Synthesis, Antimalarial Activity, and Phototoxicity of Some Benzo[h]quinoline-4-methanols

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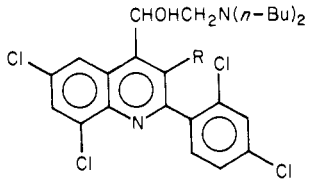
Nine α-dibutylaminomethylbenzo[h]quinoline-4-methanols were synthesized from the corresponding 1-aminonaphthalenes by the following sequence: 1-aminonaphthalene → 1*H*-benz[g]indole-2,3-dione → benzo[h]quinoline-4-carboxylic acid → acid chloride → bromomethyl ketone → epoxide → benzo[h]quinoline-4-methanol. Several acid chlorides substituted in the 3 position reacted incompletely with ethereal diazomethane but were efficiently converted, without isolation of the intermediates, to the bromomethyl ketones by reaction with ethoxymagnesium diethylmalonate, bromination, hydrolysis, and decarboxylation. Several compounds prepared, especially α-dibutylaminomethyl-2-(2′,4′-dimethylphenyl)-3-methyl-6-chlorobenzo[h]quinoline-4-methanol, showed significant antimalarial activity against *Plasmodium berghei* in infected mice but were moderately phototoxic.

Many 2-arylquinoline-4-methanols have displayed high antimalarial activity against avian[2,3] and rodent infections,[4] and at least one has shown antimalarial activity in man.[5] Unfortunately, the photosensitization caused by this class of compounds has prevented their chemotherapeutic use in the treatment or prophylaxis of human malaria.[6] The separation of the photoxicity associated with these compounds from their antimalarial activity has been the subject of a number of studies[7-12] in recent years, since the appearance of malaria caused by drug-resistant *Plasmodia*.[13,14]

The phototoxicity of the 2-arylquinoline-4-methanols has been suggested[6,15] to be due, at least in part, to the extension of nuclear conjugation by the 2-aryl group. This hypothesis was supported by the observation[6] that if the coplanarity of the 2′-substituted phenyl group in 1 with the quinoline moiety was diminished by introduction of a methyl group at the 3 position of the quinoline nucleus, the resulting compound (**2**) was eight times less phototoxic than 1. Also, while a series of 2-arylquinines in which the

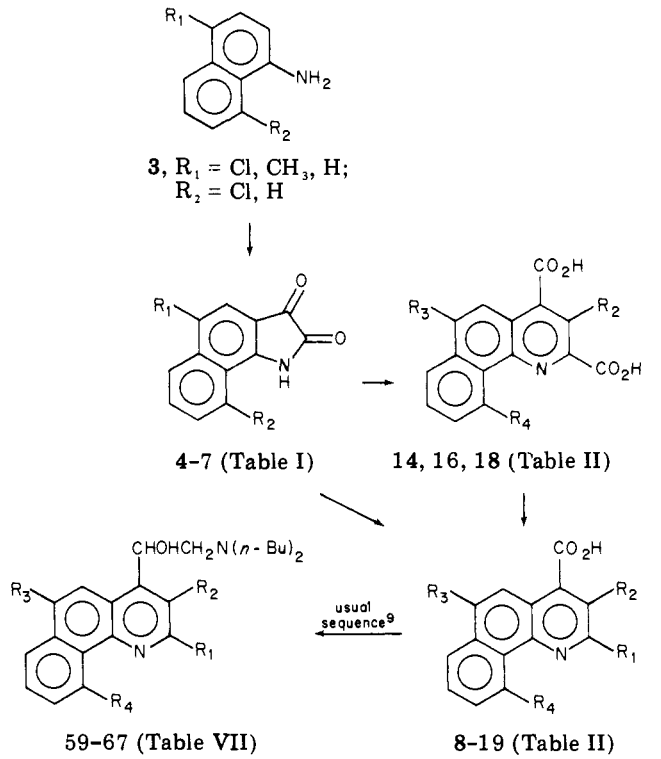


1, R = H
2, R = CH_3

2-aryl group can readily become coplanar showed severe phototoxicity,[16] quinine itself showed no phototoxicity in the same rodent test system.[6]

Two related 2-arylbenzo[h]quinoline-4-methanols prepared in the early work were highly active in an avian screen[17] and more recently a number of 2-trifluoromethyl derivatives showed high activity in rodents.[7] Unfortunately, the 2-aryl derivatives[18] and the active members of the 2-trifluoromethyl series[7] were phototoxic. Because of these results and those described above, we have prepared 2-arylbenzo[h]quinoline-4-methanols in which the coplanarity of the 2-aryl group was reduced by appropriate substitution. It was hoped this type of substitution would lower the extent of nuclear conjugation with the 2-aryl group and provide active antimalarial drugs with minimal phototoxicity. We have also prepared compounds with a *tert*-butyl group at the 2 position. This type of quaternary 2-alkyl substituent may prevent metabolic deactivation, which occurs by oxidation at the 2 position[19] in quinine, without increasing the overall conjugation of the ring

Scheme I

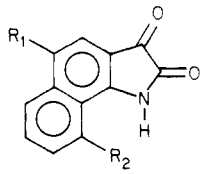


system. Several 2-unsubstituted 3-methyl candidate drugs were also prepared to evaluate this type of substitution in relation to phototoxicity and antimalarial activity.

Chemistry. The synthetic route utilized to prepare the benzo[h]quinoline-4-methanols began with the appropriately substituted 1-aminonaphthalene **3** and proceeded through the corresponding benzo[h]quinoline-4-carboxylic acid (**8–13, 15, 17, 19,** Table II) to give the target compounds (**59–67**) described in Table VII (Scheme I). The 1-aminonaphthalenes were efficiently converted directly to the 1*H*-benzo[g]indole-2,3-diones (Table I) by reaction with diethyl ketomalonate hydrate followed by hydrolysis and oxidative decarboxylation of the resulting intermediate, using a modification of the procedure previously applied to a 1-substituted 2-aminonaphthalene.[20] This procedure was distinctly superior to the Sandmeyer isatin synthesis[21] which gave little or none of the desired material when applied to 1-aminonaphthalene.

The benzo[h]quinoline-4-carboxylic acids (Table II) were prepared by two similar methods. In the case of the 2-

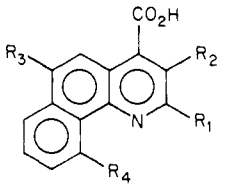
Table I. 1*H*-Benz[*g*]indole-2,3-diones



Compd	R_1	R_2	% yield	Mp, °C (crystn solvent)	Formula	Analyses
4	H	H	76	260–262 dec (EtOH–dioxane)	$C_{12}H_7NO_2$	*a*
5	CH_3	H	66	282–284 dec (dioxane)	$C_{13}H_9NO_2$	C, H, N[b]
6	Cl	H	89	284–286 dec (dioxane)	$C_{12}H_6ClNO_2$	C, H, Cl, N
7	H	Cl	87	242–244 dec (AcOH)	$C_{12}H_6ClNO_2$	C, H, Cl, N

[a] Lit. mp 254–256° [H. Cassebaum, *Chem. Ber.*, **90**, 2876 (1957)]. [b] Lit. mp >230° [W. Lagenbeck and O. Godde, *Chem. Ber.*, **70B**, 669 (1937)].

Table II. Benzo[*h*]quinoline-4-carboxylic Acids and -2,4-dicarboxylic Acids[a]



Compd	R_1	R_2	R_3	R_4	% yield	Mp, °C (crystn solvent)	Formula	Analyses[a]
8	*t*-Bu	H	H	H	60	252–253 dec (AcOH, H_2O)	$C_{18}H_{17}NO_2$	N
9	*t*-Bu	H	CH_3	H	64	241–242 dec (2-PrOH)	$C_{19}H_{19}NO_2$	N
10	*t*-Bu	H	Cl	H	56	259–260 dec (2-PrOH, H_2O)	$C_{18}H_{16}ClNO_2$	N
11	2,4-Me_2Ph	CH_3	H	H	78	302–303 dec (dioxane)	$C_{23}H_{19}NO_2$	N
12	2,4-Me_2Ph	CH_3	Cl	H	65	280–282 dec (AcOH)	$C_{23}H_{18}ClNO_2$	N
13	3,4,5-$(MeO)_3$Ph	H	Cl	H	76	266–268 dec (AcOH, dioxane)	$C_{23}H_{18}ClNO_5$	N
14	CO_2H	CH_3	H	H	90	238–240 dec (AcOH)	$C_{16}H_{11}NO_4$	N
15	H	CH_3	H	H	90	289–291 dec (AcOH, dioxane)	$C_{15}H_{11}NO_2$	N
16	CO_2H	CH_3	Cl	H	79	252–253 dec (AcOH, dioxane)	$C_{16}H_{10}ClNO_4$	N
17	H	CH_3	Cl	H	70	268–269 dec (AcOH, dioxane)	$C_{15}H_{10}ClNO_2$	N
18	CO_2H	CH_3	H	Cl	87	216–218 dec (AcOH)	$C_{16}H_{10}ClNO_4$	N
19	H	CH_3	H	Cl	57	178–180 dec (AcOH)	$C_{15}H_{10}ClNO_2$	*b*

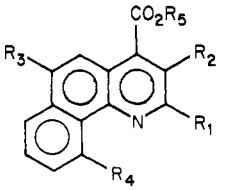
[a] Pure samples of these acids for analysis, with the exception of 10, were obtained by heating the corresponding esters (Table III) with excess ethanolic KOH followed by acidification and recrystallization from the specified solvent. [b] Not analyzed. Analysis on the ester 31.

unsubstituted 4-carboxylic acids (**15**, **17**, **19**, Table II), reaction of the corresponding isatin derivatives (**6**, **7**) with 2-ketobutyric acid in alkaline medium smoothly gave the 3-methyl-2,4-dicarboxylic acids (**14**, **16**, **18**) which were selectively decarboxylated to the desired 4-carboxylic acids. Synthesis of the 2-substituted 4-carboxylic acids (**8**–**13**, Table II) was accomplished in one step using the well-known Pfitzinger method,[22] with modification to allow preparation of the sterically hindered 2-(2′,4′-dimethylphenyl)-3-methyl and 2-*tert*-butyl derivatives. Although early workers[23] had reported no reaction between isatin and pinacolone, we have found that isatin as well as the isatin derivatives (**4**–**6**, Table I) react smoothly with pinacolone and 2,4-dimethylpropiophenone at 125–135° in strongly basic 2-methoxyethanol to furnish the desired 2-substituted carboxylic acids. Our modification of the usual Pfitzinger procedure should be valuable for the synthesis of 2-*tert*-butyl derivatives in the quinoline-4-carboxylic acid series in view of the three[8] and eight[24] stage sequences previously required for the preparation of these materials. Final purification of the acids (Table II) for elemental analysis was carried out through the esters (**20**–**31**) listed in Table III.

Once the 4-carboxylic acids were readily available in quantity, we proceeded to elaborate the amino alcohol side chain using the improved, now-classic Lutz sequence.[9] The acids were converted to the acid chlorides (**32**–**40**, Table IV) which in some cases were treated with diazomethane followed by HBr (method A) to give the corresponding bromomethyl ketones (Table V). Certain acid chlorides substituted in the 3 position reacted slowly or incompletely with diazomethane but were easily converted, without isolation of the intermediates, to the bromomethyl ketones by reaction with ethoxymagnesium diethylmalonate,[25] bromination, hydrolysis, and decarboxylation (method B). Reduction of the bromomethyl ketones with $NaBH_4$ in 2-propanol gave the epoxides (**50**–**58**, Table VI) which were smoothly opened to the target amino alcohols (**59**–**67**, Table VII) by heating with excess dibutylamine. The amino alcohol bases were syrups and were characterized as the acid oxalate or HCl salts.

Biological Activity. The antimalarial activity for the compounds synthesized is shown in Table VIII and was determined as previously described.[26] These compounds were not toxic at the highest dose administered and although all compounds prepared in this work caused some increase in mean survival time (MST) for the treated animals, only compounds **61**, **63**, **64**, and **66** with chlorine at the 6 position (R_3) showed curative properties. Based on the data for the limited number of compounds prepared in this work, chlorine substitution at the 6 position appears to play a major role in determining activity in this series. The type of substitution at the 2 position seems to be of lesser importance since the 6-chloro-2-alkyl (**61**), 2-aryl (**53** and **64**), and 2-unsubstituted (**66**) derivatives showed curative properties while three corresponding 6-unsubstituted derivatives **59**, **62**, and **65** showed little increase in MST. Likewise, when the 6-chloro substituent in **61** was

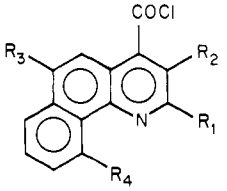
Table III. Esters of Benzo[*h*]quinoline-4-carboxylic Acids and -2,4-dicarboxylic Acids[a]



Compd	R_1	R_2	R_3	R_4	R_5	Mp, °C (crystn solvent)	Formula	Analyses
20	*t*-Bu	H	H	H	C_2H_5	93.5-97.0 (EtOH)	$C_{20}H_{21}NO_2$	C, H, N
21	*t*-Bu	H	CH_3	H	CH_3	127-129 (MeOH)	$C_{20}H_{21}NO_2$	C, H, N
22	*t*-Bu	H	Cl	H	C_2H_5	122-123 (EtOH)	$C_{20}H_{20}ClNO_2$	C, H, Cl, N
23	2,4-Me_2Ph	CH_3	H	H	CH_3	83-87 (MeOH)	$C_{24}H_{21}NO_2$	C, H, N
24	2,4-Me_2Ph	CH_3	Cl	H	CH_3	118-120 (MeOH, $CHCl_3$)	$C_{24}H_{20}ClNO_2$	C, H, Cl, N
25	3,4,5-$(MeO)_3$Ph	H	Cl	H	CH_3	182-184 (Et_2O)	$C_{24}H_{20}ClNO_5$	C, H, Cl, N
26	CO_2CH_3	CH_3	Cl	H	CH_3	101.5-103 (MeOH)	$C_{18}H_{15}NO_4$	C, H, N
27	H	CH_3	H	H	CH_3	78-80 (hexane)	$C_{16}H_{13}NO_2$	C, H, N
28	CO_2CH_3	CH_3	Cl	H	CH_3	145-145.5 (C_6H_6-MeOH)	$C_{18}H_{14}ClNO_4$	C, H, Cl, N
29	H	CH_3	Cl	H	CH_3	130.5-132.5 (C_6H_6-MeOH)	$C_{16}H_{12}ClNO_2$	C, H, Cl, N
30	CO_2CH_3	CH_3	H	Cl	CH_3	85-86 (MeOH)	$C_{18}H_{14}ClNO_4$	C, H, N
31	H	CH_3	H	Cl	CH_3	115-116 (MeOH)	$C_{16}H_{12}ClNO_2$	C, H, N

[a] Compounds 20 and 22 were prepared by standard Fischer esterification; the others were prepared by reactions of the acids with CH_2N_2. The acids used to prepare these esters were usually of varying purity, and consequently yields, although good, were not accurately determined. In these cases esters were chromatographed over a short alumina column, eluted with C_6H_6-$CHCl_3$, and recrystallized from the solvent specified.

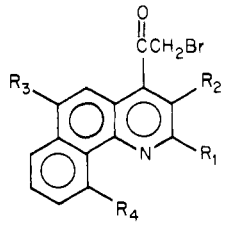
Table IV. Benzo[*h*]quinoline-4-carbonyl Chlorides[a]



Compd	R_1	R_2	R_3	R_4	% yield[b]	Mp, °C (crystn solvent)[b]	Formula
32	*t*-Bu	H	H	H	92	105-108	$C_{18}H_{16}ClNO$
33	*t*-Bu	H	CH_3	H	100	162-165	$C_{19}H_{18}ClNO$
34	*t*-Bu	H	Cl	H	96	140-142	$C_{18}H_{15}Cl_2NO$
35	2,4-Me_2Ph	CH_3	H	H	97	Syrup	$C_{23}H_{18}ClNO$
36	2,4-Me_2Ph	CH_3	Cl	H	95	118-121.5	$C_{23}H_{17}Cl_2NO$
37	3,4,5-$(MeO)_3$Ph	H	Cl	H	79	186.5-190 ($CHCl_3$)	$C_{23}H_{17}Cl_2NO_4$
38	H	CH_3	H	H	94	138-140	$C_{15}H_{10}ClNO$
39	H	CH_3	Cl	H	94	106-107	$C_{15}H_9Cl_2NO$
40	H	CH_3	H	Cl	100	145-147	$C_{15}H_9Cl_2NO$

[a] Elemental analyses were not performed on these acid chlorides; however, all compounds gave ir and NMR spectra consistent with the structures. [b] Except for 37 melting points and yields were determined on crude material.

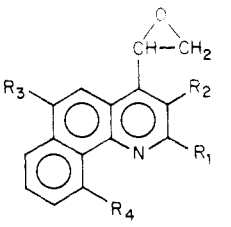
Table V. α-Bromomethyl-4-benzo[*h*]quinolyl Ketones



Compd	R_1	R_2	R_3	R_4	Method	% yield[a]	Mp, °C (crystn solvent)	Formula	Analyses
41	*t*-Bu	H	H	H	A	71	90-91 (C_6H_6-MeOH)	$C_{19}H_{18}BrNO$	C, H, N
42	*t*-Bu	H	CH_3	H	A	83	109-110 (C_6H_6-MeOH)	$C_{20}H_{20}BrNO$	C, H, N
43	*t*-Bu	H	Cl	H	A	71	96-98 (MeOH)	$C_{19}H_{17}ClBrNO$	C, H, Cl, N
44	2,4-Me_2Ph	CH_3	H	H	B[b]	44	135-138 (2-PrOH)	$C_{24}H_{10}BrNO$	C, H, N
45	2,4-Me_2Ph	CH_3	Cl	H	B[b]	65	171-173 (2-PrOH)	$C_{24}H_{19}BrClNO$	C, H, Cl, N
46	3,4,5-$(MeO)_3$Ph	H	Cl	H	A	87	177-179 ($CHCl_3$)	$C_{24}H_{19}BrClNO_4$	C, H, Cl, N
47	H	CH_3	H	H	B[b]	37	99-102 (MeOH)	$C_{16}H_{12}BrNO$	C, H, N
48	H	CH_3	Cl	H	A	45	138-140 ($CHCl_3$-MeOH)	$C_{16}H_{11}BrClNO$	C, H, Cl, N
49	H	CH_3	H	Cl	B[b]	63	120-124 (2-PrOH)	$C_{16}H_{11}BrClNO$	C, H, Cl, N

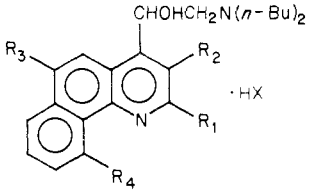
[a] Yields are based on the 4-carboxylic acid. [b] Purified by chromatography over alumina (Fisher Scientific Co. A 540) and eluted with benzene or benzene-$CHCl_3$ followed by recrystallization.

Table VI. Benzo[*h*]quinoline-4-ethylene Oxides



Compd	R_1	R_2	R_3	R_4	% yield	Mp, °C (crystn solvent)	Formula	Analyses
50	*t*-Bu	H	H	H	84	88-90 (2-PrOH)	$C_{19}H_{19}NO$	C, H, N
51	*t*-Bu	H	CH_3	H	85	138-139 (2-PrOH)	$C_{20}H_{21}NO$	C, H, N
52	*t*-Bu	H	Cl	H	90	113-116 (2-PrOH)	$C_{19}H_{18}ClNO$	C, H, Cl, N
53	2,4-Me_2Ph	CH_3	H	H	58	175-176.5 (2-PrOH)	$C_{24}H_{21}NO$	C, H, N
54	2,4-Me_2Ph	CH_3	Cl	H	62	124-126 (2-PrOH)	$C_{24}H_{20}ClNO$	C, H, Cl, N
55	3,4,5-$(MeO)_3$Ph	H	Cl	H	38	179.5-181 ($CHCl_3$-2-PrOH)	$C_{24}H_{20}ClNO_4$	C, H, N
56	H	CH_3	H	H	75	123-124 (2-PrOH)	$C_{16}H_{13}NO$	C, H, N
57	H	CH_3	Cl	H	77	127-130 (2-PrOH)	$C_{16}H_{12}ClNO$	C, H, Cl, N
58	H	CH_3	H	Cl	91	133-135.5 (2-PrOH)	$C_{16}H_{12}ClNO$	C, H, Cl, N

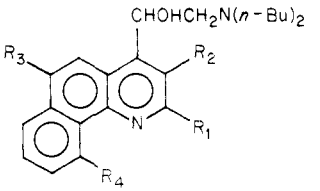
Table VII. α-Di-*n*-butylaminomethylbenzo[*h*]quinoline-4-methanol Salts



Compd	R_1	R_2	R_3	R_4	HX	% yield	Mp, °C (crystn solvent)	Formula	Analyses
59	*t*-Bu	H	H	H	$(CO_2H)_2$	80	183-185 dec (MeOH, Me_2CO)	$C_{29}H_{40}N_2O_5$	C, H, N
50	*t*-Bu	H	CH_3	H	$(CO_2H)_2$	90[a]	166-167 dec (C_6H_6-EtOH)	$C_{30}H_{42}N_2O_5$	C, H, N
61	*t*-Bu	H	Cl	H	$(CO_2H)_2$	61	173-176 dec (C_6H_6)	$C_{29}H_{39}ClN_2O_5$	C, H, N
62	2,4-Me_2Ph	CH_3	H	H	HCl	62	225-227 dec (2-PrOH)	$C_{32}H_{41}ClN_2O$	C, H, N
63	2,4-Me_2Ph	CH_3	Cl	H	HCl	67	146-151 dec ($CHCl_3$-C_6H_6)	$C_{32}H_{40}Cl_2N_2O$	C, H, N
64	3,4,5-$(MeO)_3$PhH		Cl	H	HCl	80	229-233 dec (EtOH-$CHCl_3$)	$C_{32}H_{40}Cl_2N_2O_4$	C, H, N
65	H	CH_3	H	H	HCl	70	185-188 dec (2-PrOH-H_2O)	$C_{24}H_{33}ClN_2O$	C, H, N
66	H	CH_3	Cl	H	HCl	92	178-181 dec (MeOH-Et_2O)	$C_{24}H_{32}Cl_2N_2O$	C, H, N
67	H	CH_3	H	Cl	HCl	78	183-185 dec (EtOH-2-PrOH)	$C_{24}H_{32}Cl_2N_2O$	C, H, N

[a] As the oily free base.

Table VIII. Antimalarial Activity[a] and Phototoxicity Data for Benzo[*h*]quinoline-4-methanols



Compd	R_1	R_2	R_3	R_4	ΔMST[b] or C,[c] dosage, mg/kg sc 160	320	640 (T^d)	MED[f,g] (mice), mg/kg ip
59	*t*-Bu	H	H	H		1.2	10.2 (0)	100
60	*t*-Bu	H	CH_3	H	2.7	3.5	5.9 (0)	300
61	*t*-Bu	H	Cl	H	2.2	1C	3C (0)	100
62	2,4-Me_2Ph	CH_3	H	H	4.2	4.6	5.6 (0)	300
63	2,4-Me_2Ph	CH_3	Cl	H	9.0	1C	4C (0)	*h*
64	3,4,5-$(MeO)_3$Ph	H	Cl	H	1C	3C (0[e])		80
65	H	CH_3	H	H	0.9	2.9	5.3 (0)	Negative
66	H	CH_3	Cl	H	6.9	12.9	2C (0)	400
67	H	CH_3	H	Cl	1.2	6.2	8.2 (0)	200
Quinine					0.6		4.8 (0)	Negative
2-Phenylquinine					5.8		2C (0)	10

[a] Determination of the antimalarial activity against *P. berghei* in infected mice was carried out by Dr. Leo Rane of the University of Miami, Fla. For a description of the test procedure see ref 26. [b] The change in mean survival time (ΔMST) is defined as the mean survival time for five treated mice minus the mean survival time for five control mice (6.2 days). [c] Curative; the indicated number of mice survived at least 60 days. [d] Toxic deaths at 640 mg/kg. [e] Toxic deaths at 320 mg/kg. [f] Minimum effective phototoxic dose. [g] These compounds were evaluated for phototoxicity as described in ref 4 by W. E. Rothe of Walter Reed Army Institute of Research, Washington, D.C. [h] See ref 27.

replaced by methyl the resulting **60** was much less active, as was the 10-chloro derivative **67**, which is isomeric with the curative 6-chloro compound **66**.

The phototoxicities of the benzo[h]quinoline-4-methanols prepared in this work, except for **63** which was not evaluated,[27] were determined in the animal test system[6] previously described and are shown in Table VIII. Unfortunately all compounds examined, with the exception of **65** which showed only marginal antimalarial activity, were moderately phototoxic and it may be that in this series antimalarial activity and phototoxicity are related.

Experimental Section

Melting points (Fisher-Johns apparatus) are uncorrected. Elemental analyses, indicated only by the symbols for the elements, were within ±0.4 of the calculated values. All compounds gave ir and NMR spectra consistent with the assigned structures. Ir and NMR spectra (Me_4Si internal reference) were determined using a Perkin-Elmer 21 and Varian A-60, respectively. Alumina for chromatography was purchased from Fisher Scientific Co. (A-540).

1H-Benz[g]indole-2,3-diones (4–7). These compounds were prepared from the appropriate 1-aminonaphthalene and diethyl ketomalonate hydrate,[28,29] using the following general procedure for 5-chloro-1H-benz[g]indole-2,3-dione (**6**), which was developed from, and gave more reproducible results than, that of Dethloff.[20] Syntheses of 4-methyl-1-aminonaphthalene[30] and 8-chloro-1-aminonaphthalene[31] were carried out according to the literature. A solution of 57.5 g (0.30 mol) of diethyl ketomalonate hydrate in 175 ml of AcOH was added during 0.75 h to a stirred, refluxing solution of 25.0 g (0.14 mol) of 1-amino-4-chloronaphthalene in 250 ml of AcOH. Reflux was continued 1.5 h after the addition was complete. The AcOH was then removed in vacuo and 10% aqueous KOH was added to the residue (stirring) to pH 11.0. The solution was heated to reflux and portions of 10% KOH were added to a constant pH of 10–11 (0.5 h). Air was then rapidly passed through the vigorously stirred, refluxing solution for 4.0 h. After cooling the yellow solution was filtered to remove a small amount of solid material and cautiously (CO_2 liberated) acidified with 37% HCl to pH 1.0. The brick-red precipitate was filtered, washed well with H_2O, and dried to give essentially pure **6**. Recrystallization gave pure material.

Benzo[h]quinoline-2,4-dicarboxylic Acids and -4-carboxylic Acids (8–19). The 2,4-dimethylpropiophenone used in the preparation of **11** and **12** was prepared as previously described.[32] The following procedure for 2-*tert*-butyl-6-chlorobenzo[h]quinoline-4-carboxylic acid (**10**) is representative. To a solution of 40 g (0.61 mol) of 85% KOH in 500 ml of 2-methoxyethanol was added 43.6 g (0.188 mol) of 5-chloro-1H-benz[g]indole-2,3-dione (**6**). The mixture was heated to reflux while stirring and 48.0 g (0.45 mol) of pinacolone was added in one portion. After 24 h of reflux, the solvent was evaporated in vacuo and 600 ml of H_2O added. The dark aqueous solution was washed with 3 × 300 ml of Et_2O and filtered through Celite, and the filtrate was acidified to pH 5.0 with glacial AcOH. The solid that separated was extracted into Et_2O and the Et_2O solution washed with 100 ml of H_2O and dried (Na_2SO_4). Evaporation of the Et_2O gave a light brown solid which was recrystallized from the minimum amount of PhMe to give nearly pure **10**. Recrystallization (2-PrOH–H_2O) gave pure material. Decarboxylation of the 2,4-dicarboxylic acids (**14**, **16**, and **18**) to the 2-unsubstituted 4-carboxylic acids (**15**, **17**, and **19**, respectively) was accomplished using the method of Senear.[33]

Benzo[h]quinoline-2,4-dicarboxylic Esters and -4-carboxylic Esters (20–31). These esters are described in Table III.

Benzo[h]quinoline-4-carbonyl Chlorides (32–40). These compounds were prepared by refluxing the acid with four times their weight of $SOCl_2$ for 2–4 h. Evaporation of the $SOCl_2$ in vacuo followed by evaporation of several portions of dry PhMe from the residue gave material of satisfactory purity for conversion to the bromomethyl ketones.

α-Bromomethyl 4-Benzo[h]quinolyl Ketones (41–49). Method A. Treatment of the acid chlorides **41–43**, **46**, and **48** with excess diazomethane followed by 48% HBr using the method previously reported[9] gave the corresponding bromomethyl ketones.

Method B. The following procedure for α-bromomethyl-2-(2,4-dimethylphenyl)-3-methylbenzo[h]quinolyl ketone (**44**) is typical. A solution of 41.0 g (0.12 mol) of the carboxylic acid (**11**) in 130 ml of $SOCl_2$ was refluxed 2 h. The $SOCl_2$ was removed in vacuo, and the residue was dissolved in dry Et_2O (100 ml) and filtered and the Et_2O evaporated. Dry C_6H_6 (200 ml) was added and evaporated in vacuo. A solution of the resulting acid chloride in 100 ml of Et_2O was added dropwise to a stirred solution of ethoxymagnesium diethylmalonate from 0.2 mol of diethyl malonate prepared as previously described.[25] The mixture was refluxed 4 h and poured into 100 ml of H_2O and a solution of 25 ml of H_2SO_4 in 200 ml of H_2O added. The mixture was stirred until the inorganic material had dissolved. The Et_2O layer was then dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in 350 ml of AcOH and a solution of 28.8 g (0.176 mol) of Br_2 in 70 ml of AcOH was added dropwise while stirring without external cooling. When the addition was complete, the mixture was refluxed 0.5 h, a solution of 43.0 ml of H_2SO_4 in 230 ml of H_2O was then added, and reflux continued 3 h. After concentration to ca. one-third volume in vacuo, the residue was covered with 500 ml of Et_2O and the aqueous phase neutralized to pH 11 with 10% KOH. The Et_2O was removed and the aqueous portion extracted with 200 ml of Et_2O. The combined Et_2O extract was dried with $MgSO_4$ and evaporated. The resulting dark syrup was chromatographed over a short alumina column using C_6H_6 to give slightly impure bromomethyl ketone. One recrystallization gave pure material.

Benzo[h]quinoline-4-ethylene Oxides (50–58). These compounds were prepared essentially as described[9] by reduction of the corresponding bromomethyl ketone with a large excess of $NaBH_4$ in 2-PrOH.

α-Dibutylaminomethylbenzo[h]quinoline-4-methanols (59–67). Treatment of the epoxides with refluxing Bu_2NH for 12–15 h gave the bases **59–67** after removal of excess Bu_2NH first at the H_2O pump and then in high vacuum. In several cases (**59–61**) crystalline salts could not be obtained until the crude base was chromatographed over alumina using C_6H_6–$CHCl_3$. In the remaining cases (**62–67**) the HCl salts were obtained directly after essentially complete removal of Bu_2NH in high vacuum.

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Oxindole-3-spiropyrrolidines and -piperidines. Synthesis and Local Anesthetic Activity

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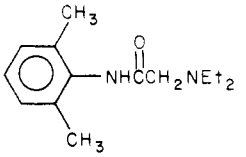
The synthesis and local anesthetic properties of five 1-dealkyloxindole-3-spiropyrrolidines and six 1-dealkyloxindole-3-spiropiperidines are described. The compounds studied include members of all five possible positional isomers of the two classes of spirooxindoles; all showed local anesthetic activity by the rat sciatic nerve block method. The coincidence of the least variability in the relative positions of basic nitrogen, amide carbonyl, and aromatic ring (compounds 1 and 6) with lowest normalized toxicity is noteworthy.

In our continuing search for novel local anesthetics,[1] we have synthesized and tested a number of oxindole-3-spiropyrrolidines and -piperidines (1–11). These compounds incorporate the principal structural moieties of the local anesthetic and antiarrhythmic drug lidocaine (12)—viz. an aromatic nucleus, an amide linkage, and a basic amino group—in a nearly rigid framework. Since both N-methylation and N-ethylation of the amide function in lidocaine congeners have been shown to result in decreased activity and increased toxicity,[2a] we have limited this study to the 1-dealkyloxindoles.



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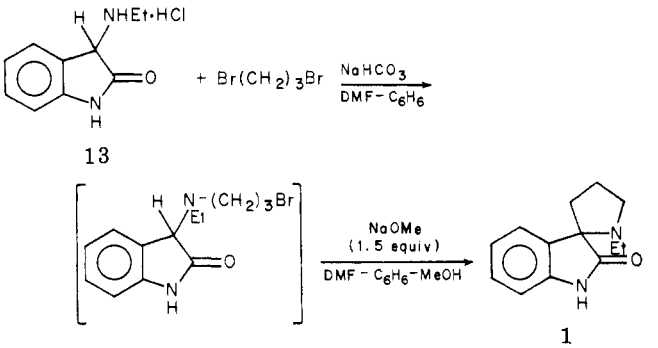
The efficacy of lidocaine has led to the preparation of many different series of *N*-aminoacylanilines,[2b–e] and there is a recognized need for local anesthetics with well-defined stereochemistry[3] for use in the study of the concept of receptor(s) involved in blockage of nerve impulses. Conformational and other stereochemical effects on local anesthetic activity have been the subject of several recent studies,[4a] some partially rigid local anesthetics have been synthesized,[4b,c] and a highly rigid molecule, tetrodotoxin, has been found to have high local anesthetic potency.[5] Nevertheless, we are aware of no attempts at molecular modification involving preparation of all possible positional isomers of a rigid local anesthetic.

The spirooxindoles discussed in this paper represent all possible isomeric types in the two classes of compounds being studied. The structural rigidity of each member is such that conformational variations in the spatial orientation of component functional groups—known to be of considerable magnitude in flexible drug molecules[6]—are restricted within a narrow range. In isomers where the basic nitrogen is located next to the spiro carbon, the activity-controlling distance between the basic nitrogen, the amide carbonyl, and the aromatic ring[2c] becomes completely fixed.

Scheme I



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1

Although designed as lidocaine congeners, however, the resemblance of the title compounds to lidocaine is only superficial, and a closer examination shows that they possess unique structural features which set them apart from all known classes of local anesthetics. Significant differences can be discerned in the stereochemistry of lidocaine and our compounds. Thus, the spirooxindoles all have the *cis*-amide configuration while the trans configuration has been deduced for the protonated form of lidocaine[7a] which is supposed to be the active form of this drug.[8] Another difference is seen in the coplanarity of the amide carbonyl group with respect to the aromatic moiety; steric hindrance precludes such a conformation in the lidocaine molecule.[7a,c] Finally, unlike in the case of