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Antimalarials. 3. 3-Substituted 1-Naphthalenemethanols[1]

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The synthesis and antimalarial activity of 22 3-substituted 1-naphthalenemethanols whose substitution was patterned after the antimalarial 2-substituted 4-quinolinemethanols are described. The compounds were active against *Plasmodium berghei* in mice, the most active being 6-chloro-α-(dibutylaminomethyl)-3-(3,4-dichlorophenyl)-1-naphthalenemethanol hydrochloride (**3b**). The naphthalenemethanols tested, **1b** and **2b**, were not photosensitizing to albino mice. Structure–activity relationships between the naphthalene and quinoline isosteres are discussed.

2-Substituted 4-quinolinemethanols, as a class, are active against avian, murine, and human malarias,[2] but most of the members of the class are photosensitizers.[3] Molecular modifications designed to reduce phototoxicity reduced antimalarial activity in most instances.[2] Rothe and Jacobus[3] have suggested that phototoxicity varies with different functional groups at the 2 position of the quinoline in a manner that indicates an association with their relative electronegativities. All quinolinemethanol antimalarials show absorption maxima in the 320–360-nm region;[4] even the relatively nonphototoxic 2-trifluoromethyl-4-quinolinemethanols have this ultraviolet absorption,[5] which is not present in naphthalene ring compounds of similar structure. Comparison of the activity and phototoxicity of phenanthrene and azaphenanthrene isosteres showed that the phenanthrene compounds were more active vs. *Plasmodium berghei* and less photosensitizing than the nitrogen-containing analogs.[6] These observations suggested a study of the biological activity of 3-substituted 1-naphthalenemethanols patterned after the active, but phototoxic, 2-substituted 4-quinolinemethanols.

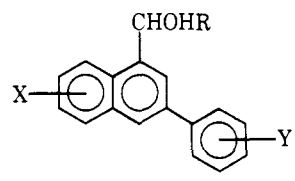
1- and 2-naphthalenemethanols were prepared some years ago by Jacobs, Winstein, and coworkers.[7] They were found to be less active than the phenanthrenemethanols and approximately as active against avian malarias[8] as the quinolinemethanols without a blocking 2-phenyl group.

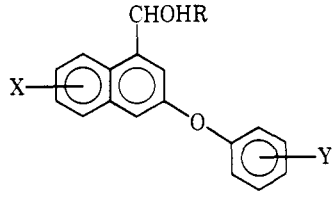
Chemistry. The 1-naphthalenemethanols prepared for this study are illustrated in Chart I. Synthesis of the 3-aryl-1-naphthalenemethanols (**1–6**) followed well-known procedures[1a,9] from the corresponding 3-aryl-1-naphthaldehydes, syntheses of which have been described.[10] The preparation of the 3-aryloxy (**7–11**) and 3-aroyl (**12**) derivatives required a different synthetic sequence, described elsewhere,[11] for the preparation of the aldehyde precursers, the 3-bromo-1-methylnaphthalenes. Conversion of the appropriately substituted 1-methylnaphthalenes to the naphthaldehydes was accomplished by the steps outlined in Scheme I.

The availability of 3-methylindanones[11] made it possible to obtain a 4-aryl-1-naphthalenemethanol (**13b**) by the pathway illustrated in Scheme II.

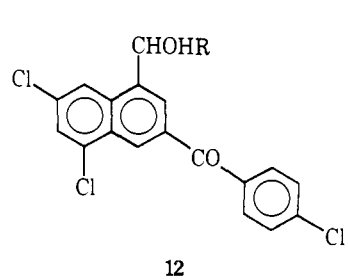
Structure–Activity Relationships. The activity (as determined by the Rane Laboratories[12]) of the 1-naphthalenemethanols vs. *Plasmodium berghei* is presented in Table I. Most of the compounds have antimalarial activity, the best of them, **3b**, being highly active. In Table II the minimum effective dose (MED) in the same test system of exactly comparable quinoline- and naphthalenemethanols is given together with comparisons in which there is a difference in the amino alcohol side chain between the two otherwise comparable compounds. Within both classes of

Chart I

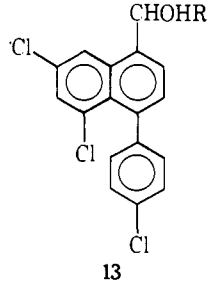




1. X = H; Y = 4-Cl
2. X = 6-Cl; Y = 4-Cl
3. X = 6-Cl; Y = 3,4-Cl_2
4. X = 7-CH_3O; Y = 4-Cl
5. X = 6-Cl, 7-CH_3O; Y = 4-Cl
6. X = 6-Cl, 7-CH_3O; Y = 3,4-Cl_2
7. X = 4-Br, 6-Cl; Y = 4-Cl
8. X = 5,7-Cl_2; Y = 4-Cl
9. X = 5,7-Cl_2; Y = 3-CF_3
10. X = 5,7-Cl_2; Y = 3,5-Cl_2
11. X = 5,7-Cl_2; Y = 3,4-Cl_2

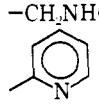


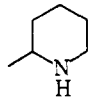
12



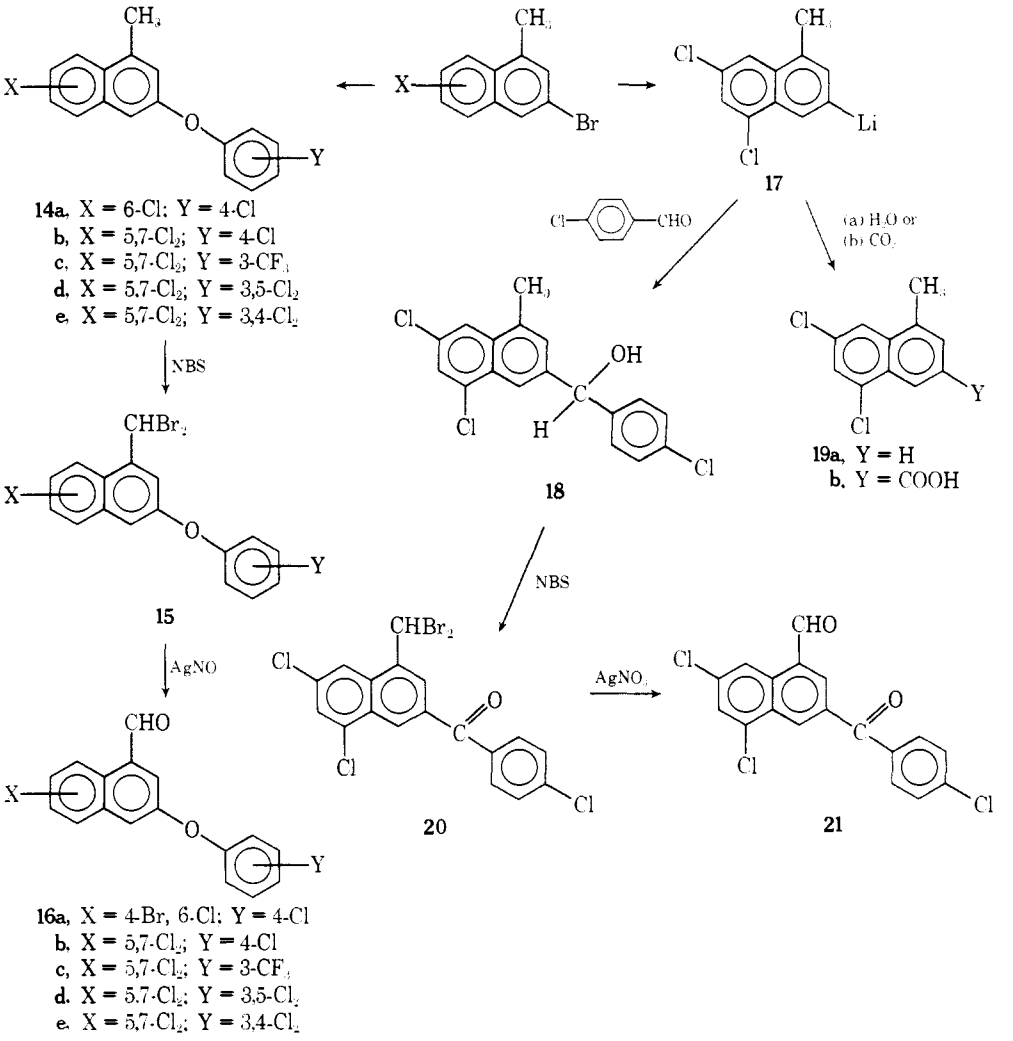
13

a. R = $-CH_2N(C_2H_5)_2$
b. R = $-CH_2N(C_4H_9)_2$
c. R = $-CH_2N(C_7H_{15})_2$
d. R = $-CH_2NHC_4H_9$





Scheme I



Scheme II

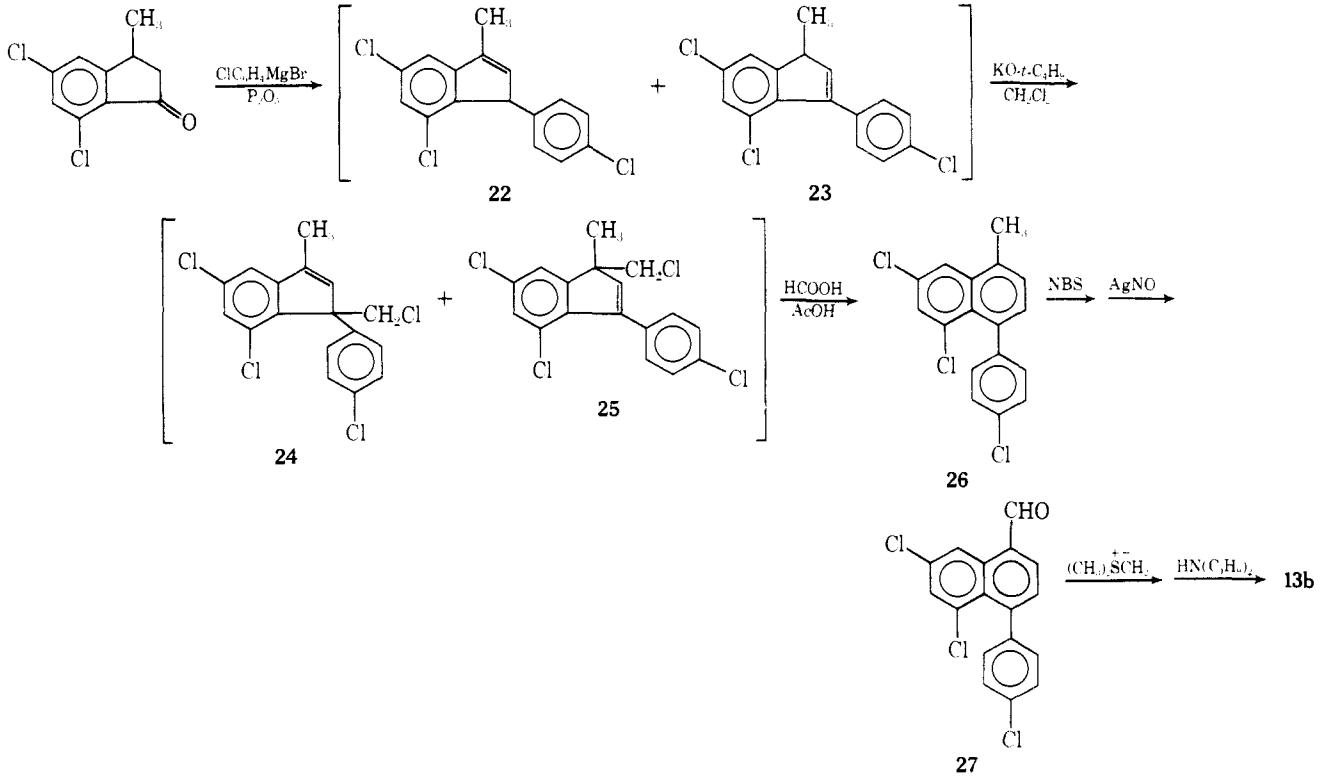
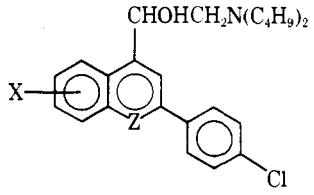


Table I. Antimalarial Activity[a] of α-Dialkylaminomethyl-1-naphthalenemethanols

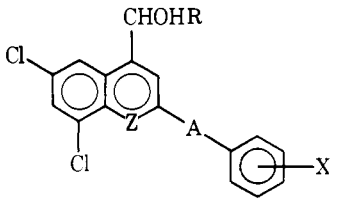
Compd	Δ MST (days) or no. of cures (C), dosage (mg/kg)						
	10	20	40	80	160	320	640
1a	0.5	1.1	4.5	12.7	5C	5C	5C
1b	1.1	2.5	8.3	5C	5C	5C	5C
1c	0.5	1.3	6.5	9.1	2C	3C	5C
2b	5.1	1C	5C	5C	5C	5C	5C
2d	8.5	13.1	14.5	2C	2C	4C	5C
3b	3C	5C	5C	5C	5C	5C	5C
3c	0.3	0.3	0.5	1.1	4.3	4.9	
4b	0.3	5.9	2C	3C	5C	5C	5C
4c	1.0	13.4	3C	5C	5C	5C	5C
5b		1.9	9.5	11.7	1C	1C	3C
5c	0.3	0.7	1.9	5.3	9.3	3C	4C
5f	0.3	0.5	13.5	16.1	2C	2C	3C
6b	0.7	4.9	11.1	13.9	2C	2C	3C
6c		0.3	0.5	0.7	2.3	5.1	8.9
6f		0.5	4.9	14.1	21.9	2C	5C
7b		4.7	5.5	7.9	10.3	11.1	
8b		3.5	4.3	6.7	8.5	10.1	
9b		1.7	4.5	6.7	8.3	9.9	
10b		2.8	5.4	6.8	10.5	11.6	2C
11b		0.9	4.9	5.7	9.3	10.1	14.3
12b	1.4	3.6	6.6	9.4	11.2	12.0	
13b		3.9	10.1	11.3	2C	3C	5C

[a]Activity vs. *P. berghei* in five mice, determined by Rane Laboratories, University of Miami, as described by Osdene and coworkers.[12] Mean survival time (MST) of infected controls was 6.1 days. Increase in survival time (Δ MST) of mice treated with a single dose of compound administered subcutaneously 72 hr after infection is considered evidence of antimalarial activity if the increase is at least 100%. Number of cures (C) is the number of mice surviving out of five at 60 days postinfection.

Table II. Comparative Antimalarial Activity of Quinoline- and Naphthalenemethanols



Compd	Z	X	MED,[a] mg/kg
b	N	7-Cl	40
2b	CH	6-Cl	20
b	N	7-Cl, 6-OCH_3	40
5b	CH	6-Cl, 7-OCH_3	40



Compd	Z	X	A	R	MED,[a] mg/kg
c	N	4-Cl	CO	$-CH_2N(C_4H_9)_2$	5
12b	CH	4-Cl	CO	$-CH_2N(C_4H_9)_2$	40
d	N	4-Cl	-O-	2-Piperidyl	10
8b	CH	4-Cl	-O-	$-CH_2N(C_4H_9)_2$	80
d	N	3,4-Cl_2	-O-	2-Piperidyl	20
11b	CH	3,4-Cl_2	-O-	$-CH_2N(C_4H_9)_2$	160

[a]Minimum effective dose is that which gives Δ MST of at least 6.1 days. [b]Data furnished by Walter Reed Army Institute of Research. [c]See ref 13. [d]See ref 14.

compounds there is some influence of the side chain on activity, but the effect is generally of lesser magnitude than that of nuclear substitution. With this reservation some useful structure–activity relationships of the isosteres are apparent.

The activity of the naphthalenemethanols was approximately the same as that of the quinoline compounds when the substitution at position 3 was aryl. Replacement of the aryl group with aroyloxy (**8b** and **11b**) or aroyl (**12b**), substitution which enhanced the activity of the quinolinemethanols,[13,14] reduced the activity of the naphthalene isosteres.

Within the naphthalenemethanol series it appears that chlorine substitution increases antimalarial activity. **3b,** which contains three chlorines, was curative at 10 mg/kg; **2b,** containing two chlorines, was inactive at that level but active at 20 mg/kg; and **1b,** containing only one chlorine, showed activity at 80 mg/kg. On the other hand, methoxyl substitution, which increased activity over that of the monochloro compound (cf. **4b** and **1b**), decreased the antimalarial activity when introduced into multichlorine-substituted compounds (cf. **5b** and **2b,** and **6b** and **3b**) (Table III).

There was some influence of side-chain substitution on activity. The most active compounds in each series were the dibutylamino derivatives, closely followed by the 2-piperidyl derivatives. In one case, **4c,** the activity of the diheptyl derivative was approximately the same as that of the dibutyl, **4b,** but in other cases (**1c, 3c, 5c,** and **6c**) the activity was lower.

More importantly, the two naphthalenemethanols tested at Walter Reed Army Institute of Research, **1b** and **2b,** were not phototoxic at dosages up to 400 mg/kg ip, while the corresponding quinoline compounds were highly phototoxic.[15] None of the intermediate compounds showed antimalarial activity (Table IV).

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded for all new compounds with a Perkin-Elmer Model 21 spectrophotometer; uv spectra of selected compounds were recorded with a Perkin-Elmer Model 450 spectrophotometer; NMR spectra were recorded for selected compounds with a Varian A-60 spectrometer. All spectra were in accord with the structures assigned. Microanalyses were performed by Microanalysis, Inc., Wilmington, Del.

3-Phenoxy-1-methylnaphthalenes (14). KOH (0.1 mol) and the substituted phenol (0.13 mol) were heated together at 160° for 3 hr under vacuum (<1 Torr). The appropriately substituted 3-bromo-1-methylnaphthalene (0.05 mol) was then added, and the solution was heated to 190°. If necessary, more of the phenol was added to assure solution of the reaction components. To this solution Cu powder (0.5 g) was added. A vigorous reaction, which subsided quickly, took place. The mixture was heated for 15 min (190°), and the cooled product was extracted with ether. The ether was removed, and from the residue the product was obtained by fractional distillation, the last fraction being the product.

4-Chlorophenyl-3-(5,7-dichloro-1-methylnaphthyl)methanol (18). A mixture of 3-bromo-5,7-dichloro-1-methylnaphthalene[11] (2.9 g), BuLi (7.6 ml of 1.33 *M* in hexane), and dry ether (30 ml) was stirred under N_2 for 2 min and then cooled in an ice–water

Table III. Naphthalenemethanols

Compd	Yield, %	Mp, °C	Crystn solvent	Mol formula	Analyses[a]
1a	45	156–159	Acetone	$C_{22}H_{24}ClNO\cdot HCl$	C, H, Cl, N
1b	55	206–209	Acetone–$CHCl_3$	$C_{26}H_{32}ClNO\cdot HCl$	C, H, Cl, N
1c	62	154–156	Acetone	$C_{32}H_{44}ClNO\cdot HCl$	C, H, Cl, N
2b	50	209–210	Acetone	$C_{26}H_{31}Cl_2NO\cdot HCl$	C, H, Cl, N
2d	66	136–138	Ether	$C_{22}H_{23}Cl_2NO$	C, H, Cl, N
2e	45	120–122	Ether	$C_{22}H_{15}Cl_2NO$	C, H, Cl, N
3b	65	224–226 (vacuum)	Acetone–MeOH	$C_{26}H_{30}Cl_3NO\cdot HCl$	C, H, Cl, N
3c	50	199–200	Acetone	$C_{32}H_{42}Cl_3NO\cdot HCl$	C, H, Cl, N
4b	60	221–222	Acetone–$CHCl_3$	$C_{27}H_{34}ClNO_2\cdot HCl$	C, H, N
4c	50	199–201	Acetone	$C_{33}H_{46}ClNO_2\cdot HCl$	C, H, Cl, N
5b	69	249–251	THF	$C_{27}H_{33}Cl_2NO_2\cdot HCl$	C, H, Cl, N
5c	67	232–234	THF	$C_{33}H_{45}Cl_2NO_2\cdot HCl$	C, Cl, N; H[b]
5e	76	205–207	THF–acetone	$C_{23}H_{17}Cl_2NO_2$	C, H, Cl, N
5f	90	219–222 dec	THF	$C_{23}H_{23}Cl_2NO_2\cdot CH_3COOH$	C, H, Cl, N
6b	43	238–239	Acetone	$C_{27}H_{32}Cl_3NO_2\cdot HCl$	C, H, Cl, N
6c	41	227–229	Acetone	$C_{33}H_{44}Cl_3NO_2\cdot HCl$	C, H, Cl, N
6e	64	166–168	Acetone–ether	$C_{23}H_{16}Cl_3NO_2$	C, H, Cl, N
6f	85	225–227	THF	$C_{23}H_{22}Cl_3NO_2\cdot CH_3COOH$	C, H, Cl, N
7b	60	159–161	Benzene–ether	$C_{26}H_{30}BrCl_2NO_2\cdot HCl$	H, N; C[c]
8b	15	105–110 dec	Acetone–ether	$C_{26}H_{30}Cl_3NO_2\cdot HCl$	C, H, Cl, N
9b	25	105–110	Ether–hexane	$C_{27}H_{30}Cl_2F_3NO_2\cdot HCl$	C, H, N
10b	13	164–166	$CHCl_3$–pet. ether	$C_{26}H_{29}Cl_4NO_2\cdot HCl$	C, H, Cl, N
11b	43	131–136	Acetone–ether	$C_{26}H_{29}Cl_4NO_2\cdot HCl$	C, H, Cl, N
12b	10	128–131	Acetone–ether	$C_{27}H_{30}Cl_3NO_2\cdot HCl$	C, H, Cl, N
13b	40	171–172	Ethyl acetate–ether	$C_{26}H_{30}Cl_3NO\cdot HCl$	C, H, Cl, N

[a] Analyses were within ±0.4% for elements indicated except where noted. [b] H: calcd, 7.79; found, 7.33. [c] C: calcd, 54.24; found, 55.09.

Table IV. Intermediate Compounds

Compd	Yield, %	Mp, °C	Crystn solvent	Mol formula	Analyses[a]
14a	50.6	80–93	Pet. ether	$C_{17}H_{12}Cl_2O$	C, H, Cl
14b	53	94–96	Et_2O	$C_{17}H_{11}Cl_3O$	C, H, Cl
14c	61	76–81	MeOH	$C_{18}H_{11}Cl_2F_3O$	C, H, Cl, F
14d	40	121–125	Et_2O	$C_{17}H_{10}Cl_4O$	C, H, Cl
14e	27	89–92	MeOH–Et_2O	$C_{17}H_{10}Cl_4O$	C, H, Cl
16a	90	Glass		$C_{17}H_9BrCl_2O_2$	C, H
16b	90	119–126	MeOH	$C_{17}H_9Cl_3O_2$	C, H, Cl
16c	86	98–101	Hexane	$C_{18}H_9Cl_2F_3O_2$	C, H, Cl, F
16d	71	133–137	Et_2O	$C_{17}H_8Cl_4O_2$	C, H, Cl
16e	65	139–140	Acetone	$C_{17}H_8Cl_4O_2$	C, H, Cl
18	52	149–151	Pet. ether–ether	$C_{18}H_{13}Cl_3O$	C, H, Cl
19a		66–69	MeOH	$C_{11}H_8Cl_2$	C, H, Cl
19b	30	315–325	Aq EtOH	$C_{12}H_8Cl_2O_2$	C, H, Cl
21	74	211–214	THF	$C_{18}H_9Cl_3O_2$	C, H, Cl
26		94–95.5	MeOH	$C_{17}H_{11}Cl_3$	C, H, Cl
27	50[b]	148–151	Et_2O	$C_{17}H_9Cl_3O$	C, H, Cl

[a] See footnote a, Table III. [b] From 22, two steps.

bath. After 0.5 min 4-chlorobenzaldehyde (0.703 g) in ether (10 ml) was added all at once to half the naphthyllithium solution. The reaction mixture was stirred for 15 min and then decomposed with saturated NH_4Cl. The ethereal layer was separated, washed until neutral, and dried (Na_2SO_4). The ether was removed and residue was crystallized.

The other half of the solution was divided into two portions. One portion was decomposed with water giving **19a** and the other was carbonated with solid CO_2 giving **19b**.

α-Alkylaminomethyl-1-naphthalenemethanols. Oxirane (0.1 mol) (prepared according to ref 1a) and amine (0.5 mol) were mixed and heated to 160° under N_2. The excess amine was removed either by distillation under reduced pressure or by fractional precipitation of the HCl salt. The ethereal solution of the amino alcohol was charcoaled, and the amino alcohol was precipitated as the HCl salt.

α-(2-Pyridyl)-1-naphthalenemethanols. *n*-BuLi (20 mmol, Foote Mineral) was diluted with Et_2O (50 ml) and cooled to −60°. 2-Bromopyridine (22 mmol) was added slowly maintaining the temperature below −50°. The solution was stirred for 15 min and the naphthaldehyde[10] (10 mmol) in THF was added slowly. Stirring was continued for 3 hr. The temperature was raised to −45°,

and the reaction mixture was decomposed with wet THF. The solution was filtered and the solvents were removed.

α-(2-Piperidyl)-1-naphthalenemethanols. PtO_2 (200 mg) was added to α-(2-pyridyl)-1-naphthalenemethanol (2 g) dissolved in THF–AcOH (50:50). The mixture was hydrogenated at room temperature and 45 lbs of H_2 pressure for 2.5 hr. The catalyst was removed, and the solvents were evaporated. The product was crystallized as the acetate.

4-(4-Chlorophenyl)-5,7-dichloro-1-methylnaphthalene (26). 5,7-Dichloro-3-methyl-1-indanone[11] (13 g) was added to a Grignard reagent prepared from 4-bromochlorobenzene (16 g) and Mg (2 g). The reaction mixture on usual work-up gave 15 g of material, which was mixed with P_2O_5 (3 g) and distilled [ca. 160–180° (0.1 mm)]. The distillate was dissolved in Et_2O and dried (Na_2SO_4), and Et_2O was removed. The residue was distilled at 170–175° (0.11 mm). The distillate (14 g) was a mixture of **22** and **23** (NMR). This mixture dissolved in cold (0°) CH_2Cl_2 (60 ml) was added to a solution of K (2.8 g) in *tert*-BuOH (30 ml). The reaction mixture was stirred overnight at room temperature, and the solvents were removed. The residue was dissolved in petroleum ether (bp 30–60), washed with H_2O, and dried. Petroleum ether was removed, and the residue was distilled [174–176° (0.15–0.20 mm)], yielding 12 g of a mixture of **24** and **25** (NMR). This mixture was refluxed with HCOOH (97%, 200 ml) for 1 week and cooled. A gummy solid was separated and washed with water and $NaHCO_3$ solution, yielding 4 g of product, **26**. The procedure is based on Bavin's work.[16]

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References and Notes

(1) (a) For the previous paper see J. S. Gillespie, Jr., S. P. Acharya, R. E. Davis, and B. K. Barman, *J. Med. Chem.*, **13**, 860 (1970). (b) Presented in part to the Division of Medicinal Chemistry at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 9–14, 1972. (c) Taken partially from R. E. Davis, M.S. Thesis, University of Richmond, Richmond, Va., 1971. (d) The work described in this paper was performed under Contract No. DA-49-193-MD-2981 and DADA-17-72-C-2078 with the U.S. Army Medical Research and Development Command. This is Contribution No. 1368 from the Army Research Program on Malaria.
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Structure–Activity Relationships of Antiarrhythmic 6-Substituted Decahydroisoquinolines

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A series of diastereoisomeric 6-benzoyloxy- and 6-benzamido-2-methyldecahydroisoquinolines has been prepared and screened for antiarrhythmic effectiveness. In a continuation of our interest in identifying significant physicochemical properties of antiarrhythmic decahydroisoquinolines, octanol–water partition coefficients and pK_a values have been determined for each member of the series. In general, antiarrhythmic activities superior to that of quinidine were observed. From a general structure–activity viewpoint, substitutions possessing greater lipophilicities produced compounds with superior antiarrhythmic properties. However, there appears to be optimal lipophilic character beyond which increased lipophilicity results in a decrease in antiarrhythmic potency. No discernible correlations with pK_a values were evident. As noted in our earlier studies the esters were more potent and more lipophilic than the corresponding amides. No obvious correlations with stereochemistry were found; however, in three pairs of diastereoisomers, the more lipophilic cis compounds were found to be the superior isomers. A surprisingly high potency was noted with a tetrahydroisoquinoline benzamide—a finding unexpected from our earlier work. The 3,4-dichlorobenzamido grouping appeared to be the substituting moiety for optimal antiarrhythmic effectiveness.

In a continuation of the established interest of our laboratories[1] in the significance of stereochemical factors in the mechanism of action of antiarrhythmic decahydroisoquinolines, an investigation of the effects of various substitutions at the 6 position of diastereoisomeric 2-methyldecahydroisoquinolines is reported. In an earlier publication[1b] we noted the similarity of the substituted decahydroisoquinolines investigated in our laboratories to the D and E rings of reserpine, which may be considered to be a 5,6,7-trisubstituted *cis*-decahydroisoquinoline.

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