}N\cdot HCl$) C, H, N.

Compound **28** (4.7 g) was dissolved in 100 of MeOH, 1 g of palladium on carbon (20%) was added, and the mixture was shaken in an atmosphere of $H_2$ for 24 h on a low-pressure hydrogenation apparatus. Filtration followed by concentration on a rotary evaporator yielded a gum which was crystallized from *i*-PrOH–$Et_2O$ (1:2) to give **8**: 3.0 g (64%); mp 177–178 °C. Anal. ($C_{23}H_{31}N\cdot HCl$) C, H, N.

***cis*-2,6-Dimethyl-α-phenyl-1-piperidinebutanol Monohydrochloride (16).** A solution of 13.0 g (0.05 mol) of 4-(2,6-dimethyl-1-piperidinyl)-1-phenyl-1-butanone in 80 mL of anhydrous $Et_2O$ was added dropwise to a suspension of 2.1 g (0.05 mol) of lithium aluminum hydride in 25 mL of anhydrous $Et_2O$. The reaction mixture was stirred at room temperature for 4 h and then cooled and neutralized with aqueous NaOH. The insoluble material was removed by filtration, and the filtrate was diluted to 400 mL by adding $Et_2O$. A solution of HCl in *i*-PrOH was added and the resulting solid was collected by filtration and recrystallized from *i*-PrOH to yield **16**: 5.9 g (50%); mp 149–150 °C. Anal. ($C_{17}H_{17}NO\cdot HCl$) C, H, N.

# Long-Acting Dihydropyridine Calcium Antagonists. 6. Structure–Activity Relationships around 4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-2-[(2-hydroxyethoxy)methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine

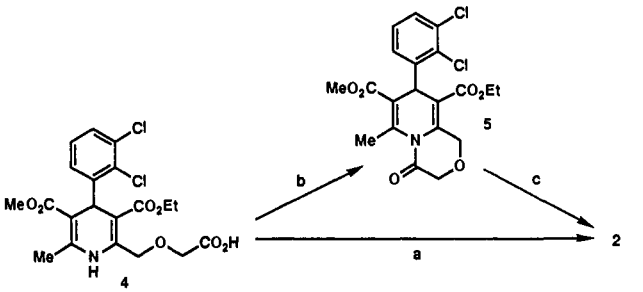
David Alker,* Simon F. Campbell, and Peter E. Cross

*Pfizer Central Research, Sandwich, Kent CT13 9NJ, United Kingdom.* *Received April 4, 1990*

The preparation of 4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-2-[(2-hydroxyethoxy)methyl]-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridine (**2**) is described, and its potent calcium antagonist activity on rat aorta ($IC_{50} = 4 \times 10^{-9}$ M) and marked tissue selectivity in vitro for vascular smooth muscle over cardiac smooth muscle are established. In order to exploit the excellent in vitro profile of compound **2**, a range of analogues were prepared but none were found to have superior calcium antagonist potency and tissue selectivity. Compound **2** has excellent in vivo activity in the anesthetized dog ($ED_{50}$ = 12 μg/kg for reduction of CVR) and a plasma half-life in the conscious dog of 7.2 h. The pharmacokinetic parameters of **2** are compared to those determined for the structurally related compounds amlodipine and felodipine. The plasma clearance for **2** (9.6 mL/min/kg) is similar to that of amlodipine and is consistent with the extended 2-substituent hindering approach to the cytochrome P-450 enzyme responsible for oxidation of the DHP ring to the corresponding pyridine.

We have recently reported[1] the synthesis of a series of novel 1,4-dihydropyridine (DHP) calcium antagonists that contain a basic side chain on the 2-position of the DHP ring. The aim of this program was to modify the physicochemical properties of the DHP 2-substituent in order to improve bioavailability and duration of action over existing agents. From this work we identified amlodipine (**1**), which fulfilled these objectives and which has recently been approved for the treatment of angina and hypertension. We have subsequently reported[2-5] that the presence of a basic center in the substituent on the 2-position of the DHP ring is not an absolute requirement for either calcium antagonist activity or selectivity for vascular over cardiac tissue. For example, DHPs in which the alkoxymethyl group in the 2-position is substituted by heterocycles[2-4] or polar functionality such as ureas or glycinamides[5] are also potent, selective calcium antagonists. Even so, the overall pharmacological and pharmacokinetic profile displayed by amlodipine has so far proved unique when compared to these diverse structural analogues. Thus, we have now replaced the amino function in amlodipine by a hydroxy group **2** since we expected that the similar steric demands and hydrogen-bonding capabilities of these bioisosteres might be reflected in similar biological activities. In addition, we have synthesized a range of analogues related to **2** in an attempt to optimize the calcium antagonist potency and selectivity in this series.

**Scheme I**[a]




[a] Reagents: (a) $BH_3$·THF; (b) CDI/4-methylmorpholine/THF; (c) $NaBH_4$/EtOH.

## Chemistry

The synthetic routes to the compounds listed in Table I are outlined in Schemes I–III. Direct reduction of the known[3] DHP acid **4** with $BH_3$·THF gave the alcohol **2** in only 13% yield and an alternative approach, which was higher yielding and more amenable to large-scale synthesis,

(1) Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Stubbs, J. K.; Burges, R. A.; Gardiner, D. G.; Blackburn, K. J. *J. Med. Chem.* **1986**, *29*, 1696.
(2) Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 562.
(3) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 2381.
(4) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1990**, *33*, 1805.
(5) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1990**, *33*, 585.

0022-2623/91/1834-0019$02.50/0 © 1991 American Chemical Society