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Potential Antimalarials. 8. Some 10-Substituted 9-Phenanthrenemethanols[1,†]

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Starting with phenanthrene or fluorenone, a series of 10-substituted and 2,7,10-trisubstituted 9-phenanthrenemethanols has been synthesized and tested for antimalarial activity by the Rane *Plasmodium berghei* test in mice. 2,7-Dibromo- (and dichloro-) 10-methoxy-9-(2-dibutylamino-1-hydroxyethyl)phenanthrene hydrochloride, which showed 4/5 cures and 2/5 cures, respectively, at 80 mg/kg, were the most active compounds tested. Selective butyllithium exchange with the 10-bromine atoms of 2,7,10-tribromo-9-methoxy- and -9-methylphenanthrene is reported.

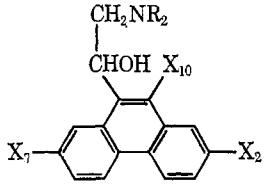
The revived interest in 9-phenanthrenemethanols as curative agents in malaria led to the synthesis of a large number of these compounds, mostly *via* a Perkin condensation followed by a Pschorr ring closure.[2] It was our purpose to develop new routes to 9-phenanthrenemethanols *via* phenanthrenes or other simple polynuclear compounds which would avoid ring closures and lead to antimalarials not available by the ordinary method of synthesis.

Earlier studies on 2-*p*-chlorophenyl-7-quinolinemethanols[3] indicated that antimalarial activity was enhanced by flanking the 2-dialkylamino-1-hydroxyethyl side chain with halogens. Thus, 9-phenanthrenemethanols substituted at the 10 position were of special interest.‡

† Contribution No. 1251 to the Army Research Program in Malaria.

‡ To completely confirm or refute the earlier lead in the 9-phenanthrenemethanol series, substituents at both the 10 and 8 positions should be present.

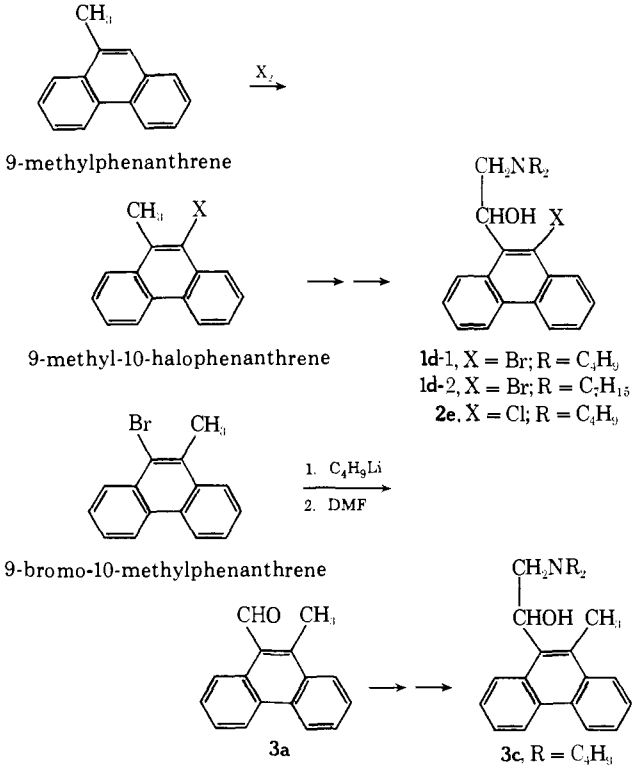
Table I. Activity[a] of 10-Substituted 9-Phenanthrenemethanols



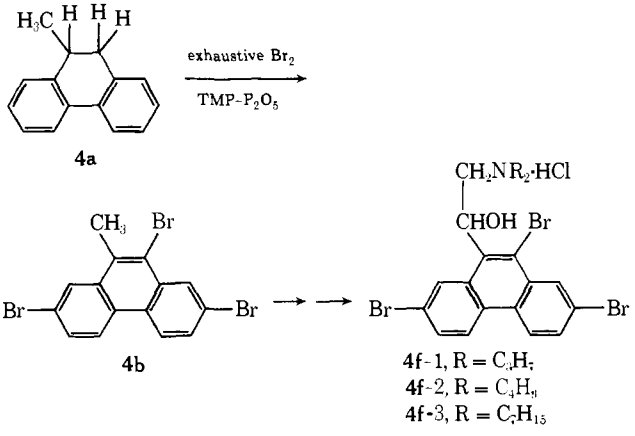
No.	X_{10}	X_2 and X_7	R	ΔMST at mg/kg,[b] days 10	20	40	80	160	320	640
1d-1	Br	H	C_4H_9	0.3	0.3	0.7	4.1	5.9	8.1	10.1
1d-2	Br	H	C_7H_{15}	1.1	2.9	6.1	8.1	1C[c]	4C	
2e	Cl	H	C_4H_9	0.3	0.3	0.5	3.9	7.9	9.5	11.5
3c	CH_3	H	C_4H_9	0.3	0.3	0.5	3.3	5.9	14.1	3C
4f-1[d]	Br	Br	C_3H_7	0.1	0.3	0.3	0.7	0.9		
4f-2	Br	Br	C_4H_9	0.5	3.1	5.5	10.1	11.1	15.1	
4f-3	Br	Br	C_7H_{15}	0.3	0.3	0.3	3.1	6.7		
5d	C_6H_5O	H	C_4H_9		0.2	0.2	0.2	1.0	5.8	15.1
6d-1	CH_3O	H	C_4H_9		0.2	0.2	0.2	0.2	0.4	0.4
6d-2	CH_3O	H	C_7H_{15}		0.2	0.2	0.4	0.6	5.8	9.2
7f-1	CH_3O	Br	C_4H_9		1.2	11.2	4C	5C		
7f-2	CH_3O	Br	C_7H_{15}				0.4	5.8	3C	
8f-1	CH_3O	Cl	C_4H_9		0.4	4.3	2C	5C		
8f-2	CH_3O	Cl	C_7H_{15}			0.4	4.0	6.8	4C	
May compound,[e] X_6 = Br	H	H	C_7H_{15}	2.1	4.5	6.7	1C	3C	4C	4C

[a] Rane *P. berghei* test on five mice. [b] Mean survival times over controls. [c] C = number of cures. [d] This compound and all below it in the table were tested as hydrochlorides, the four compounds above it as free bases. We have established from the activities of the May compound, 6-bromo-9-(2-dibutylamino-1-hydroxyethyl)phenanthrene hydrochloride, that the free base and its hydrochloride have essentially the same activities in the Rane *P. berghei* test. [e] Included for reference.

Scheme I



Scheme II



The new routes leading to 10-substituted 9-phenanthrenemethanols were as follows.

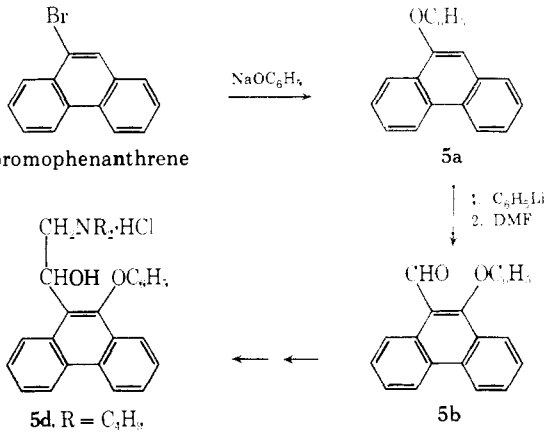
(1) Halogenation of 9-Methylphenanthrene Leading to 10-Halo- or 10-Methyl-9-phenanthrenemethanols. Although 9-halophenanthrene is not selective in giving exclusive electrophilic substitution at the 10 position, 9-methylphenanthrene had been reported[4] to give selective bromination at the 10 position. Analogous chlorination required the use of a new halogenation medium, trimethyl phosphate–phosphorus pentoxide.§ Synthesis of 10-halo-9-phenanthrenemethanols (compounds **1d**-1, **1d**-2, and **2e** in Table I) involved the conversion of the methyl group in 9-methyl-10-halophenanthrenes to the amino alcohol side chain by a method analogous to that in an earlier report.[3] Synthesis of the 10-methyl-9-phenanthrenemethanol (compound **3c** in Table I) involved the exchange of the bromine atom in 9-bromo-10-methylphenanthrene with butyllithium, followed by treatment with dimethylformamide (DMF) to give the aldehyde.[5] This was converted to the target drug by a two-step procedure *via* the epoxide[3] (see Scheme I).

(2) Halogenation of 9-Methyl-9,10-dihydrophenanthrene Leading to 2,7,10-Tribromo-9-phenanthrenemethanols. Exhaustive bromination of 9-methyl-9,10-dihydrophenanthrene (**4a**) using the trimethyl phosphate–phosphorus pentoxide halogenation medium gave 2,7,10-tribromo-9-methylphenanthrene (**4b**). Conversion of the methyl group to the amino alcohol side chain[3] gave the target compounds **4f**-1, **4f**-2, and **4f**-3 in Table I (see Scheme II).

§ Details concerning the use of trimethyl phosphate–phosphorus pentoxide as a halogenation medium will be published at a later date.

(3) Nucleophilic Substitution of 9-Bromophenanthrene Leading to 10-Phenoxy-9-phenanthrenemethanols. 9-Phenoxyphenanthrene (**5a**) was synthesized by nucleophilic displacement of the bromine atom in 9-bromophenanthrene with sodium phenoxide according to the method of Wittig, Uhlenbrock, and Weinhold.[6] Lithiation of **5a** with phenyllithium followed by treatment with DMF gave 10-phenoxy-9-phenanthrenecarboxaldehyde (**5b**), which was converted to the target drug **5d** by the usual two-step procedure[3] (see Scheme III).

Scheme III

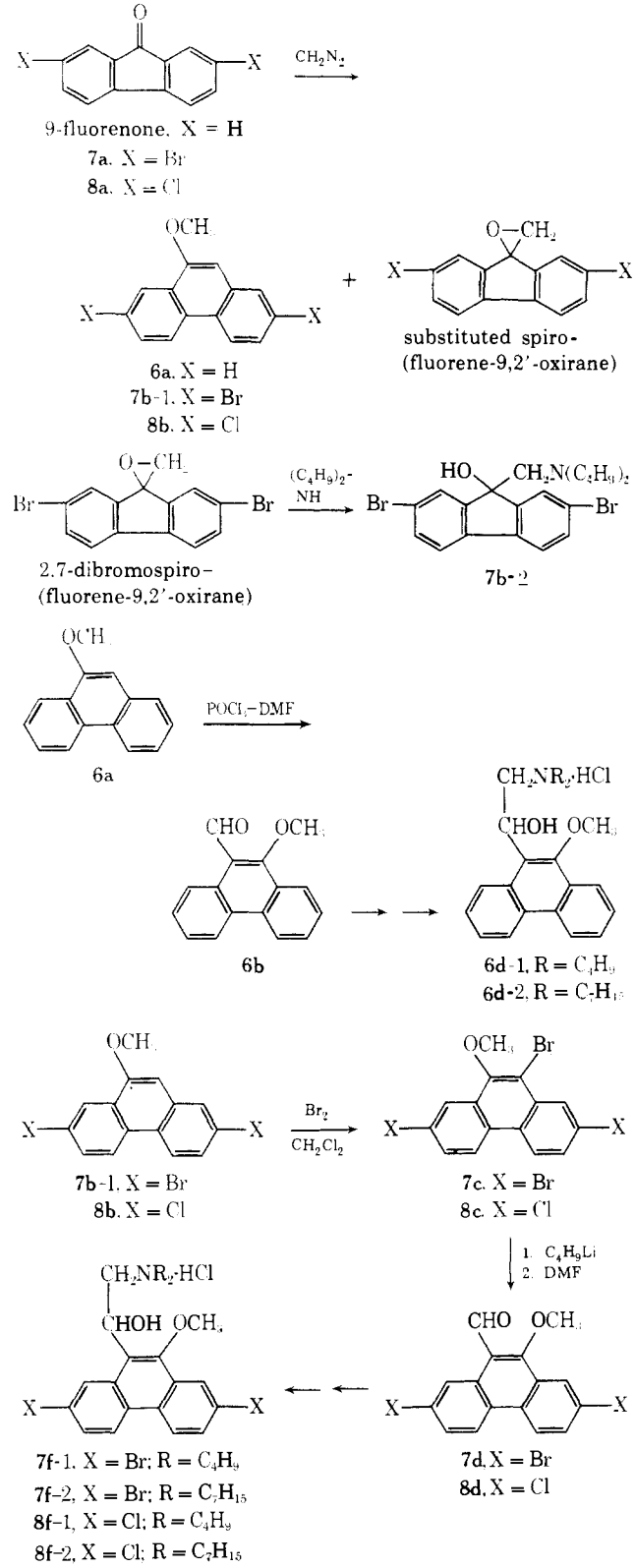


(4) Rearrangement of 9-Fluorenones Leading to 10-Methoxy-9-phenanthrenemethanols and 2,7-Dihalo-10-methoxy-9-phenanthrenemethanols. By the method of Eistert and El-Chahawi,[7] a number of 9-fluorenones were rearranged to 9-methoxyphenanthrenes by reaction with diazomethane. The analogous spiro(fluorene-9,2′-oxirane) was formed in a side reaction, at times in quantities even slightly greater than the desired product. The product was purified either by chromatography on activated silica gel or, in the case of X = Br (Scheme IV), by heating the crude product with dibutylamine. The resulting mixture was separated by acid extraction, giving the desired 2,7-dibromo-10-methoxyphenanthrene (**7b**-1) and 2,7-dibromo-9-dibutylaminomethyl-9-hydroxyfluorene (**7b**-2), which was submitted for antimalarial testing. **7b**-2 had a low but discernible antimalarial activity (ΔMST of 3.4 days at 320 mg/kg).

9-Methoxyphenanthrene (**6a**) was converted to 10-methoxy-9-phenanthrenecarboxaldehyde (**6b**) by the Vilsmeier–Haack reaction in a modification of the method of Hunsberger, Ketcham, and Gutowsky.[8] The aldehyde was converted to the target compounds **6d**-1 and **6d**-2 by the usual two-step procedure.[3] The 2,7-dihalo-9-methoxyphenanthrenes **7b**-1 and **8b** were first brominated at the 10 position, followed by butyllithium exchange and treatment with DMF.[5] The butyllithium exchange reaction was selective with the bromine atom at the 10 position, even in the presence of bromine atoms at the 2 and 7 positions (see Scheme IV). 2,7,10-Tribromo-9-methylphenanthrene (**4b**) gave a similar selective exchange with butyllithium, but the yield of aldehyde **9a** was too low for synthesis of the target drug in this case.

The antimalarial activities of all the target drugs in the Rane *Plasmodium berghei* test in mice[9] are collected in Table I. The most active compound synthesized was 2,7-dibromo-10-methoxy-9-(2-dibutylamino-1-hydroxyethyl)-phenanthrene hydrochloride (**7f**-1), which at 40 mg/kg appeared to have about twice the increased survival time as one of the candidates adopted by WRAIR for more extensive study, 6-bromo-9-(2-diheptylamino-1-hydroxyethyl)phenanthrene hydrochloride (May compound). A few others were comparable to the latter in activity. Several intermediates were submitted for antimalarial testing, but none had any detectable activity.

Scheme IV



Several new routes to substituted phenanthrenemethanols, other than Pschorr ring closure, have been opened by the study described in this paper. One depends on selective substitution of 9-methylphenanthrene, another derives from 9,10-dihydrophenanthrene, and a third by the

rearrangement of fluorenones with diazomethane to give 9-methoxyphenanthrenemethanols. In addition, a noteworthy achievement was the selective butyllithium exchanges obtained with the 10-Br substituents of 2,7,10-tribromo-9-methoxy- and -9-methylphenanthrene. The antimalarial activities against *P. berghei* were in many instances good, particularly that of 2,7-dibromo-10-methoxy-9-(2-dibutylamino-1-hydroxyethyl)phenanthrene hydrochloride (**7f**-1).

Experimental Section

Analyses (by Galbraith Laboratories, Inc., Knoxville, Tenn.) are within ±0.4% and are recorded with the Editor. Melting points are uncorrected and were taken with an A. H. Thomas Uni-Melt apparatus. Nmr spectra of new compounds were compatible with the related structures and are on file with the authors.

10-Bromo-9-(2-alkylamino-1-hydroxyethyl)phenanthrene (1d-1 and 1d-2). 10-Bromo-9-bromomethylphenanthrene (1a). 10-Bromo-9-methylphenanthrene,[4] 20.3 g (75 mmol), *N*-bromosuccinimide, 13.4 g (75 mmol), and CCl_4 (250 ml) were refluxed and irradiated with a 150-W flood lamp for 14 hr. The mixture was filtered while hot to remove succinimide and concentrated, and the residue was recrystallized from EtOH, giving fluffy, pale beige needles, 65%, mp 138.5–140.5° (lit.[6] mp 139.5–140°).

10-Bromo-9-phenanthrenecarboxaldehyde (1b). 1b was made from 1a as previously described[3] except that C_6H_6 was used as a cosolvent. Recrystallization from methylcyclohexane gave small yellow needles, 73%, mp 157–160° (lit.[4a] mp 159–160°).

10-Bromo-9-epoxyethylphenanthrene (1c) (General Epoxide Synthesis). Under N_2 sodium hydride, 1.73 g (36 mmol, 50% mineral oil dispersion), was washed well with C_6H_{14} to remove the mineral oil. Dimethyl sulfoxide (DMSO, 21.3 ml) was added, the mixture heated at 65° for 45 min, cooled to 25°, dry tetrahydrofuran (THF, 42.6 ml) added, and cooled to −10°, and trimethylsulfonium iodide (Aldrich Chemical Co.), 7.34 g (36 mmol), in DMSO (40 ml) added rapidly. After stirring for 1 min at −10°, **1b**, 5.13 g (18 mmol), in a mixture of THF (20 ml) and DMSO (60 ml) was added during 90 sec. The solution was stirred at −10° for 10 min and then warmed to 25°. The mixture was poured into ice water and extracted with ether, and the ether was dried and evaporated. The crude product was recrystallized from CH_3CN, giving pale yellow crystals: 58%; mp 115–119°; analytical sample mp 119.5–120.5°. *Anal.* ($C_{16}H_{11}BrO$) C, H.

10-Bromo-9-(2-dibutylamino-1-hydroxyethyl)phenanthrene (1d-1) (General Phenanthrenemethanol Synthesis). 1c, 2.8 g (9.36 mmol), in $(C_4H_9)_2NH$ (20 ml), was heated and stirred at 120° for 23 hr and the excess amine removed by steam distillation. The residue was chromatographed on silica gel using C_6H_6–EtOAc as the eluting solvent. The pure amino alcohol fractions [R_f 0.25 [tlc silica gel ($CHCl_3$)]] were combined and concentrated, and the residue was recrystallized from C_6H_{14}, giving pale beige crystals, 52%, mp 117.5–118.5°. *Anal.* ($C_{24}H_{30}BrNO$) C, H, Br.

10-Bromo-9-(2-diheptylamino-1-hydroxyethyl)phenanthrene (1d-2). See synthesis of 1d-1 and Table III.

10-Chloro-9-(2-dibutylamino-1-hydroxyethyl)phenanthrene (2e). 10-Chloro-9-methylphenanthrene (2a). 9-Methylphenanthrene, 26.5 g (0.138 mol), and P_2O_5, 49.4 g (0.348 mol), were dissolved in trimethyl phosphate (350 ml), the mixture was cooled to 10°, and Cl_2, 10.8 g (0.152 mol), in trimethyl phosphate (100 ml) at 0° was added during 30 min. The mixture was stirred at 10° for 1 hr and then at 25° for 3 hr. A white precipitate, part of the desired product, was separated by suction filtration, washed well with H_2O, and dried. The filtrate was poured into H_2O, concentrated NH_4OH (100 ml) added, and the mixture left overnight at 25° to convert any α-chlorinated product to the amine. The aqueous solution was extracted with Et_2O; the solution was washed with 5% HCl and with H_2O, dried, and concentrated. The combined solid product was recrystallized from EtOH, giving pale beige needles: 69%; mp 119–121°; analytical sample mp 120–121°. *Anal.* ($C_{15}H_{11}Cl$) C, H.

9-Bromomethyl-10-chlorophenanthrene (2b) was made from **2a** and *N*-bromosuccinimide as in the synthesis of 1a. The CCl_4 solution was concentrated to 200 ml and cooled, giving fluffy, pale beige needles, 90%, mp 139–140°. *Anal.* ($C_{15}H_{10}BrCl$) C, H.

10-Chloro-9-phenanthrenecarboxaldehyde (2c). The aldehyde was made from **2b** in the same manner as **1b**. Recrystallization from methylcyclohexane gave bright yellow needles, 57%, mp 145–152°. Recrystallization from $CHCl_3$ elevated the melting point to 153–155°. *Anal.* ($C_{15}H_9ClO$) C, H.

10-Chloro-9-epoxyethylphenanthrene (2d). See synthesis of 1c and Table II.

10-Chloro-9-(2-dibutylamino-1-hydroxyethyl)phenanthrene (2e). See synthesis of 1d-1 and Table III.

9-(2-Dibutylamino-1-hydroxyethyl)-10-methylphenanthrene (3c). 10-Methyl-9-phenanthrenecarboxaldehyde (3a) was made from 9-bromo-10-methylphenanthrene in 61% yield as previously described:[5] pale yellow needles from MeOH; mp 125–130°; analytical sample mp 130–131.5°. *Anal.* ($C_{16}H_{12}O$) C, H.

9-Epoxyethyl-10-methylphenanthrene (3b). See synthesis of 1c and Table II.

9-(2-Dibutylamino-1-hydroxyethyl)-10-methylphenanthrene (3c). See synthesis of 1d-1 and Table III. It should be noted in Table III that, in this case, it was necessary to use the anion of $(C_4H_9)_2NH$ [made from $(C_4H_9)_2NH$ and C_4H_9Li] to open the epoxide, apparently because of the bulkiness of the methyl group.

9-(2-Dialkylamino-1-hydroxyethyl)-2,7,10-tribromophenanthrene Hydrochloride (4f-1, 4f-2, and 4f-3). 9-Methyl-9,10-dihydrophenanthrene (4a) was prepared by the method of Rabideau and Harvey.[4b] The product, a pale yellow oil, was purified by fractional vacuum distillation, giving 65% of colorless oil boiling in the range 105–115° (0.50 mm) [lit.[4b] bp 121° (1.5 mm)].

9-Methyl-2,7,10-tribromophenanthrene (4b). 4a, 9.41 g (47.1 mmol), was dissolved in trimethyl phosphate (150 ml) and P_2O_5, 35.9 g (253 mmol), was added. The mixture was cooled to 25°, and Br_2, 37.7 g (236 mmol), in trimethyl phosphate (50 ml) was added during 1 hr at 25°. The solution was stirred at 25° for 5 hr and then at 80° for 3 hr. Soon after heating to 80° a yellow precipitate began to form. The mixture was cooled and filtered; the crude product was washed well with MeOH and with H_2O, dried, and recrystallized from CCl_4, giving fluffy beige needles, 48%, mp 224–231°. Two more recrystallizations from $CHCl_3$ elevated the melting point to 235–237°. *Anal.* ($C_{15}H_9Br_3$) Br.

9-Bromomethyl-2,7,10-tribromophenanthrene (4c) was made from 4b as in the synthesis of 1a. The CCl_4 solution was concentrated to half volume and cooled; the compound was isolated by suction filtration, washed well with H_2O, and dried, giving tiny beige needles: 77%; mp 241–243.5°; analytical sample mp 244.5–245.5°. *Anal.* ($C_{15}H_8Br_4$) Br.

2,7,10-Tribromo-9-phenanthrenecarboxaldehyde (4d). The aldehyde was made from **4c** in the same manner as 1b except that CCl_4 was used as the reaction cosolvent. Recrystallization from $CHCl_3$ gave fluffy yellow needles: 82%; mp 258–259°; analytical sample mp 258.5–260°. *Anal.* ($C_{15}H_7Br_3O$) Br.

9-Epoxyethyl-2,7,10-tribromophenanthrene (4e). See synthesis of 1c and Table II.

9-(2-Dipropylamino-1-hydroxyethyl)-2,7,10-tribromophenanthrene Hydrochloride (4f-1) (General Phenanthrenemethanol Hydrochloride Synthesis, See Table III). 4e, 1.00 g (2.19 mmol), $(C_3H_7)_2NH$ (15 ml), and *m*-xylene (10 ml) were heated at 160° for 65 hr, and the mixture was steam distilled to remove excess amine and *m*-xylene. The residue was dissolved in 100 ml of 50:50 C_6H_6–Et_2O and 75 ml of 6% HCl was added with the immediate precipitation of a white solid. After swirling for 5 min, the precipitate was filtered, washed well with H_2O and with Et_2O, dried, and recrystallized from absolute EtOH, giving pale beige crystals, 12%, mp 253–256°. *Anal.* ($C_{22}H_{25}Br_3ClNO$) C, H, N.

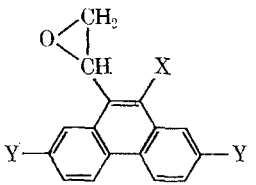
9-(2-Dibutylamino-1-hydroxyethyl)-2,7,10-tribromophenanthrene Hydrochloride (4f-2). See synthesis of 4f-1 and Table III.

9-(2-Diheptylamino-1-hydroxyethyl)-2,7,10-tribromophenanthrene Hydrochloride (4f-3). See synthesis of 4f-1 and Table III.

9-(2-Dibutylamino-1-hydroxyethyl)-10-phenoxyphenanthrene Hydrochloride (5d). 9-Phenoxyphenanthrene (5a) was prepared by the method of Wittig, Uhlenbrock, and Weinhold.[6] The crude product was purified by column chromatography on silica gel using C_6H_6–C_6H_{14} as eluting solvent, giving white powder, 79%, mp 77.5–79.5° (lit.[6] mp 77–78.5°).

10-Phenoxy-9-phenanthrenecarboxaldehyde (5b). Under N_2 a solution of C_6H_5Li was prepared by refluxing for 15 min a mixture of C_6H_6, 3.74 g (48 mmol), TMEDA (32 mmol), and C_4H_9Li, 14.2 ml (32 mmol, 2.25 *M*). After cooling to 25°, **5a**, 8.64 g (32 mmol), in anhydrous Et_2O (60 ml) was added during 15 min, and the mixture was stirred at 25° under N_2 for 6 days to allow complete equilibration to 9-lithio-10-phenoxyphenanthrene. Anhydrous Et_2O (50 ml) and THF (80 ml) were added, followed by the addition of DMF, 23.4 g (320 mmol). After stirring for 30 min at 25°, EtOH (30 ml) was added, and the ethereal solution was washed with aqueous NH_4Cl and with H_2O, dried, and concentrated. The yellow, gummy solid was triturated with C_6H_6 and

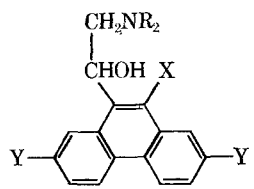
Table II. 10-Substituted 9-Epoxyethylphenanthrenes



No.	X	Y	Mp, °C	Recrystn solvent	Crude yield, %	Purified yield, %	Formula	Analyses
1c	Br	H	119.5–120.5	CH_3CN		58	$C_{16}H_{11}BrO$	C, H
2d	Cl	H	112.5–114	CH_3CN		59	$C_{16}H_{11}ClO$	C, H
3b	CH_3	H	96.5–98	*i*-C_3H_7OH		71	$C_{17}H_{14}O$	C, H
4e	Br	Br	206–207.5[a]			36	$C_{16}H_9Br_3O$	Br
5c	C_6H_5O	H	Yellow oil[b]		69		$C_{22}H_{16}O_2$	
6c	CH_3O	H	87–88.5	C_6H_{14}		78	$C_{17}H_{14}O_2$	C, H
7e	CH_3O	Br	148–157[b]		92		$C_{17}H_{12}Br_2O_2$	
8c	CH_3O	Cl	141–149[b]		100		$C_{17}H_{12}Cl_2O_2$	

[a] Analytical sample was obtained by sublimation after initial purification by chromatography on activated silica gel using 50:50 C_6H_6–C_6H_{14} as eluting solvent. [b] The crude product was used in the next step with no further purification.

Table III. 10-Substituted 9-Phenanthrenemethanols



No.	X	Y	R	Mp, °C	Chromatography solvent	Recrystn solvent	Purified yield, %	Temp of rxn, °C	Time of rxn, hr	Formula	Analyses
1d-1[a]	Br	H	C_4H_9	117.5–118.5	C_6H_6–EtOAc	C_6H_{14}	52	120	23	$C_{24}H_{30}BrNO$	C, H, Br
1d-2	Br	H	C_7H_{15}	66.5–67.5	C_6H_6	EtOH	33	120	20	$C_{30}H_{42}BrNO$	C, H, Br
2e	Cl	H	C_4H_9	114–115		C_6H_{14}	62	120	13	$C_{24}H_{30}ClNO$	C, H, Cl
3c[b]	CH_3	H	C_4H_9	69–70.5	C_6H_6–EtOAc	EtOH–H_2O	16	160	50	$C_{25}H_{33}NO$	C, H
4f-1	Br	Br	C_3H_7	253–256		EtOH	12	160	65	$C_{22}H_{25}Br_3ClNO$	C, H, N
4f-2	Br	Br	C_4H_9	251–253		EtOH–Et_2O	25	150	24	$C_{24}H_{29}Br_3ClNO$	C, H, N
4f-3	Br	Br	C_7H_{15}	231–234		EtOH–Et_2O	29	150	12	$C_{30}H_{41}Br_3ClNO$	C, H, N
5d	C_6H_5O	H	C_4H_9	219–220		EtOH	41	150	70	$C_{30}H_{36}ClNO_2$	C, H, Cl
6d-1	CH_3O	H	C_4H_9	188–189		EtOH	46	130	12	$C_{25}H_{34}ClNO_2$	C, H
6d-2	CH_3O	H	C_7H_{15}	168–169		EtOH	54	130	12	$C_{31}H_{46}ClNO_2$	C, H
7f-1	CH_3O	Br	C_4H_9	223–224		EtOH	72	130	12	$C_{25}H_{32}Br_2ClNO_2$	C, H, Br
7f-2	CH_3O	Br	C_7H_{15}	206–207		EtOH	67	130	12	$C_{31}H_{44}Br_2ClNO_2$	C, H, Br
8f-1	CH_3O	Cl	C_4H_9	224–225		EtOH	53	130	18	$C_{25}H_{32}Cl_3NO_2$	C, H, Cl
8f-2	CH_3O	Cl	C_7H_{15}	209.5–211		EtOH	55	130	12	$C_{31}H_{44}Cl_3NO_2$	C, H, Cl

[a] Compounds **1d-1**, **1d-2**, **2e**, and **3c** were purified and submitted for testing as the free base. All others are in the form of the hydrochloride salt. [b] It was necessary to use the anion of di-*n*-butylamine in the synthesis of this compound.

recrystallized from methylcyclohexane, giving beige crystals: 45%; mp 199–200.5°; analytical sample mp 200–201°. *Anal.* ($C_{21}H_{14}O_2$) C, H.

9-Epoxyethyl-10-phenoxyphenanthrene (5c). See synthesis of 1c and Table II.

9-(2-Dibutylamino-1-hydroxyethyl)-10-phenoxyphenanthrene Hydrochloride (5d). See synthesis of 4f-1 and Table III.

9-(2-Dialkylamino-1-hydroxyethyl)-10-methoxyphenanthrene Hydrochloride (6d-1 and 6d-2). 9-Methoxyphenanthrene (6a) was prepared by the method of Eistert and El-Chahawi,[7] which involves the ring enlargement of 9-fluorenone with CH_2N_2. The crude product was chromatographed on silica gel using 80% C_6H_{14}–20% C_6H_6 as eluting solvent, giving white powder, 51%, mp 92.5–94° (lit.[7] mp 95°).

10-Methoxy-9-phenanthrenecarboxaldehyde (6b) was prepared by the Vilsmeier–Haack reaction using a modification of the method of Hunsberger, Ketcham, and Gutowsky.[8] DMF, 7.3 g (0.10 mol), was added dropwise to $POCl_3$, 15.3 g (0.10 mol), the mixture cooled to 25°, and **6a**, 7.07 g (0.034 mol), added. The mixture was stirred at 80° for 2 hr, cooled to 25°, poured into ice water, extracted with Et_2O, washed with H_2O, dried, and concentrated. The residue was recrystallized from C_6H_{14}, giving pale yellow needles, 76%, mp 84.5–86° (lit.[8] mp 80.5–81.5°).

9-Epoxyethyl-10-methoxyphenanthrene (6c). See synthesis of 1c and Table II.

9-(2-Dibutylamino-1-hydroxyethyl)-10-methoxyphenanthrene Hydrochloride (6d-1). See synthesis of 4f-1 and Table III.

9-(2-Diheptylamino-1-hydroxyethyl)-10-methoxyphenanthrene Hydrochloride (6d-2). See synthesis of 4f-1 and Table III.

9-(2-Dialkylamino-1-hydroxyethyl)-2,7-dibromo-10-methoxyphenanthrene Hydrochloride (7f-1 and 7f-2). 2,7-Dibromo-9-fluorenone (7a) was prepared by the TMP–P_2O_5 method. 9-Fluorenone, 12.6 g (0.07 mol), was dissolved in trimethyl phosphate (150 ml) at 90°, and P_2O_5, 13.8 g (0.097 mol), was added. Br_2, 24.6 g (0.154 mol), in trimethyl phosphate (50 ml) was added during 30 min; the mixture was stirred at 90° for 42 hr, cooled, poured into cold H_2O, treated with $NaHSO_3$, and filtered. The yellow product was washed well with H_2O, dried, and recrystallized from HOAc, giving yellow needles, 70%, mp 201–203° (lit.[10] mp 202°).

2,7-Dibromo-9-methoxyphenanthrene (7b-1) and 2,7-Dibromo-9-dibutylaminomethyl-9-hydroxyfluorene (7b-2). 7a, 17.8 g (52.8 mmol), in 50:50 MeOH–Et_2O (800 ml) at 0° was treated with excess CH_2N_2 in Et_2O according to the method of Eistert and El-Chahawi.[7] When the sluggish reaction was shown to be complete by tlc, HOAc (5 ml) was added to destroy the excess CH_2N_2; the solution was washed with $NaHCO_3$ and with H_2O, dried, and concentrated. The yellow solid product was shown by nmr analysis to be a mixture of the desired **7b-1** (43%) and 2,7-dibromospiro(fluorene-9,2′-oxirane) (57%). The mixture was combined with C_6H_6 (50 ml) and $(C_4H_9)_2NH$ (20 ml) and heated at reflux for 12 hr. The C_6H_6 and $(C_4H_9)_2NH$ were removed by distillation and steam distillation, respectively, and the resulting solid was triturated with Et_2O, leaving **7b-1** as a pale yellow powder, 34%, mp 191–194° (lit.[7] mp 192°). Treatment of the triturate liquid with 10% HCl gave the HCl salt of **7b-2**, which was filtered, washed with H_2O and with Et_2O, and converted to the free base by treatment with dilute NH_4OH. **7b-2** was recrystallized from C_6H_{14}, giving pale yellow, transparent plates, 29%, mp 82.5–83.5°. *Anal.* ($C_{22}H_{27}Br_2NO$) C, H, Br.

9-Methoxy-2,7,10-tribromophenanthrene (7c). 7b-1, 7.42 g (20.3 mmol), was dissolved in CH_2Cl_2 (650 ml) at 25°, and Br_2, 3.57 g (22.3 mmol), in CH_2Cl_2 (50 ml) was added during 30 min. After stirring at 25° for 16 hr, the solution was washed with aqueous $NaHSO_3$ and with H_2O, dried, and concentrated, and the residue was recrystallized from $CHCl_3$–EtOH, giving fluffy, white needles, 87%, mp 188–190°. *Anal.* ($C_{15}H_9Br_3O$) C, H, Br.

2,7-Dibromo-10-methoxy-9-phenanthrenecarboxaldehyde (7d). Under N_2, C_4H_9Li, 7.34 ml (16.5 mmol, 22% in C_6H_{14}), was added in one portion to a suspension of **7c**, 6.68 g (15 mmol), in anhydrous Et_2O (1 l.) at 0°, giving a yellow-green, clear solution. After stirring for 5 min at 0°, DMF, 11.0 g (0.15 mol), was added, and the mixture was warmed to 25° and stirred at 25° for 4 hr followed by the addition of MeOH (20 ml). The mixture was washed with 10% HCl and with H_2O, dried, and concentrated. The residue was purified by chromatography on silica gel using 80% C_6H_{14}–20% C_6H_6 to elute the major side product, **7b-1**, and then 50% C_6H_{14}–50% C_6H_6 to elute the aldehyde. After concentration, **7d** was recrystallized from $CHCl_3$–EtOH, giving white, fluffy needles: 49%; mp 218.5–220°; analytical sample mp 219–221°. *Anal.* ($C_{16}H_{10}Br_2O_2$) C, H, Br.

2,7-Dibromo-9-epoxyethyl-10-methoxyphenanthrene (7e). See synthesis of 1c and Table II.

2,7-Dibromo-9-(2-dibutylamino-1-hydroxyethyl)-10-methoxyphenanthrene Hydrochloride (7f-1). See synthesis of 4f-1 and Table III.

2,7-Dibromo-9-(2-diheptylamino-1-hydroxyethyl)-10-methoxyphenanthrene Hydrochloride (7f-2). See synthesis of 4f-1 and Table III.

9-(2-Dialkylamino-1-hydroxyethyl)-2,7-dichloro-10-methoxyphenanthrene Hydrochloride (8f-1 and 8f-2). 2,7-Dichloro-9-fluorenone (8a). 2,7-Dichlorofluorenone, 19.3 g (82.4 mmol), was dissolved in boiling HOAc (250 ml), and CrO_3, 22.0 g (0.275 mol, 2.5 equiv), was added at such a rate as to maintain gentle reflux with no external heating. The mixture was heated at reflux for 5 hr, cooled, poured into H_2O, and filtered, and the product was washed with H_2O, dried, and recrystallized from HOAc, giving fluffy, yellow needles, 68%, mp 191.5–193.5° (lit.[10] mp 189°).

2,7-Dichloro-9-methoxyphenanthrene (8b). 8a, 7.4 g (19.7 mmol), in 50:50 MeOH–Et_2O (400 ml) at 0° was treated with excess CH_2N_2 in Et_2O as in the synthesis of **7b** and was worked up in the same manner. The crude product, a pale beige solid, was shown by nmr analysis to be a mixture of the desired **8b** (44%) and 2,7-dichlorospiro(fluorene-9,2′-oxirane) (56%). Chromatography on activated silica gel using 10% C_6H_6–90% C_6H_{14} gave, after concentration, white powder: 41%, mp 166–168°; analytical sample mp 167–168.5°. *Anal.* ($C_{15}H_{10}Cl_2O$) C, H, Cl.

9-Bromo-2,7-dichloro-10-methoxyphenanthrene (8c) was made from **8b** and Br_2 in the same manner as **7c**. Recrystallization from $CHCl_3$–EtOH gave fluffy, white needles, 84%, mp 185–187°. *Anal.* ($C_{15}H_9BrCl_2O$) C, H.

2,7-Dichloro-10-methoxy-9-phenanthrenecarboxaldehyde (8d) was prepared from **8c** by a procedure analogous to that for **7d**. After chromatography as in **7d**, the eluted aldehyde was recrystallized from methylcyclohexane, giving fluffy, pale yellow needles, 42%, mp 187–188°. *Anal.* ($C_{16}H_{10}Cl_2O_2$) C, H, Cl.

2,7-Dichloro-9-epoxyethyl-10-methoxyphenanthrene (8e). See synthesis of 1c and Table II.

9-(2-Dibutylamino-1-hydroxyethyl)-2,7-dichloro-10-methoxyphenanthrene Hydrochloride (8f-1). See synthesis of 4f-1 and Table III.

2,7-Dichloro-9-(2-diheptylamino-1-hydroxyethyl)-10-methoxyphenanthrene Hydrochloride (8f-2). See synthesis of 4f-1 and Table III.

2,7-Dibromo-10-methyl-9-phenanthrenecarboxaldehyde (9a) and 2,7-Dibromo-9-methylphenanthrene (9b). Under N_2, **4b**, 1.07 g (2.5 mmol), was dissolved in a mixture of anhydrous THF (200 ml) and anhydrous Et_2O (100 ml), the solution cooled to −70°, and C_4H_9Li, 1.12 ml (2.75 mmol, 22% in C_6H_{14}), added in one portion to give a bright green color. After stirring at −70° for 45 min, DMF, 1.83 g (25 mmol), was added to give a bright yellow color, the mixture stirred at −70° for 1 hr, and MeOH (25 ml) added. The solution was washed with aqueous NH_4Cl and with H_2O, dried, and concentrated. The mixture of two major components was chromatographed on silica gel using 50:50 C_6H_6–C_6H_{14} as eluting solvent. The first component eluted (250 mg) was shown by nmr analysis to be **9b**, and recrystallization from C_6H_{14} gave mp 149–150°. The amount of **9b** was too small to carry on to the phenanthrenemethanol. *Anal.* ($C_{15}H_{10}Br_2$) C, H, Br. Further elution gave the second component, shown by nmr analysis to be **9a** (190 mg); recrystallization from C_6H_{14} gave mp 229.5–232.5°. *Anal.* ($C_{16}H_{10}Br_2O$) C, H, Br.

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Synthesis of Analogs of 6-Arylthio-, 6-Arylsulfinyl-, and 6-Arylsulfonyl-2,4-diaminoquinazolines as Potential Antimalarial Agents†

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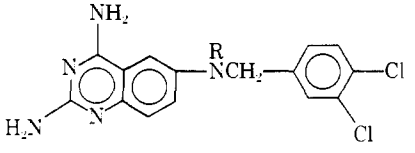
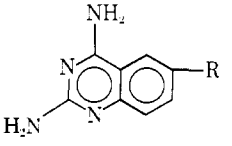
Numerous 6-arylthio-, 6-arylsulfinyl-, and 6-arylsulfonyl-2,4-diaminoquinazolines have been synthesized, many of which possess potent activity against both sensitive as well as drug-resistance strains of plasmodia. The present study describes the preparation of 23 analogs involving modifications of the substituents in the 2 and/or 4 positions of the quinazoline nucleus. Only one of the new compounds, 2-amino-4-hydroxy-6-(2-naphthylsulfonyl)quinazoline (**16a**), displayed curative activity against *Plasmodium berghei* in mice and was substantially less potent than its 4-amino counterpart **2a**.

The discovery of the antiprotozoan activity of 2,4-diaminoquinazolines as exemplified by **1a,b**[1,2] has led to the synthesis of a wide variety of compounds of this class.[3-5]



1a, R = H
b, R = NO

Of these, the most promising potential antimalarial agents are certain 6-arylthio-2,4-diaminoquinazolines and their sulfinyl and sulfonyl analogs. For example, **2a,b** are currently undergoing clinical trials since they have shown efficacy against drug-resistant strains of plasmodia.[6] Al-



2a, R = 2-$C_{10}H_7SO_2$-
b, R = 3-$(CF_3)C_6H_4S$-

though the mechanism of action of these compounds has not been fully elucidated, it is noteworthy that a variety of compounds of this type are effective inhibitors of dihydrofolate reductase isolated from either rat liver or *Streptococcus faecium* (*in vitro*).‡

In a recent communication, we described the preparation of a series of isomers and analogs of **2a,b** in which the aromatic moiety was attached to the 5 position of the quinazoline nucleus by a suitable spacer.[7] None of these displayed any significant activity against *Plasmodium berghei* in mice. However, several were found to be moderately potent inhibitors of rat liver dihydrofolate reductase.[7] The present study was initiated in order to determine the effect of altering the groups attached to the 2 and 4 positions of the quinazoline ring upon antimalarial activity. It was hoped that configurations such as 2-amino-4-hydroxy or 2-amino-4-mercapto would confer greater inhibitory action upon tetrahydrofolate-dependent enzymes such as thymidylate synthetase. Inhibitors of this type could prove to be of value when used in conjunction with 2,4-diaminoquinazolines such as **2a,b**. Physical data for the new compounds synthesized are summarized in Table I.

Chemistry. The 2-amino-4-hydroxyquinazolines **14a,b**, **15**, and **16a,b** were prepared by the standard acid-catalyzed hydrolysis of the corresponding 2,4-diamino compounds.[7,§] Two of the products **14a** and **16a** were subsequently reacted with P_2S_5 in pyridine to afford the corresponding 2-amino-4-mercapto analogs **7** and **8**. Acylation of **16a** with acetic anhydride or trichloroacetic anhydride in pyridine yielded the 2-acetamido derivatives **17** and **18**, respectively.

Synthetic routes to the remaining analogs of 6-arylthio-2,4-diaminoquinazolines are summarized in Scheme I. Standard cyclization procedures employing urea, thiourea, potassium ethyl xanthate, or formamide were employed to prepare compounds **13a,b**, **5**, **9**, and **19a,b**, respectively. The key 5-arylthioanthranilonitriles **3a,b** were prepared according to methods developed by Elslager and coworkers.§,= Similarly, the reaction of ethyl 2-amino-5-(2-naphthylthio)benzoate (**4**)§,** with thiourea and urea yielded **11** and **12**. Oxidation of the 4-aminoquinazolines **19a,b** with 30% H_2O_2 or triethylenediamine dibromide yielded the sulfoxides **20a,b**, while the corresponding sulfones **21a,b** were obtained with excess permanganate in aqueous AcOH.[7]

Alkylation of 4-amino-2-mercapto-6-(2-naphthylthio)-quinazoline (**5**) with MeI in the presence of base afforded the 2-methylmercapto derivative **6**. The reaction of the 4-amino-2-hydroxyquinazoline **13a** with P_2S_5 was attempted as an alternate route to compound **5**. However, in this case the 4-amino group was preferentially displaced yielding **10**. Proof of this configuration was provid-

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‡J. B. Hynes, W. T. Ashton, and J. H. Freisheim, unpublished results.
§Samples or synthetic procedures provided by the U. S. Army Program on Antimalarial Research.
=E. F. Elslager and coworkers, Parke, Davis and Co., unpublished results.
**F. W. Starks, Starks Associates, Inc., unpublished results.