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Relationship between Physical Properties and Antimalarial Activities of 1,4-Naphthoquinones

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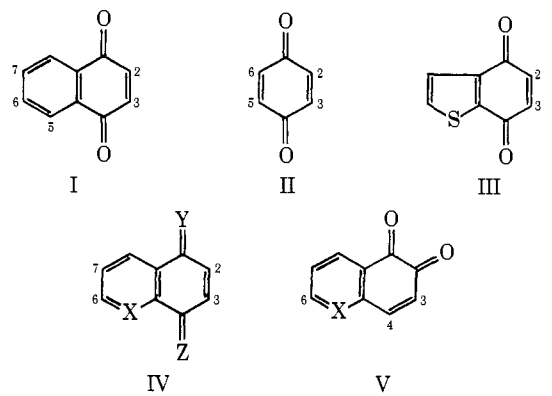
Studies have been made of the lipophilic and oxidation-reduction properties of active *vs.* inactive naphthoquinone antimalarials reported by Fieser in 1948. The results suggest that, in addition to the appropriate partition coefficient, the active quinones possess a rather limited range in ease of reduction as measured by either the energy of the lowest unoccupied molecular orbital (E_{LEMO}) or the redox potential. These results are consistent with the known chemistry and biochemistry of the molecules. The model also correctly predicts the curative properties of 28 series of related molecules (more recently) synthesized as antimalarials.

The relative potency of members of a series of drugs is often considered to be a function of differences in hydrophobic, electronic, and steric factors. In the past several years considerable advances have been made in quantitating such relationships.[1] The ability to anticipate or at least rationalize the boundaries of a series is a related but not identical problem. That is, what factors determine which compounds are members of a set and which apparent analogs will be completely inactive or act by a different mechanism of action? This sort of question implies an all-or-none or threshold type of relationship between a physical property and activity rather than the continuous correlation seen with analogs of varying potency.

The antimalarial naphthoquinones first studied by Fieser, *et al.*,[2] proved to be a very interesting example of this type of problem. In their original analysis of the structure–activity relationships of the 2-alkyl-3-hydroxy-1,4-naphthoquinones, it was shown conclusively that there is a marked dependence of potency on lipophilic character.[3] However, nonoptimum hydrophobic character does not explain the inactivity of the large number of derivatives reported to be inactive[4] (ED_{95} of >400 mg/kg in Table I). We were interested to discover if the compounds are inactive for electronic or for steric reasons.



The naphthoquinones probably exert their antimalarial activity by competing with coenzyme Q to disrupt mitochondrial electron transport.[2,5,6] On the basis of this mechanism of action we expected that the inactive molecules should differ from the active ones in oxidation-reduction properties. As a measure of these properties we calculated (1) the energy of the lowest empty molecular orbital (E_{LEMO}) by the Hückel technique and (2) the standard redox potential, E_0.

Experimental Section

Since the drugs act within the lipoidal mitochondrion, the physical properties were calculated for the uncharged species.

Partition Coefficients (P). The log P values were calculated from known values by additivity procedures.[7] Except where noted π values (log P [derivative] − log P [parent]) were taken from Fujita, *et al.*,[8] for the aromatic ring substituents. The known log P's which were used are listed in Table II. Ring systems other than 1,4-naphthoquinones were calculated as follows.

1,4-Quinolinequinone: the difference between the log P for naphthalene and quinone is 1.34. Therefore, since 1,4-naphthoquinone has a log P of 1.71, the equivalent quinoline would have a log P of 1.71 − 1.34 or 0.37. 1,4-Thionaphthenequinone: this log P was calculated in the same manner as the 1,4-quinolinequinone. The difference between the log P for naphthalene and thionaphthalene is 0.25; therefore, the log P for 1,4-thionaphthenequinone would be 1.71 − 0.25 or 1.46.

Other values can be calculated in the same way. For example, the log P for a 3-isoamyl substitution is the log P for 2-hydroxy-3-isoamyl-1,4-naphthoquinone minus the log P for 2-hydroxy-1,4-naphthoquinone or 3.87 − 1.38 or 2.49. Likewise the log P for a 3-$(CH_2)_3C_6H_{11}$ substituent is 5.31 − 1.38 or 3.93 and for 2-OH is 1.38 − 1.71 or −0.33. Log P values were calculated in this manner for all compounds reported.

It is assumed that 1,4-naphthoquinoneimine has the same log P as 1,4-naphthoquinone, or the imine group has the same contribution to P as the carbonyl group.

Log P's for the 1,2-naphthoquinones were reduced by 1.00 from that of the corresponding 1,4-naphthoquinone. This is based on the measured cyclohexane values reported in ref 7.

***E*₀.** Whenever data were available E_0 values were calculated by summing substituent effects upon E_0 of the parent or related quinone. For example, the substituent effect of a 2-methyl group was

Table I. Antimalarial Activity and Physical Properties of Quinones

Compd no.	Type	Substituent 2	3	6	7	Antimalarial ED_{95}, mg/kg Obsd[a]	Calcd[b] on basis of log P	Log P	E_{LEMO}	E_0
1	I	OH	i-C_5H_{11}	H	H	68	111	3.87[c]	−0.384	0.294
2	I	OH	$(CH_2)_3C_6H_{11}$	H	H	20	32	5.31[c]	−0.384	0.294
3	I	OH	$(CH_2)_5C_6H_{11}$	H	H	23	61	7.81	−0.384	0.294
						Curative[d] at 120				
4	I	Cl	i-C_5H_{11}	H	H	>400	29	4.64	−0.339	0.439
5	I	CH_3	i-C_5H_{11}	H	H	>400	71	4.69	−0.330	0.359
6	I	H	i-C_5H_{11}	H	H	>400	45	4.20	−0.327	0.422
7	I	SH	[e]	H	H	>400			−0.292	0.438
8	I	NH_2	i-C_5H_{11}	H	H	>400	58	4.37	−0.420	0.212
9	I	OH	$C_{10}H_{21}$	OCH_3	H	>400	28	6.47	−0.399	0.256
10	I	OH	$C_{10}H_{21}$	H	OCH_3	>400	28	6.47	−0.397	0.256
11	I	OH	$(CH_2)_4C_6H_{11}$	H	Cl	>400	29	6.69	−0.387	0.351
12	I	OH	$(CH_2)_3C_6H_{11}$	OH	H	>400	57	4.64	−0.399	0.240
13	I	OH	$C_{10}H_{21}$	Br	H	>400	35	7.17	−0.386	0.342
14	I	OH	i-C_5H_{11}	CH_3	H	Slightly active at 100 mg/kg	59	4.26	−0.385	0.277
15	I	OH	i-C_5H_{11}	H	CH_3	Slightly active at 100 mg/kg	59	4.26	−0.385	0.279
16	I	OH	$(CH_2)_3C_6H_{11}$	H	7,8-C_4H_4	>400	29	6.63	−0.310	0.418
		2	3	5	6					
17	II	OH	$C_{11}H_{23}$	OH	H	>400	71	5.04	−0.328	0.379
18	II	OH	$(CH_2)_3C_6H_{11}$	$-(CH_2)_4-$		>400	30	5.93	−0.277	0.416
19	III	$(CH_2)_3C_6H_{13}$	OH			~100	39	5.06	−0.350	0.369

[a] Reference 4 except where noted. [b] Equation 3. [c] Reference 7. [d] Reference 15. [e] The structure of the side chain was not reported.

calculated from E_0 (2-methyl-1,4-naphthoquinone) − E_0 (1,4-naphthoquinone) = 0.063 V. Except where noted the E_0's were taken from ref 9. Data were not available to allow this method of calculation for the E_0 of compounds 7, 9, and 10. In these cases the E_0 was estimated from the regression equation which relates E_0 with Hammett σ(p) constant.[10] For variations in the 2 position the relationship is

$$E_0(v) = 0.398 + 0.270\sigma_p \quad (1)$$

where n = 5, r = 0.984, and s = 0.019. For molecules substituted in the 6 position the relationship is

$$E_0(v) = 0.308 + 0.191\sigma_p \quad (2)$$

where n = 4, r = 0.982, and s = 0.011. Finally, the E_0 for molecule 10 was assumed to be equal to that of molecule 9. The E_0 values of molecules 19–22 were calculated from ref 11 and 12 as well as 9.

Hückel Molecular Orbital Calculations. The parameters used in these calculations are listed in Table III.

Calculated ED_{95} Values Based on Lipophilicity Alone. Since lipophilic factors are such an important determinant of potency in this series, one must be certain that the inactive molecules in Table I do not owe their inactivity to nonideal lipophilic character. To evaluate this possibility, the relationship between log P and potency of a series of 2-alkyl-3-hydroxy-1,4-naphthoquinones (Table IV) was formulated by the Hansch technique. Equation 3 is the result.

$$\log (1/C) = -4.02 + 1.63\,(\pm 0.37)\log P - 0.13\,(\pm 0.03)(\log P)^2 \quad (3)$$

The standard deviations of the coefficients are in parentheses. In this data set C is the molar ED_{95} vs. *P. lophurae* in ducks; n, the number of compounds, is 10; r = 0.920; $F_{2,7}$ = 19.33; s = 0.186. The optimum log P is 6.37 with 95% confidence limits of 5.94–7.73. Equation 3 represents a statistical refinement of the original observations.[3] It is also a base line from which to measure the effect of changes due to electronic and steric properties. From eq 3 and the calculated log P, the "expected" ED_{95} of each derivative in Table I was calculated. These calculations are to be used as a rough guide only, since the original data suggest that there are substantial steric effects on potency and that the potency values are precise only to within a factor of twofold.

Results

Interrelationships between Electronic Properties. The correlation between the Hammett σ constant and measured E_0 values of compounds varied at a single position has been reported previously.[13] The E_0 values are more useful in the current analysis since comparisons can be made between molecules in which the substituent is located at different positions.

As would be expected,[14] there is a high correlation between the E_{LEMO} and E_0. For all compounds in Table I except the halogen-substituted derivatives, the relationship is

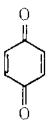
$$E_0 = 0.921 + 1.663\,(\pm 0.135)\,E_{LEMO} \quad (4)$$

In this case n = 14, r = 0.962, $F_{1,12}$ = 152, and s = 0.022. Thus, if E_{LEMO} can be calculated, then E_0 can also be estimated.

The three analogs with halogen substituents require substantially different potentials to be reduced than would be expected from the molecular orbital calculations. Adjustment of the value of the parameters of h_{Cl} within the range 1.0–3.0 and k_{C-Cl} within the range 0.4–0.8 does not improve the result. Since the E_0 values were measured and they fit the Hammett relationships (eq 1 and 2), E_0 values probably are not in error. Thus, the Hückel calculations apparently fail to take into account some factor which affects the ease of reduction of halogen-substituted naphthoquinones.

Relationship between Electronic Properties and Activity. The data in Table I confirm the hypothesis that only molecules with the appropriate ease of reduction are antimalarials. The only active naphthoquinones are those with an E_{LEMO} between −0.349 and approximately −0.390 β units or with an E_0 between +0.294 and +0.369 V.

Table II. Log P's Used in the Calculation of Partition Coefficients[a]

2	3	6	Log P (octanol–water)
Naphthoquinones (Structure I)			
H	H	H	1.71
OH	H	H	1.38
Cl	H	H	2.15
CH_3	H	H	2.20
NH_2	H	H	1.88
n-NHC_4H_9	H	H	3.11
NHC_6H_5	H	H	2.84
n-$NHNHC_4H_9$	H	H	0.95[b]
$NHCOCH_3$	H	H	1.29
n-SC_4H_9	H	H	3.29
OH	CH_3	H	1.20
OH	i-C_5H_{11}	H	3.87[b]
OH	n-$C_{12}H_{25}$	H	7.34
OH	$(CH_2)_3C_6H_{11}$	H	5.31[b]
Cl	n-NHC_4H_9	H	4.26
H	H	CH_3	2.10
$NHCOCH_3$	n-SC_4H_9	H	2.07
Other Structures			
			0.20
			3.37
			2.03
			3.12

[a] Reference 7. [b] Measured in ether–water; calculated for octanol by means of regression equations listed in ref 7.

The lack of correspondence between calculated and experimental measures of the ease of adding an electron to these molecules allows one to judge which measure is more predictive of antimalarial properties. For the halogen derivatives the E_{LEMO} properly predicts that the 2-chloro compound (no. 4) would be inactive while it is ambiguous for the 6-bromo and 7-chloro analogs (no. 11 and 13); the E_0 value erroneously suggests that all three derivatives should be active. The thionaphthenequinone (no. 19) is perhaps better predicted by E_{LEMO} then E_0. Thus, the E_{LEMO} values are better predictors of activity.

Extension of the Calculations to Newer Molecules. During the 1960's several additional series of molecules closely related to the naphthoquinones were synthesized as potential antimalarial agents.[15-22] Table V contains a listing of the structure, activity *vs. Plasmodium berghei* in mice, and physical properties of these molecules (E_0's were, in general, not available). Groups A and B include 13 types of compounds whose partition coefficient would suggest curative properties. The three active molecules in group A have an E_0 in the range associated with activity in the original data set; the other ten molecules are both inactive and outside of the postulated range of E_{LEMO}.

The series listed in part C of Table V are expected to be inactive on the basis of both hydrophobic and electronic properties. All are inactive. Finally, group D contains a series which is too hydrophilic but has the appropriate oxidation–reduction properties. They too are inactive.

Thus, a model derived from the hydrophobic and electronic properties of 29 molecules synthesized before 1950 correctly predicted the presence or absence of curative properties of 30 molecules or series of molecules synthesized since that time.

The thioether molecules (**22**) appear to fit into the same structure–activity pattern as the other naphthoquinones in spite of the fact that sulfur is easily oxidized by animals. Such oxidation would substantially increase the E_0 and decrease the partition coefficient of the administered drug.

Table III. Parameters Used in Hückel Calculations[a]

Atom (a)	h_a	Bond (a–b)	K_{ab}
C	0	C–C	1.0
C(methyl)[b]	−0.1	C–C(methyl)	0.7
$\equiv H_3$ or $=H_2$[b]	−0.5	$C\equiv H_3$ or $C=H_2$[b]	2.5
N(·)	0.4	C–N(·)	1.0
N(··)	1.0	C–N(··)	0.9
N(+)	2.0	C–N(+)	1.0
O(·)	1.2	C–O(·)	2.0
O(··)	2.0	C–O(··)	0.9
S(··)[c]	0	C–S[c]	0.8
Cl	2.0	S–S[c]	1.0
Br	1.5	C–Cl	0.4
		C–Br	0.3
		C(methyl)–O(··)	0.6
		C(methyl)–N(··)	0.6

[a] Parameters have been taken largely from B. Pullman and A. Pullman, "Quantum Biochemistry," Wiley-Interscience, New York," N. Y., 1963, and A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961. [b] Hyperconjugative model for methyl and methylene: C. A. Coulson and V. A. Crawford, *J. Chem. Soc.*, 2052 (1953). [c] Sulfur has been assumed to be pd hybridized: H. C. Longuet-Higgins, *Trans. Faraday Soc.*, **45**, 173 (1949).

Table IV. Dependence of Antimalarial Potency of 2-Hydroxy-3-alkyl-1,4-naphthoquinones on Hydrophobic Character

3 substituent	Log P (octanol–water)	Log (1/C) Obsd[a]	Log (1/C) Calcd[b]	Obsd − calcd
C_4H_9	3.35[c]	0.10	0.00	0.10
C_5H_{11}	3.85	0.33	0.35	−0.02
C_6H_{13}	4.41[c]	0.54	0.68	−0.14
C_7H_{15}	4.85	0.83	0.87	−0.04
C_8H_{17}	5.35	0.89	1.03	−0.14
C_9H_{19}	5.98[c]	1.54	1.15	0.39
$C_{10}H_{21}$	6.50[c]	1.19	1.17	0.02
$C_{11}H_{23}$	6.85	0.95	1.14	−0.19
$C_{12}H_{25}$	7.34[c,d]	1.09	1.05	0.04
$C_{13}H_{27}$	7.84	0.87	0.89	−0.02

[a] Logarithm of 1/molar ED_{95} calculated from data, ref 4. [b] Calculated from eq 1. [c] In ref 7. The other log P values are calculated. [d] Measured in ether–water and converted to log P (octanol) by means of regression equations listed in ref 7.

Discussion

The requirement for a certain ease of reduction for a quinone to be an antimalarial is consistent with their postulated mode of action. The active antimalarials are active inhibitors of electron transport.[2,5,6] Experimental evidence indicates that they compete with coenzyme Q.[5] Since the active compounds are more difficult to reduce than coenzyme Q (E_{LEMO} = 0.303 β), perhaps these molecules act as an electron sink. The optimum E_{LEMO} suggests that the source of the electrons is not strong enough to reduce molecules with an E_{LEMO} greater than −0.390 β.

The parabolic relationship between potency and partition coefficient of 2-hydroxy-3-alkyl-1,4-naphthoquinones

Table V. Observed *vs.* Predicted Curative Properties of Newer Potential Antimalarial Quinones

Compd no.	Type	x	y	z	2	3	Curative?	Log P^c	E_{LEMO}	E_0
					Group A. Proper Partition Coefficient[a] and E_{LEMO}[b]					
20	IV	N	O	O	OH	$C_{15}H_{31}$	Yes[d]	7.5	−0.378	0.383
21	IV	N	O	O	$(CH_2)_5C_6H_{11}$	OH	Yes[d]	6.5	−0.375	0.383
22	IV	N	O	O	OH	–SR	Yes[e]	7.6–8.6	−0.353	
					Group B. Proper Partition Coefficient,[a] Wrong E_{LEMO}[b]					
23	IV	N	O	O	$NHC_{16}H_{33}$	H	No[f]	7.8	−0.415	0.322
24	IV	CH	O	O	NHNHCOR	H	No[g]	1.5–8.7	−0.453	
25	IV	CH	O	O	NHR	H	No[h]	2.3–6.3	−0.421	0.232
26	IV	CH	NR	O	NHR	H	No[i]	4.1–15.1	−0.313	
27	IV	CH	NR	O	NHC_6H_5	H	No[i]	6.4–7.7	−0.300	
28	IV	CH	NC_6H_5	O	NHR	H	No[i]	4.7–7.7	−0.264	
29	IV	N	NC_6H_4-*p*-Cl	O	NHC_6H_4-*p*-Cl	H	No[i]	5.6	−0.249	
30	IV	N	NC_6H_3-3,4-$(CH_3)_2$	O	NHC_6H_3-3,4-$(CH_3)_2$	H	No[i]	5.6	−0.258	
				3	4	6				
31	V	CH	H	H	NR_2	H	No[h]	0.9–9.1	−0.422	0.295
32	V	N	Cl	H	NR_2	H	No[h,k]	1.4–6.8	−0.413	
					Group C. Wrong Partition Coefficient[a] and E_{LEMO}[b]					
				z	2	3				
33	IV	CH	O	O	$CO(CH_2)_2C_6H_{11}$	H	No[h]	4.1	−0.463	
34	IV	N	NC_6H_4-*p*-$CO_2C_2H_5$	O	NC_6H_4-*p*-$CO_2C_2H_5$	H	No[i]	4.5	−0.114	
35	IV	N	NC_6H_4-*p*OCH_3	O	NH_2	H	No[i]	1.5	−0.274	
36	IV	N	NH	O	*n*-NHC_4H_9	H	No[i]	1.5	−0.295	
37	IV	N	NC_6H_4-*p*-Cl	O	NH_2	H	No[i]	2.5	−0.260	
38	IV	N	NC_6H_3-3,4-$(CH_3)_2$	O	NH_2	H	No[i]	2.5	−0.258	
39	IV	N	NC_6H_4-*p*-OCH_3	O	NHC_6H_4-*p*-OCH_3	H	No[i]	4.5	−0.268	
40	IV	N	NC_6H_5	O	NH_2	H	No[i]	1.5	−0.257	
				3	4	6				
41	V	N		H	NR_2	H	No[k]	0.7–2.0	−0.408	
42	V	N		H		CH_3	No[i]	1.5	−0.409	
43	V	N		H	NH_2	H	No[i]	1.2	−0.407	
44	V	N		Cl	NHC_6H_4-*p*-CH_3	H	No[i]	1.5	−0.403	
45	V	N		Cl	NHC_6H_5	H	No[i]	1.3	−0.399	
46	V	CH		H	NHC_6H_4-*p*-OCH_3	H	No[i]	1.9	−0.412	
47	V	CH		H	$N(C_6H_5)(CH_2)_3N(CH_3)_2$	H	No[i]	3.4	−0.409	0.295
48	V	CH		CH_3	OH	H	No[i]	0.2	−0.534	
					Group D. Wrong Partition Coefficient,[a] Right E_{LEMO}[b]					
49	V	CH		H	OR	H	No[h,i]	1.4–3.4	−0.388	

[a] Log $P > 5.5$. [b] $-0.390 < E_{LEMO} < -0.349$. [c] The log P range of the series is given if a number of analogs in an inactive series with the same E_{LEMO} were reported. [d] Reference 15. [e] Reference 22. [f] Reference 16. [g] Reference 17. [h] Reference 18. [i] Reference 20. [j] Reference 19. [k] Reference 21.

shown in eq 3 is not restricted to whole animal tests. Turnbull, *et al.*,[5] observed that in this series the most potent inhibitor of oxygen uptake by the electron transport particle is 2-hydroxy-3-isononyl-1,4-naphthoquinone. This molecule is also the most potent isoalkyl homolog *vs. P. lophurae* in ducks. Thus, potency at the subcellular level is a good predictor of whole animal activity; for ducks, the critical lipid barrier appears to be the lipid of the electron transport particle. The structure–activity data are less complete on the relative potency of analogs *vs. P. berghei* infections in mice; however, the optimum log P is approximately 1.0 log unit higher.[23] The apparent difference in the optimum partition coefficient of naphthoquinones in ducks and mice may be a reflection of differences in the rate or extent of metabolism between the two species.

The basis of the selective toxicity of these antimalarials is not directly explained by the requirement of a certain lipophilic and electronic nature. One would expect that these molecules could inhibit electron transport equally as well in the host and as in the parasite. However, Pinder[24] suggested that malaria plasmodia are deficient in enzyme systems which produce reducing agents, specifically NADH. This suggests that perhaps the naphthoquinones are inactivated in host cells by normal constituents; whereas in the malaria plasmodia such protective substances are absent and the naphthoquinones survive long enough to kill the cell.

The requirement that analogs of a series must possess a certain electronic characteristic (E_{LEMO} or ease of reduction in this case) is not a new observation. J. C. Craig, *et al.*, reported that the only phenothiazines with appreciable anthelmintic activity are those with an oxidation potential in the range of 550–850 mV.[25] In another structure–activity study of naphthoquinones, Ikeda showed that the antibacterial activity of substituted 1,4-naphthoquinones is a function of their reduction potential.[26] Molecules with a reduction potential more negative than −0.345 V show maximal potency; those less negative show a potency roughly proportional to their reduction potential.

When one attempts to postulate a molecular mode of action of a series of drugs on the basis of their structure–activity relationships, ambiguities often arise. Thus, in this study the structure-activity and biochemical data suggest that the naphthoquinones act as electron acceptors. An alternate proposal based on the critical nature of

E_{LEMO} alone would be that these molecules act as electron acceptors in the formation of a charge-transfer bond. Such a mechanism for quinine antimalarials has been supported by molecular orbital calculations;[27] however, no biochemical evidence supports this mechanism for naphthoquinones.

A third explanation of the observed structure–activity relationships might focus on the relationships between E_{LEMO} and σ (eq 2 and 4). If σ represents electronic effects on ionization of the hydroxyl group, then one might postulate that the acid-base properties of the group at the 2 position determine activity *vs.* inactivity of the molecule. Series no. **23** was synthesized on this basis and found to be inactive.[17] In addition, the naphthoquinones act in the lipid mileau of the mitochondrion which would suppress ionization and they are competitive with coenzyme Q which is not acidic. Thus, a consideration of the biochemistry eliminates two of the three explanations and leaves only the first.

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Further Side-Chain Modification of Antimalarial Phenanthrene Amino Alcohols

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Several phenanthrene amino alcohols with specifically designed side chains attached to the 9 position have been synthesized and their structure–activity relationships in animal screening against *Plasmodium berghei* and *P. gallinaceum* have been studied. The shorter chain 3,6-bis(trifluoromethyl)-α-(alkylaminomethyl)-9-phenanthrenemethanols displayed activity at 10 mg/kg and are curative at 20 mg/kg against *P. berghei* with no toxicity to the host. Activity of the corresponding α-(2-piperidylmethyl) derivatives conforms with the postulated triangle pharmacophore for antimalarial activity.

In connection with our structure–activity relationship study on the side-chain modification of certain phenanthrene amino alcohols[1] and a comparison with 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran,[2] a triangle pharmacophore (composed of one nitrogen atom, one oxygen atom, and the center of an aromatic or heteroaromatic ring to which the side chain is attached) of definite parameters was uncovered among these antimalarial agents. It was also postulated that the nitrogen and the oxygen atoms are in close proximity and are linked by hydrogen bonds to form a five- or a six-membered ring with neighboring carbon atoms.[2] The proposed hydrogen-bond formation was subsequently confirmed by nmr studies.[3] Interestingly, a recent proposed triangulation feature for α-adrenergic receptors[4] is identical in every aspect with our proposed triangular feature. Some structurally similar 4-pyridylamino alcohols and corresponding quinoline derivatives have recently been reported to possess β-adrenergic blocking activity.[5,6]

The foregoing information prompted us to synthesize several additional phenanthrene amino alcohols with specifically designed side chains in order to gain a better understanding of the mode of action of these antimalarial compounds. The outstanding antimalarial activity displayed by several 3,6-bis(trifluoromethyl)-α-(alkylaminomethyl)-9-phenanthrenemethanols[1] suggested the preparation of shorter α-alkylaminomethyl side chain derivatives **1a–c**. Compounds **1b** and **1c** are of particular interest since the side chain of **1b** and **1c** is identical with that of ephedrine (epinephrine, adrenaline) and norephedrine (norepinephrine, noradrenaline), respectively. The proposed hydrogen-bond feature prompted the preparation of compounds of type **2, 3**, and **4**.

Chemistry. The 3,6-bis(trifluoromethyl)-α-(alkylaminomethyl)-9-phenanthrenemethanols **1a–c** were prepared by the interaction of 3,6-bis(trifluoromethyl)-9-phenanthryloxirane[1,7] (**5a**) with a primary amine or ammonia. 3,6-Dichloro-α-(2-piperidylmethyl)-9-phenanthrenemethanol