Antimalarial Arylaminopropanols†

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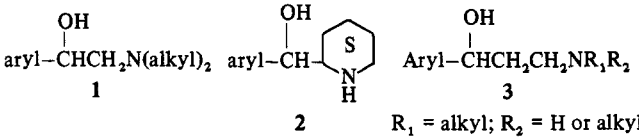
A number of aromatic nuclei are associated with significant antimalarial activity when attached to *N*-alkylaminoethanol or α-piperidylmethanol side chains. A series of *N*-monoalkyl- and *N,N*-dialkylaminopropanol side chains have now been attached to a series of these active nuclei. The preparation and antimalarial activity of the aminopropanol variants are described. The antimalarial bioassay data for the title compounds show an increase in activity when compared to standard side-chain variants. These results appear to confirm the empirical and theoretical rationale that led to their preparation.

A large series of phenanthrenes, quinolines, and related arylaminoethanols of types **1** and **2** has been prepared for antimalarial screening during the current Army Research Program on Malaria.



A comparison of the animal test antimalarial activity of a small series of type **1** and type **3** ($R_1 = R_2$ = alkyl) compounds from the Coatney and Wiselogle compilations showed equal or enhanced activity for the type **3** series[1,2] (aryl = 9-phenanthryl,[1a] 1,2,3,4-tetrahydro-9-phenanthryl,[1a] 4-chloro-1-naphthyl[1b,2]). Models of the compounds were also compared in the intercalation-DNA binding model of the proposed active site that we have been using as a predictive guide for selecting many compounds for preparation.‡ The purpose of the amino group in this model system is to form an ionic bond to a phosphate of the deoxyribose backbone. The *N*-alkyl chain (R_1 and/or R_2 = alkyl) then lies in a hydrophobic "pocket" created by the partial unwinding of the helix at the intercalation site. The predictive abilities of the model system are not as clean cut for these side-chain parameters as they are for aryl nuclei variations or for alkyl branching on the side chains, but it appeared that the desired bond could be more readily formed with the type **3** side chain than type **1**. In particular, the model system indicated that the second *N*-alkyl group in **3** (R_2 = alkyl) did not appear necessary.

We have now prepared a group of arylaminopropanols (**3**) in which the aryl groups are among the most highly active nuclei associated with the type **1** and **2** systems. The starting aromatic compounds were generally prepared by other laboratories and provided to us by the Walter Reed staff.§ The arylaminopropanols (**3**) are shown in Tables I and II along with the mouse *Plasmodium berghei* antimalarial activity results.# Table I also includes a selection of the most closely comparable type **1** compounds and the bioassay results associated with these compounds.

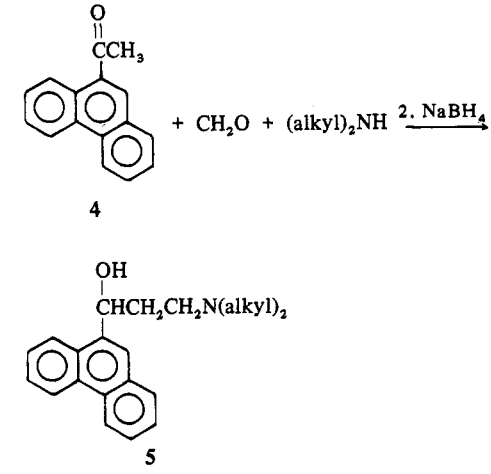
It is evident that the propanolamine modifications provide highly active compounds. The comparative data between the type **1** and type **3** compounds uniformly demonstrate an enhancement of activity for the propanolamines (**3**). The most active type **3** compounds are also comparatively more active than the racemic α-piperidyl variants (**2**) in the mouse *P. berghei* screen. The decrease in activity for the diheptyl (**27**) and dinonyl (**28**) derivatives does show a definite limit for the *n*-alkyl chain homologation.

All of the arylaminopropanols that have been tested in the chick *P. gallinaceum* screen (**19, 25, 26, 35–38**) have doubled the survival time of the test animals at some test dosage. The N-monosubstituted compounds all double survival times at 10 mg/kg.

None of the compounds shown have demonstrated any acute toxicity up to 640 mg/kg dosage under the test conditions.

Chemistry. The aminopropanols have been synthesized by four synthetic pathways. The routes are shown for the representative 9-phenanthryl system in Schemes I–IV.

Scheme I



Synthetic Scheme I followed a literature procedure for the preparation of several 9-phenanthryl- and tetrahydro-9-phenanthrylpropanolamines.[4] In our hands this Mannich sequence gave only a 2% yield of product when dibutylamine was used. As a result other methods were sought for the preparation of these compounds.

Procedures II, III, and IV all involve the preparation of the aryl aldehydes (**8**). In this and some related work we had accomplished the preparation of the hydroxymethyl derivatives **7** *via* reduction of the methyl esters (of compounds **6**) with $LiAlH_4$. Several $LiAlH_4$ reductions resulted in the hydrogenolysis of ring-halogen substituents and the BH_3 procedure was adopted with great success (Table III). All of the oxidations **7** → **8** reported in this paper were accomplished using $Pb(OAc)_4$–pyridine with the ratio of reagents, times, and temperature being quite specific for each case (Table IV). The results of this reaction were, however, quite erratic until the minor modification of presaturating

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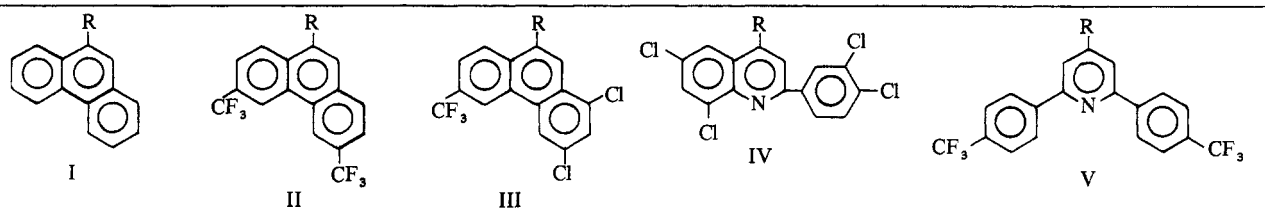
‡D. W. Henry, manuscript in preparation.

§See the footnotes, Table III, for the source laboratories.

#Biological investigation performed by Dr. Leo Rane of the University of Miami, Miami, Fla., by a published procedure.[3]

Table I. Antimalarial Bioassay Data. *N,N*-Dialkylarylaminopropanols and Related Arylaminoethanols[a]

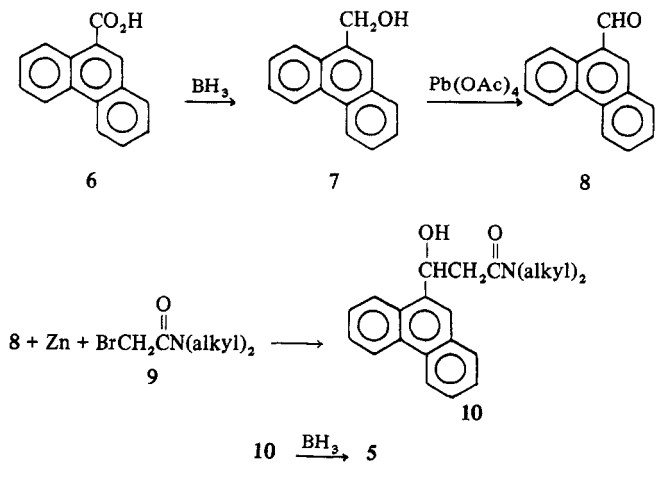


I II III IV V

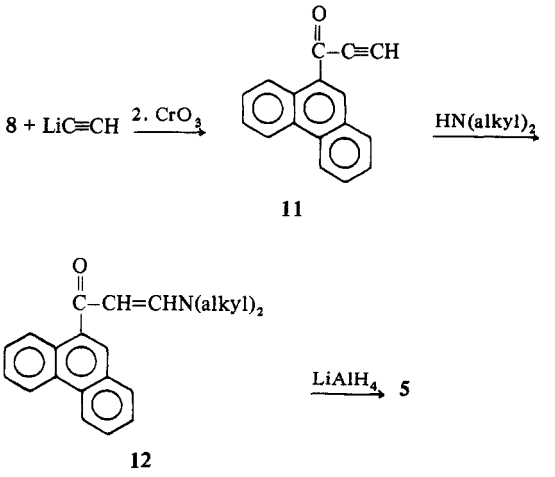
No.	R	Antimalarial activity[b] 5	10	20	40	80	160
	I						
16	$CHOHCH_2N(n\text{-heptyl})_2$[c]			4.0	4.2	5.2	9.4
17	$CHOHCH_2CH_2N(n\text{-heptyl})_2 \cdot HCl$[d]			0.5	4.7	12.2	13.7
18	$CHOHCH_2CH_2N(n\text{-butyl})_2 \cdot HCl$[e]		0.3	0.3	0.5	0.7	2.3
	II						
19	$CHOHCH_2CH_2N(CH_2CH_3)_2 \cdot HCl$		5.9	13.7	28.4/3C	29.9/4C	5C
20	$CHOHCH_2CH_2N(propyl)_2 \cdot HCl \cdot H_2O$	7.9	12.9/1C	14.2/2C	20.4/3C	18.9/4C	5C
21	$CHOHCH_2CH_2N(propyl)_2 \cdot$ maleate	6.4	13.3	15.7/1C	20.9/2C	22.9/4C	5C
22	$CHOHCH_2N(butyl)_2 \cdot HCl$[f]	4.7	5.9	1C	2C, 3C	3C, 5C	5C
23	$CHOHCH_2CH_2N(butyl)_2 \cdot$ maleate	5.5	14.5	18.4/2C	5C	5C	5C
24	$CHOHCH_2CH_2N(butyl)_2 \cdot HCl$	7.9	12.7/1C	14.9/2C	20.9/2C	21.9/4C	5C
25	$CHOHCH_2CH_2N(pentyl)_2 \cdot HCl$		7.1	12.3	14.6/2C	31.4/3C	5C
26	$CHOHCH_2CH_2N(pentyl)_2 \cdot$ maleate		7.9	13.9	23.9/4C	27.9/4C	5C
27	$CHOHCH_2CH_2N(heptyl)_2 \cdot HCl$			0.5	1.1	3.9	8.7
28	$CHOHCH_2CH_2N(nonyl)_2 \cdot$ free base	0.1	0.1	0.1	0.1	0.1	0.1
	III						
29	$CHOHCH_2N(butyl)_2$[g]	7.1	12.3	2C	4C	5C	5C
30	$CHOHCH_2CH_2N(butyl)_2 \cdot HCl$	9.3	14.9/1C	5C	5C	5C	5C
	IV						
31	$CHOHCH_2N(butyl)_2$[h]	7.3	15	3C/10	6C/10	8C/10	9C/10
32	$CHOHCH_2CH_2N(butyl)_2 \cdot HCl$	15.5	21.9/2C	5C	5C	5C	5C
	V						
33	$CHOHCH_2N(butyl)_2$[h,i]			8.7	2C	5C	5C
34	$CHOHCH_2CH_2N(butyl)_2 \cdot$ free base	4.1	14.3	5C	5C	5C	5C

[a] See Table III for source of starting materials. [b] Dosage given in mg/kg. Numbers give the extension in survival time in days over untreated mice in the standard mouse *P. berghei* assay. See footnote # for procedure. A number preceding the letter "C" indicates the number of animals out of five cured (mice surviving 60 days), the results reported for **31** were obtained on 10 mice. A combination such as 28.4/3C indicates 3 cures and an increase in survival of 28.4 days of the mice not cured. [c] 320 mg/kg, 10.4; 640, 3C. [d] 320 mg/kg, 15.5; 640, 5C. [e] May and Mossetig[4] report the preparation of **18** ($\cdot CH_3OH$) by a different route. [f] See ref 7. [g] Data supplied by Dr. R. E. Stube of WRAIR. Dr. E. A. Nodiff has kindly allowed us to use these data prior to his publication. [h] Data supplied by Dr. R. E. Strube. [i] Ash-Stevens Laboratories. Presented by T. R. Sweeney and D. P. Jacobus at the Twelfth National Medicinal Chemistry Symposium, Seattle, Washington, June 22–25, 1970.

Scheme II



Scheme III

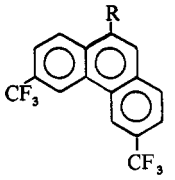


the pyridine solvent with N_2 was introduced. Under these conditions transparent, lightly colored reaction mixtures were obtained, and the yields became very reproducible.

The condensation steps **8** + **9** → **10** (Scheme II) and **8** + **13** → **14** (Scheme IV) are being reported elsewhere.[5] The yields in these reactions were quite good. The sequence shown in Scheme III was utilized for the preparation of compound **17**. In that case the sequence of reactions was nearly quantitative; however, the final reduction **12** → **5** resulted in considerable hydrogenolysis in the only large-scale reaction attempted. The addition of lithium acetylide to 3,6-bis(trifluoromethyl)phenanthrene-9-carboxaldehyde could not be forced to completion and the separation of products proved difficult. The procedure was not further investigated.

The final reduction steps **10** → **5** and **14** → **15** (Table V)

Table II. Antimalarial Bioassay Data. *N*-Monoalkylarylaminopropanols.



No.	R	Antimalarial activity[a] 5	10	20	40	80	160
35	$CHOHCH_2CH_2NH$(butyl)·HCl	9.3	3C	5C	5C	5C	5C
36	$CHOHCH_2CH_2NH$(cyclohexyl)·HCl	2.9	2C	3C	3C	5C	5C
37	$CHOHCH_2CH_2NH$(*i*-propyl)·HCl	2.7	13.1	2C	2C	3C	5C
38	$CHOHCH_2CH_2NH$(*tert*-butyl)·HCl	16.1	3C	3C	5C	5C	5C

[a]See footnote *b*, Table I.

Table III. Borane Reductions. Step 6 → 7

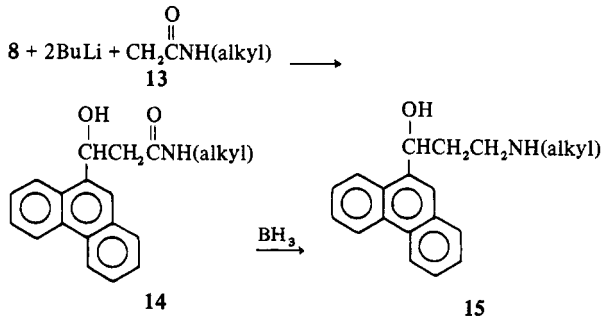
No.	Product	Yield, %	Time, hr (temp, °C)	Ratio BH_3:$ArCO_2H$	Mp, °C	Formula	Analyses
39	II, R = CH_2OH[a]	100	18 (25) 1 (66)	3:1	215–220	$C_{17}H_{10}F_6O$	C, H
40	III, R = CH_2OH[b]	97	16 (25) 2 (66)	7.2:1	190–194	$C_{16}H_9Cl_2F_3O$	C, H
41	IV, R = CH_2OH[a]	84	2 (25) 0.5 (66)	2:1	195–199	$C_{16}H_9Cl_4NO$	C, H, N
42	V, R = CH_2OH[b]	95	0.25 (25) 1.5 (66)	2:1	165–168	$C_{20}H_{13}F_6NO$	C, H, N

[a]Starting acid provided through Walter Reed Army Institute of Research by Aeroject Solid Propulsion Co., Sacramento, Calif. [b]Ash-Stevens, Inc., Detroit, Mich. 3,6-Bis(trifluoromethyl)phenanthrene-9-carboxylic acid was also prepared in these laboratories (SRI) by a photochemical route.

Table IV. $Pb(OAc)_4$ Oxidation. Step 7 → 8

No.	Product	Yield, %	Time, hr (temp, °C)	Ratio $Pb(OAc)_4$:$ArCH_2OH$	Mp, °C	Formula	Analyses
43	II, R = CHO	83	See Experimental Section (25)	See Experimental Section	182–184	$C_{17}H_8F_6O$	C, H
44	III, R = CHO	82	3.5 (25)	2:1	180–183	$C_{16}H_7Cl_2F_3O$	C, H
45	IV, R = CHO	85	1.25 (0)	2:1	200–202	$C_{16}H_7Cl_4NO$	C, H, N
46	V, R = CHO	86	1 (25)	2:1	177–185	$C_{19}H_{11}F_6NO$	C, H, N

Scheme IV



were routine. Purification and salt formation for the type **15** compounds were straightforward and were accomplished in high yield. The dialkylaminopropanols (type **5**) were usually almost pure as the initially isolated free bases (tlc, ir), but they uniformly refused to give crystalline HCl salts at this stage in the first preparations. It was generally necessary to proceed through the sequence oxalate → maleate → HCl salt, a procedure that resulted in considerable loss of product. In several repeat reactions, the HCl salts were directly preparable from the free bases with the aid of seed crystals, a procedure that resulted in a considerable saving in effort but that has not generally enhanced the yields.

In summary, several variants of a side-chain modification —the aminopropanols (**3**)—have been prepared. These side-chain modifications have resulted in a reproducible enhancement of activity against mouse *P. berghei* of at least a factor of two over the most closely comparable compounds of the aminoethanol (**1**) or α-piperidyl (**2**) types.

Experimental Section

3,6-Bis(trifluoromethyl)-9-hydroxymethylphenanthrene (39). A soln of 70 g (0.21 mole) of 3,6-bis(trifluoromethyl)phenanthrene-9-carboxylic acid in 420 ml of commercial "dry" THF was added dropwise to a stirred 0° soln of 1 *M* BH_3 in THF (420 ml, 0.42 mole) under N_2. The reaction mixt was allowed to warm to room temp and was stirred for 18 hr. An addnl 210 ml (0.21 mole) of 1 *M* BH_3 soln was then added, and the mixt refluxed for 1 hr. The THF was removed *in vacuo*, and the residue was stirred and heated with 1 l. of H_2O for about 5 min. The mixt was filtered, and the product collected as the residue, 68 g (100%) of white solid, mp 215–220°. Tlc (silica gel, Et_2O) R_f 0.87. The minimal conditions for this redn have not been examined but the fairly long reaction time at 20° followed by a short reflux appears necessary.

3,6-Bis(trifluoromethyl)phenanthrene-9-carboxaldehyde (43). To a stirred soln of 68.6 g (~0.21 mole) of 3,6-bis(trifluoromethyl)-9-hydroxymethylphenanthrene in 2100 ml of N_2-satd pyridine (commercial reagent) under N_2 was added 91 g of $Pb(OAc)_4$ (0.21 mole, solid commercial reagent). The reaction was stirred at room temp for 3 hr. An addnl 35 g (0.078 mole) of $Pb(OAc)_4$ was then added and the reaction stirred for 2 hr. The stirred reaction was cooled to *ca.* 15° and treated with about 5 l. of H_2O. The mixt was

Table V. Borane Reductions. Steps 10 → 5; 14 → 15

Compound	Yield, %	Mp, °C	Formula	Analyses
18	26	106–110	$C_{25}H_{39}NO \cdot HCl$	C, H, N
19	36	215–220	$C_{23}H_{23}F_6NO \cdot HCl$	C, H, N, Cl^-
20	(87% from 21)	230–235	$C_{24}H_{27}F_6NO \cdot HCl \cdot H_2O$	C, H, N, Cl^-
21	60	112–113	$C_{29}H_{31}F_6NO_5$	C, H, N
23	27	122–124	$C_{31}H_{35}F_6NO_5$	C, H, N
24	(67% from 23)	112–114[a]	$C_{27}H_{31}F_6NO \cdot HCl$	C, H, N, Cl^-
25	38	70–79	$C_{29}H_{35}NO \cdot HCl$	C, H, N, Cl^-
26	39	105–110	$C_{33}H_{39}F_6NO_5$	C, H, N
27	30	159–170	$C_{33}H_{43}F_6NO \cdot HCl$	C, H, N, Cl^-
28	24	Oil[b]	$C_{37}H_{51}F_6NO$	C, H, N
30	43	93–96[a]	$C_{26}H_{30}Cl_2F_3NO \cdot HCl$	C, H, N, Cl^-
32	41	83–88	$C_{26}H_{30}Cl_4N_2O \cdot HCl$	C, H, N, Cl^-
34	87	Oil[c]	$C_{30}H_{34}F_6N_2O$	C, H, N
35	75	229–230	$C_{23}H_{23}F_6NO \cdot HCl$	C, H, N, Cl^-
36	75	266–269	$C_{25}H_{25}F_6NO \cdot HCl$	C, H, N, Cl^-
37	61	249–252	$C_{22}H_{21}F_6NO \cdot HCl$	C, H, N, Cl^-
38	71	275–277	$C_{23}H_{23}F_6NO \cdot HCl$	C, H, N, Cl^-

[a] Dr. R. E. Olsen of Aeroject Solid Propulsion Co., Sacramento, Calif., has reprepared compounds **24** and **30** on a large scale. In his work he has obtained both the indicated crystalline modifications and higher melting forms: **24**, mp 190–191°; **30**, mp 203–204° (personal communication). [b] Oxalate salt, mp 143–146°. *Anal.* ($C_{39}H_{55}F_6NO_5$) C, H, N. [c] HCl salt, mp 92–100°. *Anal.* ($C_{30}H_{34}F_6NO \cdot HCl \cdot 0.5H_2O$) C, H, N, Cl^-.

filtered on sintered glass and washed with *ca.* 2 l. of H_2O. The filtration residue was transferred to a beaker and well digested with boiling C_6H_6. The C_6H_6 mixt was filtered hot on sintered glass. Most of the C_6H_6 was removed from the filtrate and petr ether (30–60°) was added to complete the crystn of the product. The collected dried product weighed 55.5 g (83%), mp 182–184°, tlc (silica gel, C_6H_6) R_f 0.7. The ir of this material is a poor guide (Nujol) as we have observed widely varying spectra in about 10 different prepn (C=O, *ca.* 5.9 μ).

In all other oxidn the entire quantity of $Pb(OAc)_4$ was added all at once.

3,6-Bis(trifluoromethyl)-9-[1-hydroxy-3-(di-*n*-pentylamino)-propyl]phenanthrene. A 0° soln of 11.9 ml of 1 *M* BH_3 in THF soln (0.0119 mole) under N_2 was treated dropwise with a soln of 4.80 g (0.0089 mole) of 3,6-bis(trifluoromethyl)-9-[3-(3-hydroxy-*N*,*N*-dipentylpropionamide)][5] in 75 ml of dry THF. The mixt was stirred for 1 hr at 0°, then overnight at 25°. Tlc (silica gel, $CHCl_3$) showed starting material R_f 0.1 and the product–boron complex at the origin. An addnl 10 ml of 1 *M* BH_3 soln was then added and after 2 hr the reaction mixt was heated to reflux. Essentially no starting material could be detected after 1 hr (tlc). The reaction mixt was cooled to 0° and treated with H_2O. The resulting mixt was extd with Et_2O, then the Et_2O layer was evapd *in vacuo* to yield 4.5 g of the product–boron complex. This complex was refluxed for 4 hr in a soln of 13 ml of 10% H_2SO_4 and 66 ml of MeOH. The cooled soln was neutralized with 1 *N* NaOH, then extd with Et_2O. After drying the Et_2O was evpd *in vacuo* to yield 3.9 g of gummy product (ir, tlc). The oxalate salt was prepd in Et_2O–EtOH using a 10% excess of oxalic acid, mp *ca.* 175° with sublimation.

Maleate Salt (26). The oxalate salt was neutralized by treatment of a THF soln with excess 1 *N* NaOH. The free base was isolated by Et_2O extn, 2.5 g. A 1-g portion of free base (0.0019 mole) was dissolved in Et_2O and treated with an Et_2O soln of 0.44 g (0.0038 mole) of maleic acid in Et_2O. The resulting ppt was collected after 1 hr, 0.89 g, mp 105–110°. This represents a 39% yield from the amide.

HCl Salt (25). The remaining 1.5-g portion of the free base was treated with excess HCl in EtOH. The EtOH was removed *in vacuo* and the HCl salt was ppt as an amorphous solid from acetone–Et_2O, 1 g, mp 70–79°. This represents a 38% yield from the amide.

3,6-Bis(trifluoromethyl)-9-[1-hydroxy-3-(*N*-isopropylamino)-propyl]phenanthrene Hydrochloride (37). This procedure is typical of each monosubstituted amine prepn. To a cold (~−5°) soln of 1 *M* BH_3 (18.5 ml, 18.5 mmoles) in THF (37 ml) under a N_2 atmosphere was added dropwise a soln of 3-[3,6-bis(trifluoromethyl)-9-phenanthryl]-3-hydroxy-*N*-isopropylpropionamide[5] (3.71 g, 8.4 mmoles) in 150 ml of THF. The reaction was stirred 1 hr at ~−5°, then overnight at room temp, and then 23 hr at 55°. More BH_3 (30 ml) was added and heating was continued at 55° for another 4 hr. The reaction was followed by tlc (Et_2O) and also by the disappearance of the carbonyl band at 6.1 μ in the ir. The reaction was cooled in ice and treated cautiously with water, then evapd to dryness *in vacuo* to give a white solid. The boron complex was destroyed by refluxing in 55 ml of MeOH and 12 ml of 10% sulfuric acid for 4 hr. The soln was cooled in ice and the pH was adjusted to 7 with 1 *N* NaOH. The white cryst sulfate was filtered off. The weight was 3.94 g, mp 274–278°. An addnl 0.441 g of sulfate was collected by adding Et_2O to the filtrate.

The sulfate was converted to the free base by suspending in aqueous MeOH and adjusting the pH to *ca.* 10 with 1 *N* NaOH. The free base was extd into Et_2O. The Et_2O was dried and evapd to dryness to give a glass, wt 2.64 g. This was converted to the white cryst HCl salt, 2.39 g (61% yield from the amide), mp 249–252°, tlc in $CHCl_3$–MeOH–2 *N* NH_4OH (40:10:1), R_f 0.6.

Phenanthrene-9-(1-prop-2-yn-1-ol). A powdery suspension of LiC≡CH–EDA complex was prepd by the addn of 3.56 g (0.036 mole) of the complex to 30 ml of dry DMF ($PhCH_3$ azeotrope) satd with purified (H_2SO_4, $CaCO_3$) HC≡CH. The HC≡CH addn was maintained, and after 2 hr a soln of 5 g (0.025 mole) of phenanthrene-9-carboxaldehyde in 30 ml of dry DMF was added dropwise at room temp. The reaction was stirred an addnl 1 hr while adding HC≡CH, then sealed and stirred overnight. The reaction was hydrolyzed by the addn of H_2O and the resulting mixt was extd with Et_2O. The removal of Et_2O *in vacuo* gave an oily solid, which was shown to be a mixt of starting material and product by ir.

The crude reaction was chromatographed on silica gel (C_6H_6 elution) to yield 3.3 g of product, mp 120–128° (58% yield). The remainder of the starting material was recovered.

Phenanthrene-9-(1-prop-2-yn-1-one) (11). Phenanthrene-9-(1-prop-2-yn-1-ol), 2.3 g, 0.01 mole, was dissolved in 5 ml of Me_2CO. The stirred soln was cooled to 0° and treated slowly with 3.5 ml of a soln prepd from 20 g of CrO_3, 57 ml of H_2O, and 17 ml of concd H_2SO_4. The reaction was stirred 2.5 hr at 0° and then partitioned between Et_2O and H_2O. The Et_2O layer was washed with H_2O and dried. The Et_2O was removed *in vacuo* to yield 2.3 g of product, which was pure by ir, but showed a trailing edge on tlc (silica gel–C_6H_6). The crude material was chromatographed on a 27 × 3 cm column of silica gel (C_6H_6 elution). The first 450 ml of eluant returned 2.08 g (91%) of product that was pure by tlc, mp 108–110°. *Anal.* ($C_{17}H_{10}O$) C, H.

Phenanthrene-9-[1-prop-(3-diheptylamino)-2-en-1-one] (12, R = Heptyl). Phenanthrene-9-(1-prop-2-yn-1-one) **(11)**, 1.84 g (0.008 mole), was stirred at room temp as a suspension in 60 ml of MeOH. The suspension was treated with 1.7 g (0.008 mole) of diheptylamine in 20 ml of MeOH according to the general procedure of McMullen and Stirling.[6] Nearly complete solution was achieved at the end of the addition. After 20 hr, tlc still indicated the presence of two components. After 68 hr only one component was shown by tlc, but a slight ppt was present. The reaction mixture was then filtered and the MeOH was removed *in vacuo* to yield 3.38 g of a clear oil. The oil was chromatographed on a 30 × 3 cm column of silica gel (C_6H_6 elution). A small amount of impurity was removed in the early fractions (60-ml fractions); then 3.06 g (86.5%) of pure product was collected in fractions 17–19 as a viscous liquid. *Anal.* ($C_{31}H_{41}NO$) C, H, N.

9-[1-Hydroxy-3-(di-*n*-heptylamino)propyl]phenanthrene Hydrochloride (17). The enamine (**12**, R = heptyl) (3.06 g, 0.007 mole), dissolved in 80 ml of THF, was treated with 1.06 g (0.028 mole) of

$LiAlH_4$. The mixt was stirred at room temp for 29 hr. The reaction was hydrolyzed with H_2O and extracted with Et_2O. The Et_2O soln was evapd *in vacuo* to yield 3.0 g of crude product. Tlc showed a number of spots (silica gel-C_6H_6). The crude reaction product was chromatographed on a 28 × 3 cm column of silica gel (C_6H_6 elution, 60-ml fractions). Fractions 6–12 gave 500 mg of the starting amino ketone (15%) (nmr, ir). Fractions 22–29 (10% Et_2O) gave 500 mg of product (nmr, ir, elemental analysis of the HCl salt). Other fractions were unidentified, although final 100% Et_2O elution gave 800 mg of material that appeared to be a trialkylamine. The HCl salt of the product was prepd in EtOH-Et_2O as white crystals, mp 119–122° (15% yield).

A 100-mg probe run had given a nearly quantitative yield of product **17**.

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Antimalarial Phenanthrene Amino Alcohols. 2. Trifluoromethyl-Containing 9-Phenanthrenemethanols†,[1]

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A series of mono-, di-, tri-, and tetrasubstituted 9-phenanthrene amino alcohols has been prepd in which each compd bears at least one CF_3 group. A number of these compds, tri- and tetrasubstituted with a combination of CF_3 and Cl groups, are the most active, nontoxic amino alcohols to emerge from the vast primary screen (*Plasmodium berghei*, mouse) of the Army's Research Program on Malaria. The most effective member of the series, 6,7-dichloro-2,4-bis(trifluoromethyl)-α-(di-*n*-propylaminomethyl)-9-phenanthrenemethanol·HCl (**159**), is 100% curative at 5 mg/kg and active at concentrations as low as 1.25 mg/kg.

Antimalarial enhancement of 9-phenanthrenemethanols by introduction of CF_3 groups or a combination of CF_3 and halogen was described earlier.[1] In an effort to approach the optimal substitution pattern for this series we have synthesized the compds included in Table I.

Chemistry. The preparative routes were essentially those described in paper 1.[1] Details have been tabulated in the Experimental Section.

Biology. Table I includes murine antimalarial data for 48 new CF_3-contg 9-phenanthrene amino alcohols. The distribution of these compds among the curative, active, and inactive categories, at each dose, is shown in Table II.

Most of the new compds were active or curative at doses as low as 10 mg/kg. Conspicuous exceptions were the derivs with one or more nonhalogenic groups (**125, 126, 127, 131**). In fact, the 6-CF_3, 3-COOH deriv (**126**) was the only one in the entire series completely inactive at even the highest concentrations. It would seem that the preferred substituents are those which combine a positive Hansch π constant[2] with a positive Hammett σ constant.[3]

The most active compds (**113, 129, 135–139, 142, 159**), with 60–100% cures at 20 mg/kg, were mainly tri- and tetrasubstituted with a combination of Cl and CF_3 groups. The best of these (**135, 137, 138, 159**), with 60–100% cures at 10 mg/kg, all had two of their substituents at positions 2 and 4.

Among the side chains, the piperidyl, Pr, Bu, and Am derivs were all quite good. Compds with the heptyl side chain retained considerable activity but were less effective than the others.

The compds **135, 137, 138**, and **159** are the most active, nontoxic amino alcohols to emerge from the vast primary screen of the Army's Research Program on Malaria.

Experimental Section‡

4,5-Dichloro-2-nitrophenylacetic Acid. Method A. Commercial 3,4-dichlorobenzoic acid (Eastman), suspended in concd H_2SO_4, was nitrated with mixed acid (modification of the method of Claus and Bucher[4]) to give 77% of 4,5-dichloro-2-nitrobenzoic acid. This material was identical with that obtd on oxidation ($KMnO_4$ in aqueous Me_2CO) of authentic 4,5-dichloro-2-nitrobenzaldehyde[5] thereby proving its structure. This nitrobenzoic acid was converted to the corresponding nitrophenylacetic acid in the usual manner (Table III, footnote *y*); mp 133–136° (C_6H_6-ligroin), yield 68%. *Anal.* ($C_8H_5Cl_2NO_4$) C, H, N.

Method B. To a mixt of 34 ml of HNO_3 (*d* 1.42) and 375 ml of concd H_2SO_4 at −20° was added, in one portion, 95 g (0.46 mole) of 3,4-dichlorophenylacetic acid (Research Organic/Inorganic Chemical Corp., Sun Valley, Calif.). The reaction temp rose to −5° and was then maintained at −10° to −5° for 0.5 hr and at −5° to 0° for 1 hr. The resulting white mass was poured into 1.8 kg of crushed ice and the white solid was washed, dried, extd with boiling ligroin (ext discarded), and crystd from aqueous HOAc; yield 95 g (83%), mp 132–134°. The ir spectrum of this material was identical with that of the analytical sample obtd *via* method A.

3,5-Bis(trifluoromethyl)benzaldehyde. A mixt of 3,5-bis(tri-

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‡Satisfactory spectra were obtd where required for structural detn; ir as Nujol mulls on Perkin-Elmer 137B Infracord; nmr (by Sadtler Research Laboratories, Philadelphia, Pa.) on Varian A-60A. Mp's were detd in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorr. Where analyses (Microanalysis, Inc., Wilmington, Del.) are indicated only by symbols of the elements analytical results were within ±0.4% of the theor values.