Pharm. Soc. Jpn., 69, 248 (1949).

- (23) M. R. Harnden and R. R. Rasmussen, J. Med. Chem., 12, 919 (1969).
- (24) J. M. D. Aron-Samuel, U.S. Patent 3567826 (1971).
- (25) U. H. Lindberg and J. Pedersen, Acta Pharm. Suecica, 5, 15 (1968).
- (26) L. M. Yagupolskil and V. I. Troitskaya, Zh. Obshch. Khim., 30, 3129 (1960); Chem. Abstr., 55, 17564a (1961).
- (27) C. E. Maxwell, "Organic Syntheses", Collect. Vol. III, Wiley,

New York, N.Y., 1955, p 305.

- (28) British Patent 867273 (1961); Chem. Abstr., 55, 21152a (1961).
- (29) P. N. Rylander and E. Campaigne, J. Org. Chem., 15, 752 (1950).
- (30) E. C. Taylor and W. A. Ehrhart, J. Org. Chem., 28, 1108 (1963).
- (31) K. Nakajima, Nippon Kagaku Zasshi, 81, 323 (1960); Chem. Abstr., 56, 406a (1962).

Antimalarials. 3. 3-Substituted 1-Naphthalenemethanols¹

J. Samuel Gillespie, Jr.,* Satya Prakash Acharya, Dwight A. Shamblee, and Richard E. Davis

Virginia Institute for Scientific Research, Richmond, Virginia 23229. Received June 23, 1975

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)-1naphthalenemethanol 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 Jacobus³ 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 nitrogencontaining analogs.⁶ These observations suggested a study of the biological activity of 3-substituted 1-naphthalenemethanols patterned after the active, but phototoxic, 2substituted 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 malarias⁸ 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-methylindanones¹¹ 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 Laboratories¹²) 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

Scheme I



Scheme II



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

	Δ MST (days) or no. of cures (C), dosage (mg/kg)						
Compd	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
2 b	5.1	1C	5C	5C	5C	5C	5C
2d	8.5	13.1	14.5	2C	2C	4C	5C
3 b	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	
8 b		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

^aActivity 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.

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

Table II. Comparative Antimalarial Activity of Quinoline- and Naphthalenemethanols



^aMinimum effective dose is that which gives Δ MST of at least 6.1 days. ^bData furnished by Walter Reed Army Institute of Research. ^cSee ref 13. ^dSee ref 14.

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 3bromo-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-methylnaphthalene¹¹ (2.9 g), BuLi (7.6 ml of 1.33 M in hexane), and dry ether (30 ml) was stirred under N₂ for 2 min and then cooled in an ice-water

Compd	Yield, %	Mp,°C	Crystn solvent	Mol formula	Analyses ⁴
1a	45	156-159	Acetone	C ₂₂ H ₂₄ ClNO·HCl	C, H, Cl. N
1b	55	206-209	$Acetone-CHCl_3$	C ₂₆ H ₃₂ C1NO•HC1	C, H, Cl, N
1c	62	154-156	Acetone	C ₃₂ H ₄₄ ClNO•HCl	C, H, C1, N
2 b	50	209-210	Acetone	C ₂₆ H ₃₁ Cl ₂ NO·HCl	C, H, Cl, N
2 d	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 (vacuu m)	Acetone-MeOH	C ₂₆ H ₃₀ Cl ₃ NO·HCl	C, H, Cl, N
3c	50	199-200	Acetone	C ₃₂ H ₄₂ Cl ₃ NO•HCl	C, H, Cl, N
4 b	60	221-222	$Acetone-CHCl_3$	C ₂₇ H ₃₄ CINO ₂ ·HCl	C, H. N
4c	50	199-201	Acetone	C ₃₃ H ₄₆ ClNO ₂ •HCl	C, H, Cl, N
5b	69	249-251	THF	C ₂₇ H ₃₃ Cl ₂ NO ₂ •HCl	C, H, Cl, N
5c	67	232-234	THF	$C_{33}H_{45}Cl_2NO_2$ ·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 ₂ NO ₂ ·CH ₃ COOH	C, H, Cl, N
6b	43	238-239	Acetone	$C_{27}H_{32}Cl_3NO_2$ ·HCl	C, H, Cl, N
6c	41	227-229	Acetone	$C_{33}H_{44}Cl_3NO_2 \cdot HCl$	C, H, CI, N
6e	64	166-168	Acetone-ether	$C_{23}H_{16}Cl_{3}NO_{2}$	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	$C_{26}H_{30}BrCl_2NO_2$ ·HCl	Η, N; C ^σ
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	$C_{27}H_{30}Cl_2F_3NO_2$ ·HCl	C, H, N
10b	13	164-166	$CHCl_3$ -pet. ether	C ₂₆ H ₂₉ Cl ₄ NO ₂ ·HCl	C. H, Cl, N
11b	43	131-136	Acetone-ether	C ₂₆ H ₂₉ Cl ₄ NO ₂ ·HCl	C, H, Cl, N
12b	10	128-131	Acetone-ether	$C_{27}H_{30}Cl_3NO_2 \cdot HCl$	C, H, Cl, N
1 3 b	40	171 - 172	Ethyl acetate-ether	C ₂₆ H ₃₀ Cl ₃ NO•HCl	C, H, Cl, N

Table III. Naphthalenemethanols

^aAnalyses were within ±0.4% for elements indicated except where noted. ^bH: calcd, 7.79; found, 7.33. ^cC: 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 ₂ O	C, H, C1
14b	53	94-96	Et ₂ O	C ₁₇ H ₁₁ Cl ₃ O	C. H. Cl
14c	61	76-81	MeOH	$C_{18}H_{11}Cl_{2}F_{3}O$	C. H. Cl. F
14d	40	121-125	Et ₂ O	$C_{17}H_{10}Cl_4O$	C. H. CI
14e	27	89 92	MeOH-Et ₂ O	$C_{17}H_{10}Cl_4O$	C, H, Cl
16a	90	Glass	-	C ₁₇ H ₉ BrCl ₂ O ₂	C. H
16b	90	119-126	MeOH	$C_{17}H_{9}Cl_{3}O_{2}$	C. H. Cl
16c	86	98-101	Hexane	C ₁ ,H _y Cl _y F ₂ O ₂	C. H. Cl. F
16d	71	133-137	Et_2O	C ₁₇ H ₃ Cl ₄ O ₂	C. H. Cl
16e	65	139-140	Acetone	C ₁₇ H _s Cl ₄ O ₂	C. H. CI
18	52	149-151	Pet. ether-ether	$C_{18}H_{13}Cl_{3}O$	C. H. Cl
19a		66-69	MeOH	C ₁₁ H ₀ Cl ₂	C. H. Cl
19b	30	315-325	Ag EtOH	$C_{12}H_{0}C_{12}O_{2}$	C. H. CI
21	74	211-214	THF	$C_{13}H_{0}C_{12}O_{2}$	C. H. Cl
26		94-95.5	MeOH	C ₁₇ H ₁₁ Cl ₂	C. H. Cl
27	50°	148-151	Et ₂ O	$C_{17}H_9Cl_3O$	C, H, Cl

^aSee footnote a, Table III. ^bFrom 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 NH₄Cl. The ethereal layer was separated, washed until neutral, and dried (Na₂SO₄). 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-I-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 Et₂O (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 naphthaldehyde¹⁰ (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 H₂ 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 indanone¹¹ (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 Et₂O and dried (Na₂SO₄), 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°) CH₂Cl₂ (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 H₂O, 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 NaHCO₃ solution, yielding 4 g of product, 26. The procedure is based on Bavin's work.¹⁶

Acknowledgments. The authors wish to thank Dr. William J. Welstead, Jr., and Mr. Ashby F. Johnson, A. H. Robins Company, Inc., Richmond, Va., for NMR spectra. The assistance of Dr. R. E. Strube, Walter Reed Army Institute of Research, is gratefully acknowledged.

References and Notes

 (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.

- (2) P. E. Thompson and L. M. Werbel, "Antimalarial Agents: Chemistry and Pharmacology," Academic Press, New York, N.Y., 1972, pp 79-89.
- (3) W. E. Rothe and D. P. Jacobus, J. Med. Chem., 11, 366 (1968).
- (4) E. R. Atkinson and A. J. Puttick, J. Med. Chem., 13, 537 (1970).
- (5) C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, J. Med. Chem., 14, 926 (1971).
- (6) Personal communication, R. E. Strube, Walter Reed Army Institute of Research, Washington, D.C.
- (7) T. L. Jacobs et al., J. Org. Chem., 11, 21, 27, 157, 163, 215, 223, 229 (1946).
- (8) F. Y. Wiselogle, Ed., "A Survey of Antimalarial Drugs, 1941– 1945," J. W. Edwards, Ann Arbor, Mich., 1946.
- (9) A. R. Patel, C. J. Ohnmacht, D. P. Clifford, A. H. Crosby, and R. E. Lutz, J. Med. Chem., 14, 198 (1971).
- (10) J. S. Gillespie, Jr., S. P. Acharya, D. A. Shamblee, and R. E. Davis, *Tetrahedron*, **31**, 3 (1975).
- (11) J. S. Gillespie, Jr., S. P. Acharya, and D. A. Shamblee, J. Org. Chem., 40, 1838 (1975).
- (12) Results were reported to us by Walter Reed Army Institute of Research. Test method is described in T. S. Osdene, P. B. Russell, and L. Rane, J. Med. Chem., 10, 431 (1967).
- (13) A. J. Saggiomo, S. Kano, T. Kikuchi, K. Okubo, and M. Shinbo, J. Med. Chem., 15, 989 (1972).
- (14) C. R. Wetzel, J. R. Shanklin, Jr., and R. E. Lutz, J. Med. Chem., 16, 528 (1973).
- (15) Personal communication, W. E. Rothe, Walter Reed Army Institute of Research, Washington, D.C.
- (16) P. M. G. Bavin, J. Chem. Soc., 5484 (1964).

Structure–Activity Relationships of Antiarrhythmic 6-Substituted Decahydroisoquinolines

Ian W. Mathison* and Richard R. Tidwell[†]

Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, Tennessee 38163. Received April 10, 1975

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 laboratories¹ 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.

[†] The work reported constitutes a segment of the dissertation submitted by R.R.T. to the University of Tennessee Center for the Health Sciences in partial fulfillment of the Doctor of Philosophy degree requirements in medicipal chemistry.