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Relationship of Nonspecific Antiarrhythmic and Negative Inotropic Activity with Physicochemical Parameters of Propranolol Analogues

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In an attempt to separate the nonspecific antiarrhythmic activity of propranolol from its negative inotropic effects, analogues containing hydrophilic and lipophilic substituents on the nitrogen and on the naphthyl ring were prepared and tested in an isolated tissue preparation. Though it had been predicted that analogues containing a very hydrophilic group on the nitrogen would have the highest antiarrhythmic/negative inotropic effect ratio, it was found that both effects increased identically when the lipophilicity of either the nitrogen or ring substituent was increased.

Compounds can exhibit antiarrhythmic activity by a variety of different mechanisms.[1] A number of compounds have antiarrhythmic activity associated with membrane stabilizing properties, and these are often referred to as nonspecific in their action and include such drugs as quinidine, procainamide, lidocaine, and propranolol in high doses.[2,3] These compounds are thought to exert their antiarrhythmic action by altering the physicochemical properties of the lipid bilayer of the cardiac sarcolemma, thereby interfering with the operation of the ion channel through which depolarizing current flows.[1]

With regard to the structure–activity relationships of the nonspecific antiarrhythmic agents, most of the compounds contain a secondary or tertiary amine group that is separated by two or three carbons from a second group that is capable of hydrogen bonding (e.g., alcohol, ester, and amide).[2] There is also a lipophilic aromatic group adjacent to the hydrogen-bonding group. It is thought that the lipophilic aromatic ring penetrates into the bilayer of the cell membrane, thereby altering its physicochemical properties, while the protonated nitrogen interacts with some polar group at the exterior of the membrane, possibly displacing calcium ion.[2] The net result of these interactions is to decrease the conductance of the membrane to depolarizing ions.

In addition to antiarrhythmic activity, these compounds also decrease cardiac contractility. There is some evidence to indicate that at least a part of the negative inotropic activity is due to intracellular events.[4,5] Besch and Watanabe[5] suggested that the decrease in contractility produced by nonspecific antiarrhythmic agents was due to depletion of calcium stores in the cardiac sarcoplasmic reticulum. However, Langer[6] suggested that the sarcoplasmic reticulum served only as a mechanism for removal of calcium ions after the contractile process. He proposed a carrier for calcium in the sarcolemma as the source of contractile calcium ions.

Therefore, while it is generally accepted that the site of action for nonspecific antiarrhythmic activity is at the external surface of the cardiac cell membrane, there is considerable disagreement as to the site of action for the negative inotropic activity. If the antiarrhythmic and negative inotropic activities are due to separate mechanisms, it should be possible to separate the two activities and synthesize antiarrhythmic agents devoid of negative inotropic actions. Baird and Hardman[7] found a direct correlation between the concentration of nonionized procaine and negative inotropic activity in the isolated turtle heart ventricle. Procaine ethochloride, a quaternary salt, exhibited the same qualitative effects on conduction time as did procaine, but the quaternary salt lacked negative inotropic activity. This appears to support the contention that the ability to cross the sarcolemma is important in determining the effect on contractility.

Hellenbrecht et al.[8] demonstrated that, for a series of β-adrenergic blocking agents, the ability to alter myocardial conduction velocity could be correlated with physicochemical parameters such as hydrophobicity (log P) and surface activity. The compounds tested were ring-substituted compounds and it was demonstrated that increasing the polarity of the aromatic ring decreased the effect on conduction velocity. In a further study, Hellenbrecht et al.[9] evaluated the effect of two series of β-adrenergic blockers on conduction velocity in the frog heart and cardiac contractility in an in vivo cat preparation. The compounds studied were both ring-substituted (alkyl substituents) and N-substituted (alkyl substituents) and encompassed a wide range of hydrophobicities. They found that both conduction velocity and contractility could be linearly correlated with the hydrophobicity of the

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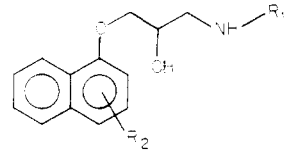
Table I. Correlation of Biological Activity with Physical Properties

compd[f]	R_1	R_2	$-\log ED_{30}$ (MDF)[a]	$-\log ED_{40}$ (contractility)[b]	selectivity index[c]	log P
1	$CH(CH_3)_2$	2,4-Br_2	5.10 ± 0.15[d]	5.53 ± 0.04[d]	0.4 ± 0.1[d]	2.71 ± 0.01[d]
2	$CH(CH_3)_2$	4-Cl	5.20 ± 0.06	5.26 ± 0.12	0.9 ± 0.4	2.00 ± 0.01
3	$CH(CH_3)_2$	H	5.43 ± 0.07	5.21 ± 0.10	1.7 ± 0.2	1.08 ± 0.01
4	$CH(CH_3)_2$	4-OH	4.60 ± 0.03	4.39 ± 0.20	1.8 ± 0.8	0.39 ± 0.01
5	$CH(CH_3)_2$	4-NH_2	5.02 ± 0.12	4.92 ± 0.20	1.6 ± 0.6	−0.27 ± 0.02
6	$CH(CH_3)_2$	4-SO_2NH_2	3.58 ± 0.10	3.35 ± 0.02	1.7 ± 0.5	−0.51 ± 0.02
7	$(CH_2)_2CH_3$	H	5.64 ± 0.08	5.38 ± 0.08	1.8 ± 0.2	2.08 ± 0.02
8	$(CH_2)_3OCH_3$	H	5.45 ± 0.15	5.40 ± 0.26	1.5 ± 1.5	1.28 ± 0.01
9	$(CH_2)_3NH_2$	H	4.50 ± 0.10	4.47 ± 0.04	1.0 ± 0.2	−0.19 ± 0.01
10	$(CH_2)_3CONH_2$	H	4.89[e] ± 0.10	4.79[e] ± 0.06	1.4[e] ± 0.5	0.31 ± 0.09
11	$(CH_2)_3CO_2H$	H	3.41 ± 0.28	3.02 ± 0.24	2.0 ± 0.9	0.21 ± 0.01
12	$(CH_2)_3N^+(CH_3)_3Cl^-$	H	3.08 ± 0.16	3.06 ± 0.06	1.1 ± 0.3	−1.89 ± 0.09

[a] Negative log of the molar drug concentration necessary to reduce the maximum driving frequency 40%. [b] Negative log of the molar drug concentration necessary to reduce the tissue contractility 40%. [c] ED_{30} (contractility)/ED_{30} (MDF). [d] Standard deviation. [e] Tissue bath contained 4×10^{-8} M propranolol to suppress weak adrenergic agonist activity observed in a few of the tissue preparations. [f] See Table II for structure.

Table II. Statistical Analysis of Biological Activity



$\log (1/ED) = \alpha \log P + \beta (\log P)^2 + \gamma$

series	biological act.	α	β	γ	r	N
R_1	MDF[a]	0.70 ± 0.18[b]		4.34 ± 0.56	0.869[c]	7
R_2	MDF	0.33 ± 0.20		4.53 ± 0.58	0.626	6
R_2	MDF	0.94 ± 0.49	0.29 ± 0.21	4.60 ± 0.53	0.787	6
R_1	contractility	0.65 ± 0.22		4.21 ± 0.68	0.801	7
R_2	contractility	0.49 ± 0.19		4.33 ± 0.55	0.787	6
R_1, R_2	rate[d]	0.57 ± 0.16		4.11 ± 0.69	0.745	12
R_1, R_2[e]	rate	0.52 ± 0.08		4.30 ± 0.33	0.913	11

[a] MDF = maximum driving frequency. [b] Standard error. [c] Correlation coefficient. [d] Percent decrease in spontaneous rate. [e] Same series as above, but the zwitterionic carboxylic acid 11 was omitted.

molecule. They concluded that the hydrophobicity of the entire molecule was more important that the hydrophobicity of either the aromatic ring of the N substituent individually. However, only hydrophobic alkyl N substituents were tested and the effect of very polar substituents was not studied.

Assuming that the negative inotropic effect of nonspecific agents is due to an intracellular event and that the antiarrhythmic activity is due to an effect at the extracellular membrane surface, one should be able to synthesize a compound with decreased negative inotropic activity while maintaining the antiarrhythmic activity by maintaining the lipophilicity of the aromatic portion of the molecule buried in the lipid bilayer membrane while increasing the polarity of the N substituent that is at the aqueous interface. This would allow the aromatic portion of the molecule to interact with the lipid bilayer while decreasing the ability of the compound to partition across the membrane and exert intracellular effects.

To investigate this hypothesis, we chose to synthesize two series of propranolol analogues (Table I). In one series, the polarity of the N substituent was varied, while in the other series the polarity of the aromatic ring was varied. The ability of the compounds to reduce the maximum driving frequency of the isolated rabbit atrium was used as a measure of the nonspecific antiarrhythmic activity, while the negative inotropic activity was determined from the effect on contractility in the same preparation.

Chemistry. These compounds were synthesized by the route described by Crowther and Smith.[19] The appropriately substituted naphthol was reacted with epichlorohydrin, followed by isopropylamine, to synthesize the ring-substituted series. The N-substituted series was synthesized by reacting the appropriate amine with 1,2-epoxy-3-(1-naphthoxy)propane.

Results and Discussion

Assuming that the site of action for nonspecific antiarrhythmic activity is at the outer membrane surface and the negative inotropic activity is within the cytoplasm, one would expect to find different slopes for plots of log P vs. biological activity for the N-substituted series. That is, since the lipophilicity of the aromatic ring, which must interact with the cell membrane, remains constant, the nonspecific antiarrhythmic activity should not vary greatly with log P for the entire molecule. This is based on the assumption that the N substituent simply protrudes into the extracellular fluid and has little effect on the interaction of the molecule with the membrane. Therefore, for a plot of antiarrhythmic activity vs. log P, the slope should be relatively small.

On the other hand, one would expect the negative inotropic activity to show a more pronounced dependence on lipophilicity as the molecule must cross the cell membrane in order to reach cytoplasmic sites of action. Therefore, a plot of log P vs. negative inotropic activity for the N-substituted series should have a slope greater than that for antiarrhythmic activity.

As can be seen from Figures 1 and 2, the slopes of the two plots were not significantly different (0.70 ± 0.18 vs. 0.65 ± 0.22). With the exception of the zwitterionic

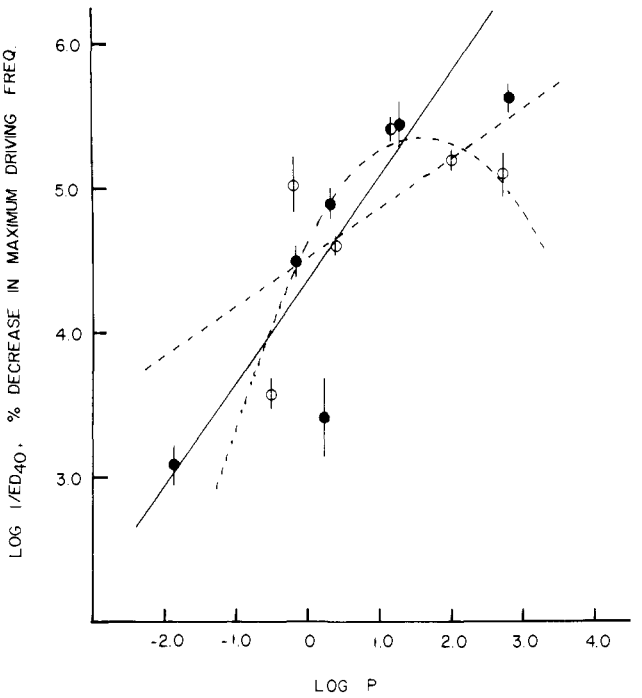


Figure 1. Correlation between antiarrhythmic activity and drug lipophilicity: N-substituted series (—●—) and ring-substituted series (— —○— —) with linear and parabolic regression models. Vertical bars indicate standard deviations.

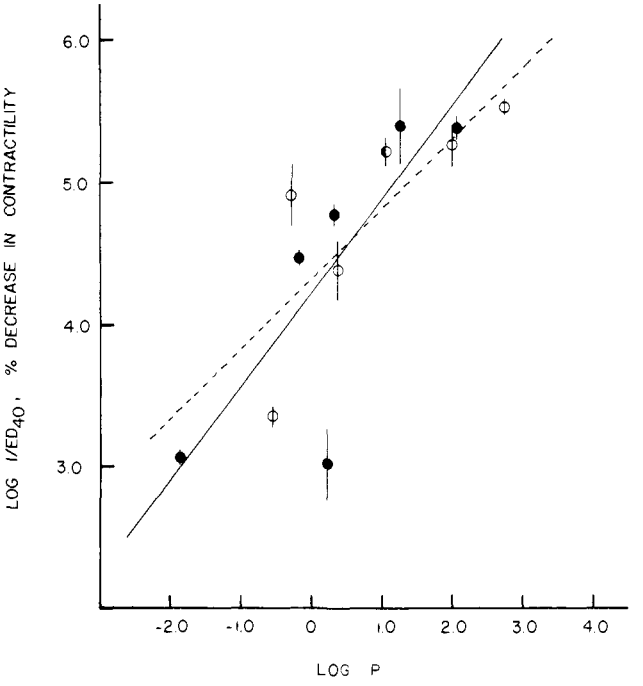


Figure 2. Correlation between negative inotropic activity and drug lipophilicity: N-substituted series (—●—), ring-substituted series (— —○— —).

carboxyl analogue, correlation of both types of activity has the same lipophilic requirements for either reaching or interacting with the site of action.

For the ring-substituted series, the antiarrhythmic activity was found to have a slightly better data fit using a parabolic rather than a linear model (Table II). Though the correlation coefficient and the standard error of the estimate was smaller when the parabolic model was used, because of the lack of compounds in the very lipophilic region (log P = 4) and the limited number of compounds in general, there was not a strong justification for the more

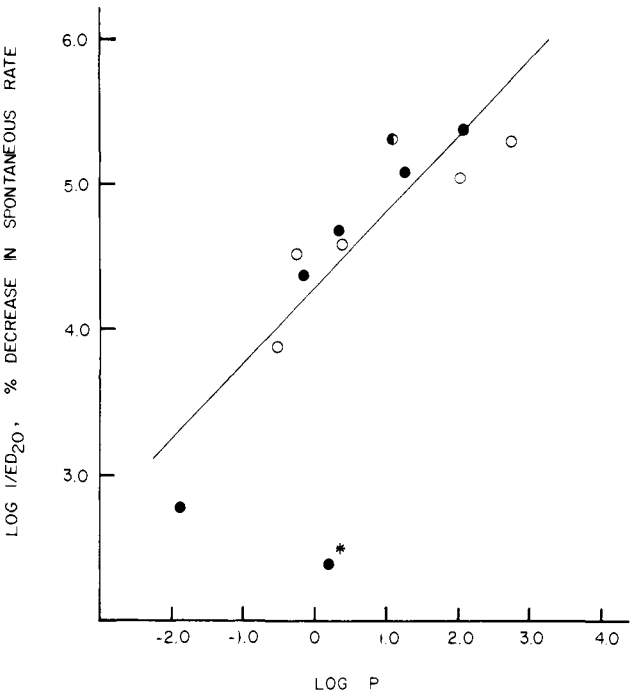


Figure 3. Correlation between negative chronotropic activity and drug lipophilicity: N-substituted series (—●—), ring-substituted series (— —○— —). The asterisk indicates that the zwitterionic derivative 11 was omitted from the regression.

complex model. However, Hellenbrecht et al.[9] had demonstrated that for a large series of ring-substituted β-adrenergic blockers, the nonspecific depressant activity was best correlated with a parabolic model.

From the hypothesis of this study, one would have expected that the antiarrhythmic activity and the negative inotropic activity would show nearly identical dependencies on the lipophilicity of the aromatic portion of the molecule. Indeed, it was observed that the slopes of the curves were not significantly different for both types of activity in the ring-substituted series (Table II).

The effect of the lipophilicity of the substituent on the spontaneous rate of tissue preparation was nearly identical for both the N-substituted and ring-substituted series (Figure 3). Since the drug concentrations used were considerably higher than needed for β-blockage, it would appear that the observed relationship between the slowing of the heart rate and the lipophilicity of the compound is also nonspecific in nature. As in the other biological tests, the zwitterionic carboxylic analogue 11 was considerably less active than expected.

In conclusion, the data presented do not support the hypothesis that the site for negative inotropic activity is behind a lipid barrier while the site for nonspecific antiarrhythmic activity is at the cell surface. Whereas one would have expected the antiarrhythmic activity of the N-substituted series to exhibit a much smaller dependence on lipophilicity than inotropic activity, both activities showed essentially the same dependence. It is possible that the difference in lipophilicity which would reflect the action of the drug at the extracellular site of the cell membrane as opposed to an intracellular site is obscured by the lipophilic requirements for penetrating the tissue mass in the test preparation. Otherwise the data seem to indicate that the site of action for both types of activity is extracellular or that a hydrophobic N-alkyl group is essential for both types of activity. Regardless of the site of action it appears that the selectivity of the drug for nonspecific antiarrhythmic activity relative to negative inotropic activity cannot be improved simply by placing

a polar group on the N substituent.

Experimental Section

A. Synthesis. Melting points were obtained on a Mel-Temp apparatus and are corrected. IR data were recorded on a Beckman IR-33 spectrophotometer, UV data on a Beckman Acta III spectrophotometer, and NMR data on a Jeolco C-60-HL spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Mass spectral data were obtained on a Du Pont Model 21-492 mass spectrometer. Samples of propranolol were graciously provided by Henry L. LeMien, Jr., of Ayerst Laboratories.

1,2-Epoxy-3-(1-naphthoxy)propane (13). This was synthesized as described by Kurinara et al.[11] A mixture of 14.4 g (0.10 mol) of 1-naphthol, 13.0 g (0.14 mol) of epichlorohydrin, 40 mL of dioxane, 4.9 g (0.12 mol) of NaOH, and 10 mL of H_2O was heated at reflux for 2.5 h. The cooled reaction mixture was poured into 100 mL of benzene and allowed to stand overnight at room temperature. The benzene was separated and the aqueous layer was extracted with 350 mL of Et_2O in six portions. The organic extracts were combined and dried ($MgSO_4$). After removal of the drying agent the solvent was evaporated in vacuo. Distillation gave 10.6 g (53%) of the desired product: bp 118–122 °C (0.25 mm) [lit.[11] bp 140 °C (0.2 mm)]; n^{24}_D 1.6112 (lit.[12] n^{20}_D 1.6140).

Compounds **2**, **4**, **7**, and **8** were synthesized as described by Crowther and Smith,[10] and melting points were in agreement with the literature values.

1-[(3-Aminopropyl)amino]-3-(1-naphthoxy)-2-propanol Hydrochloride (9). To 37.0 g (0.50 mol) of 1,3-diaminopropane was added 5.0 g (25 mmol) of **13** in 10 mL of Et_2O with stirring. The solution was heated on a steam bath for 1.5 h and cooled, and the excess 1,3-diaminopropane was removed by azeotropic distillation with toluene in vacuo. The residue was crystallized from Et_2O–EtOH to give 3.0 g (44%) of white crystals: mp 71–74 °C. A portion of this was dissolved in Et_2O–EtOH and ethereal HCl was added to neutrality. The precipitate was collected by filtration and recrystallized from Et_2O–EtOH to give the monohydrochloride: mp 133–134 °C; NMR (base, $CDCl_3$) δ 1.65 ($CH_2CH_2CH_2$, 2, m), 2.8 ($CH_2NCH_2CH_2CH_2N$, 6, m), 4.2 (OCH_2CHOH, 3, m), 6.7–8.5 (naphthyl, 7, m); mass spectrum (70 eV) m/e (rel intensity) 274 (1), 186 (5), 144 (28), 113 (46), 87 (100). Anal. ($C_{16}H_{23}ClN_2O_2$) C, H, N.

4-(Benzyloxycarbonylamino)butyramide (14). 4-(Benzyloxycarbonylamino)butyric acid was synthesized from 4-aminobutyric acid and benzyl chloroformate by a general procedure for protecting the amino group of amino acids.[13] This was used in the synthesis of compound **14** as follows. To 5.0 g (21 mmol) of 4-(benzyloxycarbonylamino)butyric acid in 100 mL of dry benzene was added 5.0 g (42 mmol) of oxalyl chloride at room temperature over a period of 15 min. The solution was then refluxed for 1 h and cooled, and the solvent was removed in vacuo. Additional quantities of dry benzene were added and evaporated to remove excess oxalyl chloride. To the yellow residue containing the acid chloride was added 75 mL of NH_4OH (sp gr 0.88) and the suspension was stirred at room temperature for 20 min. The mixture was extracted with CH_2Cl_2 (4 × 100 mL), and the organic layer was separated, filtered through anhydrous $MgSO_4$, and evaporated in vacuo. The white solid that resulted was slurried with petroleum ether and collected by filtration to give 3.0 g (60%) of product: mp 125–128 °C; IR (KBr) 1695 (carbamate C=O) and 1655 cm^{-1} (amide C=O). This was used without further purification.

4-Aminobutyramide Hydrobromide (15). Synthesis of **15** by the action of liquid ammonia on esters of 4-aminobutyric acid as described by Jako'biec[14] was unsuccessful, resulting chiefly in the formation of 2-pyrrolidinone. It was, however, synthesized readily from 4-(benzyloxycarbonylamino)butyramide (**14**). To 30 mL of HBr in AcOH (ca. 11%) was added 3.0 g (12 mmol) of **14** and the solution was stirred for 30 min at room temperature. The mixture was then poured into absolute Et_2O and collected by filtration, yielding a white hygroscopic solid. This was slurried with dry benzene and the benzene was evaporated in vacuo. This was repeated several times to aid in removing excess HBr. The product was recrystallized from *i*-PrOH to give 2.0 g (90%) of white needles: mp 127–129 °C (lit.[14] 126–128 °C); IR (KBr) 1675 cm^{-1} (amide C=O).

4-[[3-(1-Naphthoxy)-2-hydroxypropyl]amino]butyramide Hydrochloride (10). To 4.0 g (22 mmol) of 4-aminobutyramide hydrobromide (**15**) in 100 mL of dioxane–H_2O (3:1) was added 1.8 g (11 mmol) of $K_2CO_3 \cdot 1.5H_2O$ and 2.2 g (11 mmol) of 1,2-epoxy-3-(1-naphthoxy)propane (**13**). The mixture was refluxed 2.5 h, the solvent was evaporated in vacuo, and the product was slurried with H_2O and extracted with CH_2Cl_2. The organic layer was filtered through anhydrous $MgSO_4$ and evaporated in vacuo to give 1.8 g (54%) of the free base. This was converted to the HCl salt by dissolving in a small amount of methanolic HCl and evaporating the solvent to dryness in vacuo. The HCl salt was recrystallized from *i*-PrOH–H_2O to give white crystals: mp 192–194 °C; IR (KBr) 1670 cm^{-1} (amide C=O); NMR (base, CD_3OD) δ 1.8 ($CH_2CH_2CH_2$, 2, m), 2.2 (CH_2CONH_2, 2, br t), 2.7 ($NHCH_2$, 2, t), 2.85 (CH_2NH, 2, d), 4.2 (OCH_2CHOH, 3, m), 6.8–8.5 (naphthyl, 7, m); mass spectrum (70 eV) m/e (rel intensity) 302 (1), 285 (4), 142 (100). Anal. ($C_{17}H_{23}ClN_2O_3$) C, H, N.

4-[[3-(1-Naphthoxy)-2-hydroxypropyl]amino]butyric Acid Hydrochloride (11). To 5.0 g (48 mmol) of 4-aminobutyric acid in 80 mL of dioxane–H_2O (3:1) was added 1.9 g (48 mmol) of NaOH in 5 mL of H_2O. To this was added 5.0 g (25 mmol) of 1,2-epoxy-3-(1-naphthoxy)propane (**13**) in 10 mL of dioxane with stirring, and the mixture was refluxed 5 h. To the cooled mixture was added 100 mL of H_2O, and the solution was extracted with Et_2O to remove any excess **13**. The solution was acidified with excess concentrated HCl and allowed to stand overnight. The product crystallized upon standing, was collected by filtration, and recrystallized from EtOH to give 3.0 g (39%) of product: mp 185–187 °C; IR (KBr) 1715 cm^{-1} (acid C=O); NMR (CD_3OD) δ 2.05 ($CH_2CH_2CH_2$, 2, m), 2.5 (CH_2CO_2H, 2, m), 3.2 (CH_2NCH_2, 4, m), 4.25 (OCH_2CHOH, 3, m), 6.8–8.5 (naphthyl, 7, m); mass spectrum (70 eV) m/e (rel intensity) 285 (4), 144 (18), 98 (100). Anal. ($C_{17}H_{22}ClNO_4 \cdot 0.5H_2O$) C, H, N.

[3-[3-(1-Naphthoxy)-2-hydroxy-1-propylammonio]-1-propyl]trimethylammonium Dichloride (12). 3-(Trimethylammonio)-1-propylammonium dichloride (**16**) was synthesized as described by Price et al.[15] To 4.0 g (20 mmol) of **16** in 50 mL of absolute EtOH was added 1.4 g (20 mmol) of NaOEt in 25 mL of absolute EtOH. The NaCl formed was removed by centrifuging and decanting. To the solution was added 4.0 g (20 mmol) of 1,2-epoxy-3-(1-naphthoxy)propane (**13**), and the solution was refluxed 48 h. The solvent was removed in vacuo and the resulting gum was slurried with 1 N HCl. This was extracted with Et_2O to remove any remaining **13**. The aqueous layer was separated and evaporated to dryness in vacuo and the residue was dissolved in a minimum quantity of $CHCl_3$–CH_3OH (4:1). This was placed on a column (20 × 1000 mm, silica gel, Davison Chemical Co.) and eluted with $CHCl_3$–CH_3OH (4:1). After removal of the solvent and recrystallization of the residue from cold absolute EtOH, 150 mg (2%) of hygroscopic white crystals was obtained: mp 150–152 °C; NMR (D_2O) δ 2.5–3.0 ($CH_2CH_2CH_2$, 2, m), 3.4–4.0 [$CH_2NCH_2CH_2CH_2N(CH_3)_3$, 6, m], 3.6 [$N(CH_3)_3$, 9, s], 4.55 ($OCH_2CHOH$, 3, m), 7.0–8.8 (naphthyl, 7, m); mass spectrum (70 eV) m/e (rel intensity) 303 (1), 257 (2), 243 (3), 230 (3), 141 (100). Anal. ($C_{19}H_{30}Cl_2N_2O_2 \cdot H_2O$) C, H, N.

4-Hydroxynaphthalene-1-sulfonamide (17). 4-(Ethoxycarbonyloxy)-1-naphthalenesulfonyl chloride (**18**) was synthesized as described by Zincke and Ruppersberg.[16] To 15.0 g (48 mmol) of **18** in 100 mL of dimethoxyethane (DME) under N_2 and with cooling was added 100 mL of DME saturated with NH_3, and the mixture was stirred for 2 h at room temperature. The NH_4Cl formed was removed by filtration and the solvent was evaporated in vacuo. The residue was dissolved in Et_2O and refrigerated overnight. The precipitate, consisting of both protected and unprotected product, was dissolved in 60 mL of EtOH–HCl (1:1) and refluxed 2 h. The volume was then reduced to about 15 mL in vacuo and filtered. The residue, 6.0 g (56%), was recrystallized from dilute EtOH: mp 215–217 °C (lit.[17] 217 °C from 4-aminonaphthalene-1-sulfonamide); IR (KBr) 3300 and 3400 (sulfonamide NH_2 stretching), 1340 and 1150 cm^{-1} (sulfonamide SO_2 stretching).

4-(2,3-Epoxypropoxy)naphthalene-1-sulfonamide (19). To 3.0 g (13 mmol) of 4-hydroxynaphthalene-1-sulfonamide (**17**) in 20 mL of dimethoxyethane was added 1.2 g (13 mmol) of anhydrous $KHCO_3$ in 5 mL of H_2O and 1.2 g (13 mmol) of epichlorohydrin. The mixture was refluxed for 3 h, cooled, and

poured into 200 mL of CH_2Cl_2. A precipitate formed and after thorough agitation the mixture was filtered. The filtrate was dried ($MgSO_4$) and evaporated in vacuo, leaving a 2.0-g residue. This was placed on a column (silica gel, Brinkman, 230-400 mesh, 168 g) and eluted at 60 psi with 4% EtOH in $CHCl_3$. The product thus obtained was recrystallized from EtOH-$CHCl_3$ (1:1), giving 200 mg (11%) of **19**: mp 160-162 °C.

4-[3-(Isopropylamino)-2-hydroxypropoxy]naphthalene-1-sulfonamide Hydrochloride (6). To 300 mg (1.1 mmol) of 4-(2,3-epoxypropoxy)naphthalene-1-sulfonamide (**19**) was added 50 mL of isopropylamine. The solution was refluxed 72 h and the excess isopropylamine was removed in vacuo. The residue was dissolved in MeOH and excess concentrated HCl was added. The solution was evaporated in vacuo. The residue was dissolved in a minimum quantity of hot EtOH, treated with a small amount of activated charcoal, and filtered. While hot, sufficient Et_2O was added to cause cloudiness, and the mixture was boiled until clear and allowed to cool. The crystals were collected to give 170 mg (41%) of product: mp 213-215 °C; IR (KBr) 1310 and 1150 cm^{-1} (sulfonamide SO_2 stretching); UV max (H_2O) 297, (NaOH) 297 nm; NMR (base, acetone-d_6) δ 1.1 [$CH(CH_3)_2$, 6, d], 2.9 (CH_2NHCH, 3, m), 4.3 (OCH_2CHOH, 3, m), 6.9-8.9 (naphthyl, 6, m); mass spectrum (70 eV) m/e (rel intensity) 323 (1), 294 (2), 223 (3), 72 (100). Anal. ($C_{16}H_{23}ClN_2O_4S$) C, H, N.

1-(Isopropylamino)-3-(4-amino-1-naphthoxy)-2-propanol Dihydrochloride (5). To 5.0 g (26 mmol) of **4**-amino-1-naphthol in 80 mL of H_2O was added 3.0 g (29 mmol) of Ac_2O followed by 2.5 g (30 mmol) of NaOAc with vigorous stirring under N_2. The mixture was stirred at room temperature for 30 min and the precipitate was collected by filtration, giving 3.7 g (71%) of crude 4-acetamido-1-naphthol. Without further purification, this was added to 80 mL of H_2O, together with 2.5 g (27 mmol) of epichlorohydrin and 0.7 g (18 mmol) of NaOH. This mixture was stirred at room temperature for 6 h. The precipitate was collected, giving 3.0 g (65%) of crude 1,2-epoxy-3-(4-acetamido-1-naphthoxy)propane. Without further purification, this was added to 25 mL of isopropylamine, and the solution was refluxed overnight. The excess isopropylamine was removed in vacuo, and the residue was dissolved in EtOH–concentrated HCl (1:1) and refluxed for 24 h. Evaporation of the solvent in vacuo and recrystallization of the residue from *i*-PrOH–Et_2O gave 300 mg (7%) of **5**: mp 155 °C dec; NMR (D_2O) δ 1.6 [$CH(CH_3)_2$, 6, d], 3.65 (CH_2NHCH, 3, m), 4.5 (OCH_2CHOH, 3, m), 7.1–8.8 (naphthyl, 6, m); mass spectrum (70 eV) m/e (rel intensity) 274 (14), 259 (64), 116 (100). Anal. ($C_{16}H_{24}Cl_2N_2O_2 \cdot 0.5H_2O$) C, H, N.

1-(Isopropylamino)-3-(2,4-dibromo-1-naphthoxy)-2-propanol (1). To 10.0 g (39 mmol) of 1-(isopropylamino)-3-(1-naphthoxy)-2-propanol (**3**) in 75 mL of CCl_4 was added, with stirring, 15.7 g (98 mmol) of Br_2 over a period of 1 h. The mixture was then refluxed for 5 h. The product precipitated from solution as the HBr salt and was collected by filtration and recrystallized from $CHCl_3$ to give 4.9 g (31%) of the HBr salt: mp 220–221 °C. A small quantity of the HBr salt was converted to the base by basic extraction into Et_2O, followed by drying ($MgSO_4$) of the Et_2O layer and evaporation to dryness. Recrystallization of the base from cyclohexane–petroleum ether gave a white solid: mp 98–100 °C; NMR (base, $CDCl_3$) δ 1.1 [d, 6, $C(CH_3)_2$], 2.5–3.1 (m, 3, $CHNCH_2$), 3.9–4.3 (m, 3, OCH_2CHOH), 7.4–7.7 (m, 2, naphthyl $H_{6,7}$), 7.8 (s, 1, naphthyl H_3), 8.0–8.3 (m, 2, naphthyl $H_{5,8}$); mass spectrum (salt, 70 eV) m/e (rel intensity) 419 (2), 417 (2), 405 (9), 403 (18), 401 (9), 73 (100). Anal. ($C_{16}H_{20}Br_3NO_2$) C, H, N. For confirmation of the position of substitution at the 2 and 4 positions, a sample of 2,4-dibromo-1-naphthol[13] was reacted with epichlorohydrin in the presence of base (NaOH) to give the epoxide which upon reaction with isopropylamine gave the free base **1**. Recrystallization from cyclohexane–petroleum ether gave a white solid: mp 98–100 °C. A mixture melting point with the free base obtained from bromination of **3** as described above did not differ from that of the pure material; NMR and IR data were identical with those obtained above.

B. Partition Coefficients. 1-Octanol was purified[18] by washing with successive equal volumes of 0.1 N sulfuric acid solution, 0.1 N sodium hydroxide solution, and distilled water. The octanol was then distilled and the fraction distilling at 195–196 °C was collected. The distilled octanol was shaken with phosphate buffer of pH 7.0, and the two layers were separated and retained for the partitioning experiments.

Partition coefficients were determined as described by Hellenbrecht et al.[8] For most of the compounds tested, a solution of 0.05 mg/mL was adequate to obtain an absorbance reading of around 0.90. A stock solution was prepared in octanol-saturated buffer. The absorbance of the stock solution was determined at the wavelength maximum in the 300-nm region of the spectrum. The desired quantity of the stock solution was pipetted into a 50-mL centrifuge tube along with the desired quantity of buffer-saturated octanol. The ratio of octanol to buffer was chosen to give an absorbance reading in the range of 0.2–0.7 in most cases. Where the compound was very soluble in the octanol layer (e.g., the 2,4-dibromo derivative **1**), 10-cm UV cells were used to obtain an acceptable absorbance reading. The samples were run in triplicate. Partitioning took place in a thermostated shaker bath which oscillated at 200 oscillations per minute over a period of 2 h. The temperature was maintained at 37 °C. After partitioning, the samples were centrifuged at 2000 rpm for 4 min to separate the two phases. The buffer layer was then pipetted into a UV cell and the absorbance was determined at the wavelength maximum in the 300-nm region of the spectrum. The partition coefficient was then calculated from the formula

$$P = (A_{std} - A_{ext})/A_{ext}f$$

where A_{std} = absorbance of the stock solution before extraction, A_{ext} = absorbance of the buffer layer after extraction, and f = ratio of the volume of the octanol layer to the volume of the buffer layer.

C. Pharmacology. Vaughan Williams and Szekeres[19] demonstrated that the maximum driving frequency (MDF) of isolated atria as proposed by Dawes[20] is a good screening procedure for antiarrhythmic activity. This procedure was used to determine the antiarrhythmic potency and effect on contractility of the compounds synthesized.

Tissue preparation was similar to that described by Levy.[21] Determination of MDF, effect on contractility, and treatment of data were similar to that of Levy et al.[22] White New Zealand rabbits weighing 2–3 kg were stunned by a blow to the head, the throat was cut, and the animal was bled for about 30 s. The heart was quickly removed and placed in a dish containing oxygenated physiological solution. The ventricles were clipped open to allow any remaining blood to be cleared from the heart. The heart was then transferred to a second dish, and the right atrial chamber was dissected free from the remainder of the heart, taking care not to damage the sinoatrial node. The right atrium was then transferred to fresh solution for mounting. At all times the tissue was immersed in oxygenated physiological solution at approximately 37 °C. The atrium was attached to a tissue holder in contact with a pair of bar electrodes of platinum embedded in the holder. The broad base of the tissue near the sinoatrial node was secured to the holder with 000 silk suture. The assembly was placed in a tissue bath and the free end of the atrium was attached to a Narco Bio-Systems photoelectric force transducer. A 1.0-g tension was applied to the tissue. The tissue bath was of the overflow type and was surrounded by water maintained at 37.5 °C by a constant temperature pump. The bath was vigorously oxygenated via a sintered-glass gas-delivery tube placed directly underneath the tissue support base. The gas composition was 95% O_2 and 5% CO_2. The physiological solution was as described by Levy and Richards[22] and was of the following composition (g/L): NaCl 6.84, KCl 0.35, $CaCl_2$ 0.28, $MgSO_4 \cdot 7H_2O$ 0.29, KH_2PO_4 0.16, $NaHCO_3$ 1.05, and dextrose 1.00.

The tissue was allowed to stabilize for 90 min before control readings were taken. The tissue was stimulated by a Grass S-44 stimulator with pulses of 2-ms duration through platinum bar electrodes in contact with the tissue near the broad base near the sinoatrial node. Responses were recorded on a Narco Bio-Systems Model DMP-4B physiograph. After a 60-min stabilization period, the threshold was determined by setting the stimulator at a stimulation rate of 240 pulses per minute and gradually increasing the voltage until the tissue consistently followed the stimulator. An average of three threshold values was used. The voltage was then set at 2.5 times the threshold value for the remainder of the study on a given tissue. This was to make certain that the tissue would follow the stimulator at higher doses of the drug when the

threshold is sometimes increased.

The procedure for determining the maximum driving frequency was as follows. The spontaneous rate was determined and a recording was made with the tissue stimulated at a frequency of 20% greater than the spontaneous frequency. This frequency was used to determine the contractile strength of the tissue by measurement of the peak height for the remainder of the study on the tissue. The driving frequency was then increased slowly until the tissue failed to follow the stimulator as indicated by skipped beats followed by supramaximal contractions. The determination was repeated twice and an average of the three values was used as the MDF. After the control readings were taken, the lowest concentration of the drug (as the hydrochloride or hydrobromide salt) to be tested was added to the bath in a small volume of buffer solution (0.1–0.4 mL). Readings were taken at 15 min after addition of the compound and the second dose was added to the bath without washing. The second reading was taken 15 min later and the procedure was repeated until the MDF was decreased by about 60% of control. Usually four to six data points could be obtained in a cumulative manner. Three tissues were used for each compound tested.

The percent decrease in response (MDF or peak height) was plotted vs. the logarithm of the molar concentration of drug, and a straight line was fitted to the data by linear regression. The log dose required to decrease the response by 40% was determined graphically (log ED_{40}). The values from the three tissues were averaged and standard deviations were then calculated for the replicates.

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Antimalarials. 4. Trichloronaphthalene Amino Alcohols[1]

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An improved procedure for the synthesis of naphthalene amino alcohols is described. Four new compounds were prepared and tested by Rane Laboratories for activity vs. *Plasmodium berghei* in mice. All compounds were active, the most active being 1-[3-(4-chlorophenyl)-5,7-dichloro-1-naphthyl]-3-(di-*n*-butylamino)propanol hydrochloride (**16b**). Structure–activity relationships between the naphthalene and quinoline isosteres are discussed.

3-Substituted 1-naphthalenemethanols have been shown to be active against *Plasmodium berghei* in mice.[1a] The activity is approximately the same as that of the better known 4-quinolinemethanols, although the structure–activity relationships operative for the quinoline compounds do not in all cases apply to the naphthalene isosteres.

Earlier synthetic procedures[2,3] were incapable of producing the 3-phenyl-5,7-dichloronaphthalenemethanols, isosteric with highly active 4-quinolinemethanols, because of the difficulty of ring closure meta to two chlorines. We have now devised a scheme which has provided a facile route to the compounds and is, with appropriate modifications, applicable to the general synthesis of 1-methyl-3-arylnaphthalenes, starting materials for the antimalarial naphthalenemethanols.

Chemistry. The synthetic sequence to the 1-methylnaphthalene **9** is illustrated in Scheme I. Previously described procedures[1a] were followed to obtain the naphthalene amino alcohols from **9**. 3,5-Dichloro-α-methylstyrene (**4**) was obtained in excellent overall yield (90%) from the acid **1**. Brown and Lane's[4] method of specific hydrobromination yielded only the desired 2-(3,5-dichlorophenyl)-1-bromopropane (**5**) in 70% yield. In the alkylation step the use of 1.5 equiv of (4-chlorophenyl)acetic acid increased the yield of pure 2-(4-chlorophenyl)-4-(3,5-dichlorophenyl)pentanoic acid (**6**) to 90% from the 50–60% range obtained with equimolar quantities.

Investigation to determine the optimum conditions for the cyclization of **6** revealed that no reaction occurred unless the polyphosphoric acid (PPA) reaction mixture was heated above 140 °C. At 185 and 190 °C a 1:3 mixture of the expected tetralin **7** and 3-(4-chlorophenyl)-5,7-dichloro-1-methylnaphthalene (**9**) was obtained. Further experimental evidence is required to explain this unexpected result.

Conversion of **7** to **9** through the dihydronaphthalene **8** proceeded routinely, except that the aromatization of **8** required reaction with dichlorodicyanoquinone (DDQ) when chloroanil failed to accomplish the dehydrogenation.

Structure–Activity Relationships. The activity[5] (as determined by Rane Laboratories) of the trichloronaphthalene amino alcohols vs. *P. berghei* is presented in

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