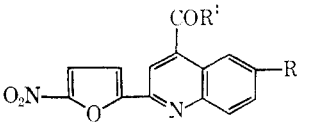
TABLE I



			Minimum inhib conc, μg/ml[a]								
No.	R	R'	Es-2[b]	SaD-13	Ps-10	Pr-12	Ae-6	Er-4	Mi-12	StA-1	StB-12
3	H	OH	25	>50	>50	>50	>50	≤0.75	25	1.5	6.25
4	Cl	OH	12.5	>50	>50	>50	>50	0.75	1.25	0.38	1.5
5	H	OC_2H_5	0.75	>50	>50	>50	>50	≤0.19	0.38	>50	>50
6	H	$CONH_2$	≤0.19	0.75	>50	>50	>50	1.5	1.5	1.5	1.5
Nitrofurazone			3	3	>100	100	100	12.5	12.5	6	12.5

[a] Minimum inhibitory concentration is the lowest concentration of compound that prevents visible growth of bacteria after 24 hr of incubation. Es-2 = *Escherichia coli*, SaD-13 = *Salmonella typhosa*, Ps-10 = *Pseudomonas aeruginosa*, Pr-12 = *Proteus valgaris*, Ae-6 = *Aerobacter aerogenes*, Er-4 = *Erysipelothrix insidiosa*, Mi-12 = *Staphylococcus aureus*, StA-1 = *Streptococcus pyogenes*, and StB-12 = *Streptococcus agalactiae*. [b] The Norwich Pharmacal Co. strain number.

It was chilled, diluted with Et_2O, and filtered. Recrystallization of the product from aqueous DMF (charcoal) gave **5** as yellow needles, mp 174–175°, yield 8 g (23.5%). *Anal.* ($C_{16}H_{12}N_2O_5$) C, H, N. Ir showed a C=O stretching band at 1700 cm^{-1} (CO_2Et).

2-(5-Nitro-2-furyl)cinchoninamide (6).—A solution of 59 g (0.21 mole) of **3** in 455 ml of $SOCl_2$ was refluxed for 5 hr. Excess $SOCl_2$ was removed under reduced pressure and the residue was poured cautiously into ice–NH_4OH. The resulting mixture was neutralized with HCl and filtered. Recrystallization of the residue from aqueous DMF (charcoal) gave **6** as yellow microneedles decomposing at 288–289°, yield 22 g (38%). *Anal.* ($C_{14}H_9N_3O_4$) C, H, N. Ir showed a C=O stretching band at 1670 cm^{-1} ($CONH_2$).

Acknowledgments.—The author is grateful to Mr. Grant Gustin and Mr. Marvin Tefft for the elemental analyses, Mrs. Patricia Curtis for the nmr spectra, Mr. Warren Smith for assistance in the preparation of these compounds, and to members of the Medical and Veterinary Microbiology Sections for the testing data.

Potential Antimalarials. Some Novel α-(Disubstituted Aminomethyl)-9-phenanthrenemethanols[1]

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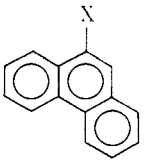
As part of the current Army Research Program on Malaria, we undertook the synthesis of some new 9-phenanthrenemethanols as potential, curative agents against the drug-resistant strain of *Plasmodium falciparum*. The basis for this investigation is given by the fact that, during the search for effective antimalarials during World War II, a number of simple α-(dialkylaminomethyl)-9-phenanthrenemethanols showed significant therapeutic effect against blood-induced *Plasmodium gallinaceum* malaria;[2] particularly outstanding in this class is 6-bromo-α-(diheptylaminomethyl)-9-phenanthrenemethanol.[3] The work here described is concerned with the preparation of some simple (unsubstituted) 9-phenanthrenemethanols with novel side chains, most of which contain certain functional groups, as shown in Table II.

Chemistry.—The route[4] I → II → III was successfully applied for the preparation of the target compounds **7**, **8**, and **10**, in which the intermediate ketones (**2** and **4**) were isolable, in good yield, as stable, crystalline compounds (Table I). With other secondary amines, the route was unsatisfactory, resulting in failure to obtain the corresponding amino ketones[5] (II), either as the free bases, or as their HCl salts. The conversion of I into



I, X = $COCH_2Br$
II, X = $COCH_2NRR'$
III, X = $CHOHCH_2NRR'$
IV, X = $CHOHCH_2Br$
V, X = CH—CH_2 (O)

II was also complicated by disparities in the basicities of the various amines employed. Whereas, for example, diallylamine (pK_a = 9.3) and N-(2-hydroxyethyl)-cyclohexylamine (pK_a = 10.1) reacted rapidly with I, the reaction with N-(2-cyanoethyl)cyclohexylamine (pK_a = 8.2) was sluggish and incomplete. As an alternative procedure,[6] the latter amine was treated with the bromohydrin IV to give the desired methanol; however, it was discovered that the epoxide[7] V, formed during the conversion, was the reacting species. When treated directly with the oxide V, the secondary amine reacted only when a proportion of its HBr salt was present. For preparative purposes, it was more convenient to prepare **12** from IV, in which the HBr salt was generated *in situ*. In contrast, N-(2-hydroxyethyl)cyclohexylamine reacted readily with V, *without*

(1) This work was supported by U. S. Army Medical Research and Development Command, Contract DADA17-67-C-7144. Contribution No. 515 to the Army Research Program on Malaria.

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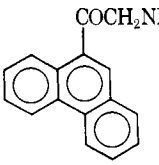
TABLE I

DISUBSTITUTED AMINOMETHYL 9-PHENANTHRYL KETONES (II)

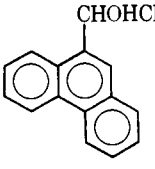


No.	R	R′	Form	Mp, °C	Yield, %	Solvent of crystn	Formula	Analyses
1	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	HCl salt	127–129	50	THF–MeOH–Et_2O	$C_{22}H_{22}ClNO$	N; C,[a] H,[b] Cl[c]
2	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	Base	89–90	90	THF–*i*-PrOH–MeOH		
3			HCl salt	161–162	79[d]	MeOH–THF–Et_2O	$C_{22}H_{18}ClNO$	C, H, Cl, N
4	CH_2CH_2CN	CH_2CH_2CN	Base	90–91	71	MeOH–*i*-PrOH		
5			HCl salt	179–180	82	MeOH–THF–Et_2O	$C_{22}H_{20}ClN_3O$	C, H, Cl, N
6	C_6H_{11}	CH_2CH_2OH	Picrate	152–158	54	EtOH	$C_{30}H_{30}N_4O_9$	H, N; C[e]

[a] C: calcd, 75.07; found, 74.20. [b] H: calcd, 6.30; found, 6.72. [c] Cl: calcd, 10.08; found, 9.19. [d] Based on crystalline, free ketone. [e] C: calcd, 60.27; found, 60.99.

TABLE II

α-(DISUBSTITUTED AMINOMETHYL)-9-PHENANTHRENEMETHANOLS (III)



No.	R	R′	Form	Mp, °C	Yield, %	Solvent of crystn	Formula	Analyses
7	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	HCl salt	152–157	39	MeOH–THF–Et_2O–pentane	$C_{22}H_{24}ClNO$	C, H, Cl, N
8	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	Base	108–109	84	MeOH–*i*-PrOH–H_2O	$C_{22}H_{19}NO$	C, H, N
9			HCl salt	129–130	86[a]	THF–MeOH–Et_2O	$C_{22}H_{20}ClNO$	C, H, Cl, N
10	CH_2CH_2CN	CH_2CH_2CN	HCl salt	133–136	60	MeOH–THF–Et_2O	$C_{22}H_{22}ClN_3O$	C, H, Cl, N
11	C_6H_{11}	CH_2CH_2CN	Picrate	176–180	25	THF–MeOH	$C_{31}H_{31}N_5O_8$	C, H, N
12			HCl salt	116–120, 150–158	90[b]	MeOH–THF–Et_2O	$C_{25}H_{29}ClN_2O$	C, H, Cl, N
13	C_6H_{11}	CH_2CH_2OH	Picrate	112–128	80	THF–MeOH	$C_{30}H_{32}N_4O_9 \cdot H_2O$	C, H, N
14			HCl salt	Amorphous	97[b]		$C_{24}H_{30}ClNO_2$	C, H, Cl, N
15	CH_2CH_2COOH	CH_2CH_2COOH	Dipolar ion	176–178	39	H_2O	$C_{22}H_{33}NO_5$	C, H, N
16	$CH_2CH_2CH_2NH_2$	$CH_2CH_2CH_2NH_2$	$\cdot 3HCl$[c]	200–210	55	Abs EtOH–Et_2O	$C_{22}H_{32}Cl_3N_3O$	C, H; Cl,[d] N[e]

[a] Based on crystalline **8**. [b] Based on picrate. [c] Extremely hygroscopic. [d] Cl: calcd, 23.09; found, 22.52. [e] N: calcd, 9.12; found, 8.07.

catalysis. Acid-catalyzed hydrolysis of α-(dipropionitriloaminomethyl)-9-phenanthrenemethanol hydrochloride (**10**) gave the bis(2-carboxyethyl) derivative (**15**) as the dipolar ion; reduction[8] of **10** with $NaBH_4$–$AlCl_3$ afforded α-[bis(3-aminopropyl)aminomethyl]-9-phenanthrenemethanol, obtained crystalline as the trihydrochloride salt (**16**).

Biological Activity.—All amino ketone hydrochlorides (Table I), all target phenanthrenemethanol hydrochlorides, **15** (Table II), **2** ketoxime, and bromohydrin IV have been submitted for screening. Available screening results disclose that **1**, **3**, **5**, **7**, **9**, **10**, **15**, and IV showed no significant antimalarial activity against *Plasmodium berghei* in mice,[9] and that **3**, **5**, **10**, IV, and **2** ketoxime were likewise ineffective in suppression of oocysts or sporozoites of *P. gallinaceum* in the mosquito test.[10]

Experimental Section

Melting points were determined with a Kofler hot stage and ir spectra were recorded with a Perkin-Elmer Model 457 spectrophotometer. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Dipropionitriloamine (Eastman) was purchased from Fisher Scientific Co., Houston, Texas; diallyl- and dipropargylamines and 9-acetylphenanthrene were purchased from Aldrich Chemical Co., Milwaukee, Wisc.; and N-(2-cyanoethyl)cyclohexylamine and N-(2-hydroxyethyl)cyclohexylamine were furnished gratis by Abbott Laboratories, North Chicago, Ill. Where analyses are indicated by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

Amino Ketones (II). General Method.—To a solution of 1 mmole of ω-bromo-9-acetylphenanthrene[4] (I) in 1 ml of anhydrous THF was added 5 ml of Et_2O, and to this was added 3 mmoles of the secondary amine. The mixture was stirred for 18 hr under exclusion of moisture, the separated HBr salt of the secondary amine was filtered off and rinsed well with Et_2O, and the filtrate was evaporated to dryness under diminished pressure at 25°. Ketones **2** and **4** were obtained directly from the syrupy residue by crystallization (Table I).

Amino Ketone Hydrochlorides (1, 3, and 5). General Method.—For crystalline **2** or **4**, the product was dissolved in a small volume of THF and a calculated amount of HCl in Et_2O was added. The precipitate that formed was filtered off and recrystallized as given in Table I, affording either **3** or **5**, respectively. Similar treatment of the syrupy diallylamino ketone, obtained by the preceding method, gave an oily product (**1**); therefore, the solvents were evaporated and, from the resulting syrup, crystals were obtained from the solvent mixture shown in Table I. Pure, hygroscopic **1** was secured only after repeated recrystallization.

Picrate (6).—N-(2-Hydroxyethyl)cyclohexylaminomethyl 9-

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(9) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
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phenanthryl ketone, obtained as an impure syrup by the general method given (*vide supra*) for 3 mmoles of **I**, was dissolved in 40 ml of absolute EtOH containing 3 mmoles of picric acid, crystallization being complete after 3 days.

Dipropargylaminomethyl 9-Phenanthryl Ketoxime.—A mixture of the amino ketone (**2**) (1.224 g, 4 mmoles) and $HONH_2 \cdot HCl$ (840 mg, 12 mmoles) in 10 ml of absolute EtOH and 5 ml of dry pyridine was refluxed for 2 hr. The mixture was transferred to a small beaker, H_2O was added to incipient turbidity, and the beaker was left in the open for 3 hr. The resulting crystals were filtered off, and four recrystallizations from EtOH–H_2O gave pure oxime; yield 261 mg (20%), mp 159–160°. *Anal.* ($C_{22}H_{18}N_2O$) C, H, N.

9-Phenanthrenemethanols (III) *via* Amino Ketones (II). General Method.—To a solution of 4 mmoles of either **1**, **2**, or **4** in 30 ml of THF and 175 ml of *i*-PrOH was added 152 mg (4 mmoles) of $NaBH_4$, and the mixture was stirred for 18 hr under exclusion of moisture. Me_2CO (30 ml) was added, the solvent was evaporated under diminished pressure, and the residue was coevaporated three times with 30-ml portions of MeOH. For **7** and **10**, the residue was dissolved in 50 ml of $CHCl_3$, and the solution was washed with two 30-ml portions of H_2O and then dried (Na_2SO_4). It was filtered, and the solvent was evaporated under diminished pressure, leaving a syrupy residue that was dissolved in 15 ml of THF. A calculated amount of HCl in Et_2O was added, the mixture was evaporated to dryness, and the products were crystallized as indicated in Table II. Compound **8** was obtained as a crystalline product without prior conversion into its hydrochloride (**9**), which could be prepared from **8** in a manner similar to that for **7** and **10**.

α-(Bromomethyl)-9-phenanthrenemethanol (IV).—To a solution of 12 g (40 mmoles) of **I** in 120 ml of THF and 480 ml of MeOH, precooled to 5°, was added, with stirring, 1.526 g (40 mmoles) of $NaBH_4$, in small portions at intervals of 2 min, the addition being complete in *ca.* 15 min. The mixture was stirred for 1.5 hr at 5–10° and then warmed to room temperature. The mixture was transferred to a 3-l. beaker, H_2O was slowly added, with stirring, to give a total volume of 2.5 l., and the beaker and contents were kept in a well-ventilated hood for 3 hr. The resulting precipitate was collected and recrystallized from THF–EtOH, giving 9.11 g (75%) of IV, mp 153–154.5°, $\nu_{max}^{CHCl_3}$ 3610 cm^{-1} (CHOH), R_f 0.30 on silica gel DF-5 (Camag) with 1:1 $CHCl_3$–benzene. *Anal.* ($C_{16}H_{13}BrO$) C, H, Br.

9-(Epoxyethyl)phenanthrene[7] **(V).**—To a suspension of 2.11 g (7 mmoles) of IV in 90 ml of absolute MeOH, precooled to 0°, was added 500 mg of Na, in small pieces, with stirring. The mixture became clear in 12 min and was kept at 0° for an additional 15 min. The solvent was removed under diminished pressure at 25°, the residue was suspended in 100 ml of H_2O, and the suspension was extracted with two 150-ml portions of Et_2O. The extract was washed (H_2O), dried (Na_2SO_4), and filtered, and the filtrate was evaporated under diminished pressure at 25° to a colorless syrup, homogeneous on tlc: $\nu_{max}^{CCl_4}$ 1260 (weak), 900, and 850 cm^{-1} (epoxide). An absorption band at 3610 cm^{-1} (CHOH) was absent. The product V was identical (ir and tlc) with a sample prepared from 9-phenanthrenecarboxaldehyde by the method[7] of Duncan and coworkers.

α-[N-(2-Cyanoethyl)cyclohexylaminomethyl]-9-phenanthrenemethanol Picrate (11) and Hydrochloride (12).—A mixture of 4.82 g (16 mmoles) of IV and 14.6 g (96 mmoles) of N-(2-cyanoethyl)cyclohexylamine was heated at 77–81° in a dry atmosphere. After 43 hr, the mixture was cooled and extracted with 100 ml of 1:4 $CHCl_3$–Et_2O, and the extract was filtered. The filtrate was evaporated to a syrup, which was stirred with 100 ml of 1 *M* HCl, and the supernatant liquid was decanted. The residue was dissolved in 250 ml of $CHCl_3$, and the solution was washed [1 *M* HCl (100 ml), H_2O (100 ml), 1% aqueous NaOH (100 ml), H_2O (two 100-ml portions)]. The $CHCl_3$ solution was dried (Na_2SO_4) and filtered, and the filtrate was evaporated under diminished pressure, leaving a syrupy residue that was dried for 24 hr in a vacuum desiccator (P_2O_5). The dried syrup was dissolved in 20 ml of THF, a hot solution of 3.66 g (14.3 mmoles) of picric acid in 100 ml of MeOH was added, and the mixture was heated, with stirring, to remove most of the THF, whereupon the picrate (**11**) began to crystallize.

The picrate (**11**) (2.4 g) was suspended in 250 ml of $CHCl_3$ and the suspension was shaken in a separatory funnel with 120 ml of 1% aqueous NaOH. The $CHCl_3$ layer was extracted with two 75-ml portions of 1% aqueous NaOH and two 75-ml portions of H_2O, dried (Na_2SO_4), filtered, and evaporated under diminished pressure at 30°. The residue was dissolved in 15 ml of THF, and 1.8 ml of 2.26 *M* HCl in Et_2O was added. Et_2O was added to incipient turbidity, inducing crystallization, with additional Et_2O being added, in small volumes at intervals, until crystallization of **12** was complete.

α-[N-(2-Hydroxyethyl)cyclohexylaminomethyl]-9-phenanthrenemethanol Picrate (13) and Hydrochloride (14).—A mixture of 1.5 g (7 mmoles) of V and 6.02 g (42 mmoles) of N-(2-hydroxyethyl)cyclohexylamine was heated at 78–82° for 24 hr, with occasional stirring. The mixture was dissolved in 200 ml of $CHCl_3$, and the solution was washed [8% HCl (three 100-ml portions), 1% NaOH (100 ml), H_2O (two 100-ml portions)]. The $CHCl_3$ layer was dried (Na_2SO_4) and filtered, and the filtrate was evaporated to dryness under diminished pressure at 30°, leaving a yellowish syrup, which was dissolved in 20 ml of THF, followed by the addition of 1.77 g (6.9 mmoles) of picric acid in 75 ml of hot MeOH. The mixture was heated, with stirring, to remove most of the THF, whereupon crystallization of the picrate (**13**) commenced.

The picrate (**13**) (3.42 g, 5.6 mmoles) was suspended in 220 ml of $CHCl_3$ (separatory funnel) and shaken with 100 ml of 1% aqueous NaOH, until dissolution was complete. The $CHCl_3$ layer was washed [1% aqueous NaOH (two 50-ml portions), H_2O (two 50-ml portions)], dried (Na_2SO_4), and filtered. The filtrate was evaporated to dryness under diminished pressure at 30°, the resulting clear syrup was dissolved in 15 ml of dry THF, and 3.1 ml of 2.26 *M* HCl in Et_2O was added. The mixture was evaporated under diminished pressure at 30°, leaving the hydrochloride (**14**) as a white foam, which was dried in a vacuum desiccator (P_2O_5) for 24 hr.

α-[Bis(2-carboxyethyl)aminomethyl]-9-phenanthrenemethanol (15).—A suspension of the methanol hydrochloride (**10**) in 8 ml of 9 *M* HCl and 8 ml of *p*-dioxane was refluxed in an oil bath (105°) for 4 hr. The dark brown mixture was cooled, sufficient 10% aqueous NaOH was added to make it alkaline, and the resulting mixture was heated to 80°. It was then filtered with a little Darco G-60 decolorizing carbon, the pH of the filtrate was adjusted to about 4 with 1 *M* HCl, and the mixture was kept overnight at room temperature. The separated product **15** was recrystallized by acidifying an alkaline solution to pH 3–4.

α-[Bis(3-aminopropyl)aminomethyl]-9-phenanthrenemethanol Trihydrochloride (16).—To a solution of 2.3 g (7 mmoles) of **10** in 10 ml of purified Diglyme was added 50 ml of 1 *M* $NaBH_4$. To this mixture was added (dry box) 6.6 g (15 mmoles) of $AlCl_3$, in small portions with stirring. Stirring was continued for 2 hr, H_2O (25 ml) was carefully added, with stirring, and the mixture was made alkaline with 10% aqueous NaOH. It was then extracted with $CHCl_3$ (three 100-ml portions), and the $CHCl_3$ extracts were combined, washed with H_2O (150 ml), and dried (Na_2SO_4). The solution was filtered, and the filtrate was evaporated to dryness under diminished pressure at 35°, leaving a residue [$\nu_{max}^{CHCl_3}$ 3610 (OH), 3390 (asym NH), and 3315 cm^{-1} (sym NH)], which was dissolved in 20 ml of THF. To this was added 10 ml of 2.24 *M* HCl in Et_2O, followed by the addition of 50 ml of Et_2O. The resulting precipitate was filtered off inside a dry box, in which subsequent recrystallizations were performed.

Esters of Undecanoic Acid with Potential Long-Lasting Insect-Repellent Activity[1]

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We have previously reported on the design and synthesis of novel grisan and coumaranone derivatives anticipated to exert insect repellency following systemic

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