Structure–Activity Relationship Studies on Antimalarial Phenanthrene Amino Alcohols Modification of the Side Chain†

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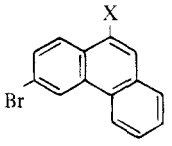
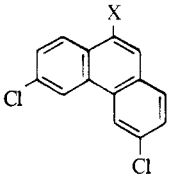
Substituted phenanthrenes with a variety of amino alcohol side chains attached to the 9 position have been prepared and their structure–activity relationship in animal screening against *Plasmodium berghei* and *P. gallinaceum* has been studied. Several compounds possess activity at 10 mg/kg and are curative at 20 mg/kg against *P. berghei* with no toxicity to the host. In this investigation it was found that (1) the antimalarial activity of compounds of type $ArCHOHCH_2NHR$ are of slightly higher order than that of type $ArCHOHCH_2NR_2$; (2) alkyl *N*-substitution in the α-piperidyl function on the side chain yields compounds of comparable activity; (3) diastereomers possess different antimalarial activity; (4) the basicity of the N on the side chain plays an important role in antimalarial activity; (5) compounds with more than one basic N atom on the side chain are usually inactive and sometimes toxic to host animals; and (6) the order of activity of 3 substituted phenanthrene rings studied (with identical amino alcohol side chains) is: 3,6-bis(trifluoromethyl)- > 3,6-dichloro- > 6-bromophenanthrene.

The quinoline amino alcohols, which are structurally related to quinine, display good antimalarial activity but the more active 2-aryl substituted compounds possess undesirable phototoxicity[1-4] which precludes their use as practical antimalarial drugs. The analogous phenanthrene amino alcohols, on the other hand, are found to be devoid of phototoxicity[5] though somewhat less active than the quinoline congeners. In connection with the general program of searching for more suitable antimalarial agents, structural modification studies of phenanthrene amino alcohols have been conducted in this laboratory. This report is concerned with the modification of the amino alcohol side chain, which is attached to the 9 position of the following phenanthrenes: 6-bromo-, 3,6-dichloro-, and 3,6-bis(trifluoromethyl)phenanthrene.

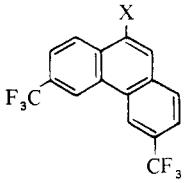
Chemistry. 6-Bromo-9-phenanthrenecarboxylic acid (**1a**), one of the 3 basic starting materials for our study, was prepared by a reported procedure.[6,7] 3,6-Dichloro-9-phenanthrenecarboxylic acid (**2d**) was obtained by acid hydrolysis of the corresponding 9-cyano compound 2c. The latter was prepared by bromination of 3,6-dichlorophenanthrene‡ followed by treatment of the bromo compound **2b** with $Cu_2(CN)_2$ in DMF. The overall yield of **2d** from **2a** was greater than 50%. 3,6-Bis(trifluoromethyl)phenanthrene-9-carboxylic acid‡ (3a) was provided by WRAIR.



1a, X = CO_2H
b, X = CH_2OH
c, X = CHO



2a, X = H
b, X = Br
c, X = CN
d, X = CO_2H
e, X = CH_2OH
f, X = CHO



3a, X = CO_2H
b, X = CH_2OH
c, X = CHO

To study the effect of piperidyl N-substitution on antimalarial activity, two 6-bromo-α-(*N*-substituted 2-piperidyl)-9-phenanthrenemethanols (**7** and **10**) were prepared. The intermediate **5a**, which in earlier WRAIR screening programs was shown to have a good activity against *P. berghei*, was readily obtained by catalytic hydrogenation of 9-(6-bromophenanthryl) 2-pyridyl ketone (**4a**). Since direct alkylation of the secondary amino group of **5a** with alkyl halide or with a mixture of formaldehyde and formic acid under the Eschweiler-Clarke condition was unsuccessful, the *N*-Bu derivative **7** was prepared through LAH reduction of the diacylated intermediate **6**. For the preparation of the *N*-Me compound **10**, the ketone **4a** was methylated at first, and the resulting methylpyridinium salt **8** was subjected to catalytic hydrogenation. In contrast to the hydrogenation of the N-*un*methylated ketone **4a**, reduction of the C=O of **8** was rather difficult and it was necessary to treat the intermediate **9** with $NaBH_4$ to yield the desired product **10**. Compound **10** was also prepared by an alternative route: the ketone **4a** was initially reduced by $NaBH_4$, and the resulting alcohol **11** was methylated (to yield **12**) and hydrogenated to give **10**. Structure **10** contains two asymmetric carbon atoms and it is of interest to note that two diastereomers (**10a**, mp 272–274° dec; **10b**, mp 191–193° dec) were obtained by the second (**4a** → **11** → **12** → **10**) route but only the higher melting isomer **10a** was isolated by the first (**4a** → **8** → **9** → **10**) route.

3,6-Dichloro-α-(2-piperidyl)-9-phenanthrenemethanol (**5b**) was originally prepared by Nodiff§ by catalytic hydrogenation of the corresponding ketone **4b** with PtO_2 in ethanolic HCl. The melting point of the HCl salt of **5b** was reported§ to be 298–300°. When the hydrogenation was carried out under the same conditions except that concd HCl was used, the HCl salt of the product **5b** melted at 320–322° dec. Diastereomerism may again have played a role here.

9-(6-Bromophenanthryl) 2-quinolyl ketone (**13a**) and the corresponding bis(trifluoromethyl) compound **13b** were prepared by treatment of **1a** and 3a, respectively, with 2-lithioquinoline. Catalytic hydrogenation of **13a** with PtO_2 in aq ethanolic HCl gave 6-bromo-α-[2-(1,2,3,4-tetrahydro)-quinolyl]-9-phenanthrenemethanol (**14**). Reduction of the carbonyl group of **13b** with $NaBH_4$ followed by hydrogenation yielded a decahydro compound **15**. Attempts to prepare the corresponding decahydro analog of the Br compound resulted in hydrogenolysis of the nuclear Br.

For a general correlation study of the side chain amino function and antimalarial study, the following 9-phenan-

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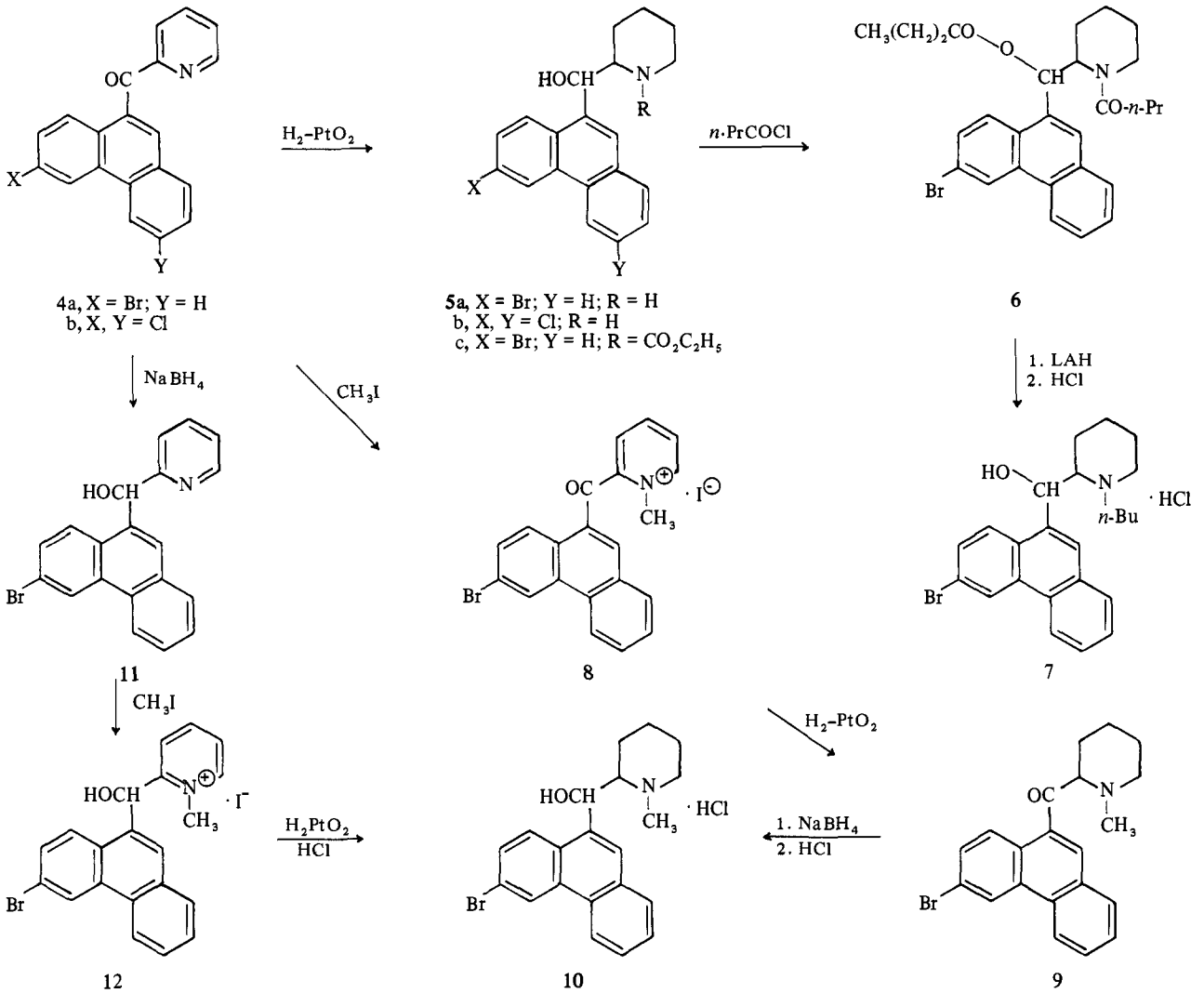
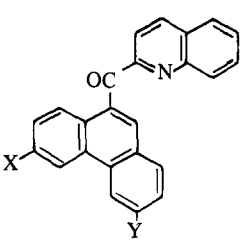
‡Prepared by Aerojet-General Corporation under contract and supplied by WRAIR.

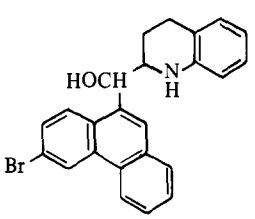
§E. A. Nodiff and M. P. Tyagi, Special Report to WRAIR, January 1970. Dr. Nodiff, private communication.



threnemethanols (**16a–r**) were prepared by the interaction of the appropriate phenanthreneoxirane with a substituted amine following the general procedure of Duncan, *et al.*[8]



13a, X = Br; Y = H
b, X, Y = CF_3



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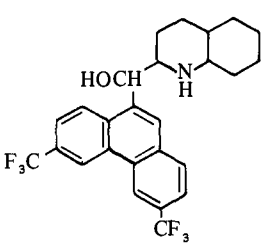

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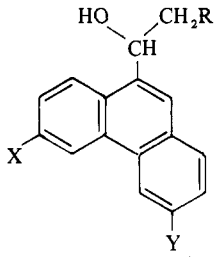
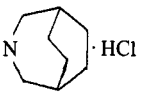
Biological Activity. Antimalarial results of the aforementioned compounds# are given in Table I. Among compounds studied, 3,6-bis(trifluoromethyl)-α-(1-propylbutylaminomethyl)-9-phenanthrenemethanol hydrochloride (**16n**) and 3,6-bis(trifluoromethyl)-α-(propylaminomethyl)-9-phenanthrenemethanol hydrochloride (**16o**) are highly active at 10 mg/kg and are curative at 20 mg/kg against *P. berghei.* Activity of 3,6-bis(trifluoromethyl)-α-(butylaminomethyl)-9-phenanthrenemethanol hydrochloride (**16p**) is comparable. No toxicity was observed with these compounds even at a dosage of 640 mg/kg.

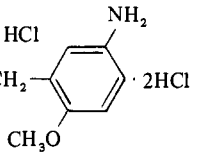
The following generalizations can be deduced as a result of our structure–activity study and comparison with other related compounds. (1) The order of activity of 3 substituted phenanthrene rings studied, with identical amino alcohol side chains, is 3,6-bis(trifluoromethyl)- > 3,6-dichloro- > 6-bromophenanthrene. (2) The activity of phenanthrene amino alcohols of type $ArCHOHCH_2NHR$ seems to be of a higher order than that of type $ArCHOHCH_2NR_2$ against *P. berghei* (compare **16p** *vs.* **16h**). (3) Alkyl substitution on the N atom in the α-piperidyl function of **5a** does not increase the original activity (compare **7**, **10a**, **10b** *vs.* **5a**). In some cases introduction of an alkyl group facilitates separa-

#Antimalarial tests were performed by Dr. Leo Rane and results were provided through the Walter Reed Army Institute of Research. For details of test procedure see T. S. Osdene, *et al.*[9]

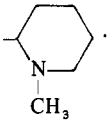


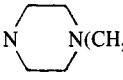
16a, X = Br; Y = H; R =  · HCl

b, X = Br; Y = H; R = $N(CH_2)_8$ · HCl

c, X = Br; Y = H; R = $N(C_2H_5)CH_2$  · 2HCl

d, X = Br; Y = H; R = 

e, X = Br; Y = H; R = $NHCH_2$  · 2HCl

f, X = Br; Y = H; R =  $N(CH_2)_3N(CH_3)_2$ · 3HCl

g, X = Br; Y = H; R = $N[(CH_2)_2N(C_2H_5)_2]_2$ · 3HCl
h, X, Y = Cl; R = $N[(CH_2)_3CH_3]_2$ · HCl
i, X, Y = Cl; R = $N[(CH_2)_4CH_3]_2$ · HCl
j, X, Y = Cl; R = $NHCH(CH_2)_5$ · HCl
k, X, Y = CF_3; R = $NHCH(CH_2)_5$ · HCl
l, X, Y = CF_3; R = $NHCH(CH_3)_2$ · HCl
m, X, Y = CF_3; R = $NHCH(C_2H_5)_2$ · HCl
n, X, Y = CF_3; R = $NHCH[(CH_2)_2CH_3]_2$ · HCl
o, X, Y = CF_3; R = $NH(CH_2)_2CH_3$ · HCl
p, X, Y = CF_3; R = $NH(CH_2)_3CH_3$ · HCl
q, X, Y = CF_3; R = $NH(CH_2)_3CH(OC_2H_5)_2$
ra, X, Y = CF_3; R = $NHC(CO_2CH_3)HCH(CH_3)_2$ · HCl (lower mp isomer)
rb, X, Y = CF_3; R = $NHC(CO_2CH_3)HCH(CH_3)_2$ · HCl (higher mp isomer)

tion of diastereomers. (4) Diastereomers possess different activity and toxicity (compare **10a** *vs.* **10b**). (5) The basicity of the N atom in the α-piperidyl function seems to play an important role with respect to antimalarial activity. Substitution on N with an ethoxycarbonyl (**5c**) or an alkyl carbonyl group (**6**, wherein the OH group is also substituted) abolishes the original activity (compare also **12** *vs.* **10**). (6) The importance of the basic center on the side chain can be further demonstrated by the fact that the activity of several 6-bromophenanthrene aminomethanols having bulky groups substituted at the N atom ("concealed" basic centers) on the side chain is reduced (compare **16a**, **16b**, **16c**, *vs.* **5a**). (7) On the other hand, the presence of more than one basic N on the side chain not only nullifies the antimalarial activity, but sometimes may also increase toxicity to the host (compare **16e**, **16f**, **16g** *vs.* **5a**).

Of the active phenanthrene amino alcohol antimalarials, the interatomic distance between the O and the N atom on the side chain and the distances between each hetero atom and the phenanthrene ring may be fixed and definite. It has been proposed that similar receptor sites may be involved among many amino alcohols of this type as well as quinine and related cinchona alkaloids.[10]

Experimental Section††

6-Bromo-9-phenanthrenemethanol (1b). To a suspension of 15 g (0.05 mole) of 1a in 150 ml of THF was added dropwise, with stirring, over 0.5 hr, 75 ml of 1.0 *M* borane in THF (Ventron). The suspended acid dissolved during the course of the addition. Upon its completion, the reaction mixt was stirred for an addl 3 hr at room temp. A mixt of 1 ml of concd HCl and 10 ml of H_2O was then added cautiously. The solvent was evapd *in vacuo* to 100 ml and an equal vol of EtOH was added. The mixt was chilled and filtered. There was obtd 12.8 g (88% yield) of 1b as off-white needles, mp 158–160°. An analytical sample was prepd by recrystn from EtOH, mp 160–161°. *Anal.* ($C_{15}H_{11}BrO$) C, H.

3,6-Dichloro-9-phenanthrenemethanol (2e), mp 174–175° (MeOH), and **3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (3b)**, mp 218–220° (Me_2CO–MeOH), were prepd by B_2H_6 reduction of 2d (in 94% yield) and **3a** (in nearly quant yield), respectively. *Anal.* ($C_{15}H_{10}Cl_2O$) C, H; ($C_{17}H_{10}F_6O$) C, H.

6-Bromo-9-phenanthrenecarboxaldehyde (1c). To a suspension of 8.6 g (0.03 mole) of 6-bromo-9-phenanthrenemethanol in 200 ml of boiling MeCN was added a soln of 33.0 g (0.06 mole) of ceric ammonium nitrate dissolved in a minimum amt of H_2O. Addl MeCN (approximately 30 ml) was added to bring all reactants into soln at the boiling point. The reaction mixt was placed on the steam bath and heated for 2 hr while solvent was allowed to escape. At the end of this period the vol of the reaction mixt had been reduced to 150 ml and the product had begun to cryst. The reaction mixt was then chilled and the product removed by filtration. There was obtd 7.2 g (81% yield) of 1c as buff needles, mp 138–140°. An analytical sample was obtd on crystn from EtOH, mp 140–141°. *Anal.* ($C_{15}H_9BrO$) C, H.

3,6-Dichloro-9-phenanthrenecarboxaldehyde (2f), mp 190–192° ($CHCl_3$), and **3,6-bis(trifluoromethyl)-9-phenanthrenecarboxaldehyde (3c)**, mp 170–172°, were prepd by $Ce(NH_4)_2(NO_3)_6$ oxidn of 2e (in 85% yield) and 3b (in 96% yield), respectively. *Anal.* ($C_{15}H_8Cl_2O$) C, H; ($C_{17}H_8F_6O$) C, H.

9-Bromo-3,6-dichlorophenanthrene (2b). Purified 3,6-dichlorophenanthrene,‡ 9.88 g (0.04 mole), was dissolved with heating in 400 ml of AcOH. To this soln was added, in 1 portion, 5 ml of Br_2. After the reaction mixt had been refluxed for 4 hr, another portion of 5 ml of Br_2 was introduced, and heating was contd for 10 hr. This process was repeated once more. The mixt was dild with 500 ml of H_2O, and the solid product pptd was collected by filtration. There was thus obtd 12.1 g (93% yield) of the desired product as white needles, mp 161–163°. It was recrystd from $CHCl_3$ to give analytically pure 2b, mp 164–165°. *Anal.* ($C_{14}H_7BrCl_2$) C, H.

3,6-Dichloro-9-phenanthrenecarboxylic Acid (2d). A mixt of 3.26 g (0.01 mole) of 2b and 1.0 g (0.0055 mole) of $Cu_2(CN)_2$ was heated in 80 ml of DMF under reflux for 6 hr. The reaction mixt was poured into a soln of 4 g of $FeCl_3$ in 20 ml of H_2O and 5 ml of HCl *in a hood*. After 30 min, 400 ml of H_2O was added and the ppt was collected by filtration. The dried intermediate, 9-cyano-3,6-dichlorophenanthrene (2c), melted at 195–198°. It was hydrolyzed, without further purification, by heating in a mixt of 250 ml of AcOH, 25 ml of H_2SO_4, and 25 ml of H_2O under reflux for 3 days. The acid soln was dild with 400 ml of H_2O, and the solid product was collected by filtration. It was recrystd once from Me_2CO to give 1.60 g of 2d as white crystals, mp 279–282° (overall yield 55%). Addl 0.2 g of less pure material was recovered when the mother liquor was concd, mp 275–280°. The pure acid was obtd by further recrystn from Me_2CO, mp 284–285°. *Anal.* ($C_{15}H_8Cl_2O_2$) C, H.

In a parallel experiment, the intermediate, 9-cyano-3,6-dichlorophenanthrene (2c) was isolated, purified, and identified: white needles (from Me_2CO); mp 215–216°. *Anal.* ($C_{15}H_7Cl_2N$) C, H, N.

9-(6-Bromophenanthryl) 2-Pyridyl Ketone (4a). To a soln of 30 ml of BuLi (1.6 *M* in hexane) in 10 ml of dry THF was added, at −40°, under N_2, with stirring, a soln of 7.6 g (0.048 mole) of freshly distd 2-bromopyridine in 15 ml of dry THF in 10 min. The dark soln was stirred at −40° for 30 min. It was then cooled to −60° and a soln of 4.9 g (0.016 mole) of 1a in 120 ml of dry THF was added in 30 min. After 3 hr, the mixt was allowed to warm to 0° and 30 ml of H_2O-satd Et_2O and 30 ml of H_2O were slowly added in

††All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. The uv absorption spectra were determined with a Beckman DK-2 spectrophotometer. Absorption bands of ir spectra have been taken and were as expected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

Table I. Phenanthrene Amino Alcohols

Compd	Mp, °C	Yield, %	Formula[a]	Antimalarial activity[b] Dosage, mg/kg 10	20	40	80	160	320	640
5b	320-322 dec	22	$C_{20}H_{19}Cl_2NO \cdot HCl$	0.5	1.1	15.1	3C	5C	5C	
				(0.0	0.0	0.0	3.8	8.4	9.6)[c]	
5c	209-211	36	$C_{23}H_{24}BrNO_3$		0.1	0.1	0.1	0.1	0.1	
				(0.0	0.0	0.0	0.0	0.0)[c]		
6	153-155	57	$C_{28}H_{32}BrNO_3$		0.3	0.3	0.5	0.7	0.7	0.9
7	252-253 dec	61	$C_{24}H_{28}BrNO \cdot HCl$		0.3	0.3	7.0	14.2	3C	5C
10a	272-274 dec	25	$C_{21}H_{22}BrNO \cdot HCl$[d]	0.3	0.3	0.4	7.3	3C	4C	5C[e]
								(4.2)[c]		
10b	191-193 dec	40	$C_{21}H_{22}BrNO \cdot HCl$[f]	0.7	0.7	0.9	5.9	14.4	5T	
				(0.0	0.0	0.0	5T	5T	5T)[c]	
12	218-220 dec	75	$C_{21}H_{17}BrINO$		0.1	0.1	0.1	0.1	0.1	0.1
14	163-164	24	$C_{24}H_{20}BrNO$		0.3	0.3	0.5	0.7	3.3	8.0
15	218-220	79	$C_{26}H_{25}F_6NO$	0.8	10.4	3C	5C	5C	5C	5C
16a	207-209	70	$C_{24}H_{26}BrNO \cdot HCl$		0.1	0.1	0.3	0.3	0.3	1.3
				(0.0	0.0	0.0	0.0	0.0	0.0)[c]	
16b	256-258	39	$C_{24}H_{28}BrNO \cdot HCl$		0.3	0.3	0.3	0.5	1.9	4.9
				(0.0	0.0	0.0	0.0	0.0	2T)[c]	
16c	250-252	69	$C_{26}H_{27}BrN_2O_2 \cdot 2HCl$		0.3	0.3	0.5	3.7	5.1	3C
				(0.0	0.0	0.0	0.0	0.0	1.2)[c]	
16d	277-278	67	$C_{23}H_{24}BrNO \cdot HCl$		0.4	0.4	0.6	3.9	6.8	11.9
16e	159-161	61	$C_{23}H_{27}BrN_2O \cdot 2HCl$		0.1	0.3	0.3	0.3	0.7	0.7
								(0.0/120)[c]		
16f	248-250	55	$C_{25}H_{32}BrN_3O \cdot 3HCl$		0.1	0.1	0.1	0.3	0.3	5T
								(0.0/120)[c]		
16g	214-215	72	$C_{28}H_{40}BrN_3O \cdot 3HCl$		0.3	0.3	0.3	0.9	5T	5T
								(0.9)[c]		
16h	221-223	36	$C_{24}H_{29}Cl_2NO \cdot HCl$	3.3	8.6	13.9	3C	5C	5C	5C
				(0.0	0.0	0.0	5.4	8.5	13.0)[c]	
16i	187-189	29	$C_{30}H_{41}Cl_2NO \cdot HCl$		0.3	2.5	3.1	9.5	16.1	5C
16j	266-268	41	$C_{22}H_{23}Cl_2NO \cdot HCl$	0.3	0.4	6.5	13.0	2C	5C	5C
16k	285-287 dec	14	$C_{24}H_{23}F_6NO \cdot HCl$	3.1	10.1	1C	2C	5C	5C	5C
				(0.0	5.8	7.0	9.4	10.0	10.4)[c]	
16l	265-267 dec	16	$C_{21}H_{19}F_6NO \cdot HCl$	10.5	12.9	15.9	3C	5C	5C	5C
				(2.2	4.6	7.0	8.4	9.6	12.6)[c]	
16m	233-234 dec	15	$C_{23}H_{23}F_6NO \cdot HCl$	13.7	16.2	5C	5C	5C	5C	5C
16n	243-245 dec	14	$C_{25}H_{27}F_6NO \cdot HCl$	17.7	2C	5C	5C	5C	5C	5C
				(0.0	0.0	5.6	5.6	6.0	6.6)[c]	
16o	254-256	44	$C_{21}H_{19}F_6NO \cdot HCl$	15.0	5C	5C	5C	5C	5C	5C
				(3.2	6.0	8.2	11.0	12.0	12.0)[c]	
16p	248-250 dec	12	$C_{22}H_{21}F_6NO \cdot HCl$	8.1	1C	3C	5C	5C	5C	5C
				(4.0/30, 5T/60, 5T/120)[c]						
16q	130-132	43	$C_{26}H_{29}F_6NO_3$	0.5	0.9	5.4	10.4	3C	4C	5C
16ra	220-222	12	$C_{24}H_{23}F_6NO_3 \cdot HCl$		0.1	0.1	0.1	0.1	0.1	0.1
16rb	243-245	10	$C_{24}H_{23}F_6NO_3 \cdot HCl$		0.3	0.3	0.5	0.5	0.9	3.1

[a] Correct analyses for C, H, and N were obtained for all compounds. [b] Test data supplied by Walter Reed Army Institute of Research, Increase in mst (mean survival time) of the controlled group is reported, mst for controlled mice infected with *P. berghei*, 6.5 ± 0.5 days; C (curative): the no. of mice surviving at 60 days past infection; T (toxic): the no. of deaths occurring on days 2-5 after infection. Five mice were used per test run. See also ref 9. [c] Test data (increase in mst) of chicks infected with *P. gallinaceum* are listed in parentheses, mst for controlled chicks infected with *P. gallinaceum*, 4 days. T (toxic): the no. of deaths occurring within 2 days after injection. [d] Hydrate. [e] For comparison, activity of **5a** between 20-640 mg/kg is 0.6, 1.8, 9.6, 2C, 3C, and 5C. [f] Hemihydrate.

succession. After 30 min of stirring, the upper phase was sepd and concd under reduced pressure to a vol of about 30 ml. The ppt was collected by filtration, washed with Et_2O, and dried to give 4.5 g (75% yield) of the desired product, mp 182-184°. A sample for analysis was recrystd from EtOH-THF (1:1): mp 183-185°; ν_{max} 6.1 (C=O), 6.35, 6.4 μ; $\lambda_{max}^{pH\,1}$ 255 (ε 63,300), 356 mμ (5200). *Anal.* ($C_{20}H_{12}BrNO$) C, H, N.

3,6-Dichloro-α-(2-piperidyl)-9-phenanthrenemethanol Hydrochloride (5b). In 500 ml of boiling EtOH was dissolved 2.6 g of 3,6-dichloro-9-phenanthryl 2-pyridyl ketone§ (4b). The soln was treated with charcoal and filtered. The filtrate was then mixed with 4 ml of concd HCl and hydrogenated at room temp in the presence of 0.1 g of PtO_2 at 4.5 kg/cm² for 4 hr. The catalyst was removed and the filtrate was evapd to dryness. The residue was washed with cold MeOH and recrystd twice from MeOH to give 0.65 g (22% yield) of analytically pure **5b** as white needles: mp 320-322° dec (lit.§ mp 298-300°). Its ir spectrum was nearly identical with that of the lower melting compd.§ *Anal.* ($C_{20}H_{19}Cl_2NO \cdot HCl$) C, H, N.

6-Bromo-α-[2-(1-ethoxycarbonylpiperidyl)]-9-phenanthrenemethanol (5c). To a suspension of 7.4 g (0.02 mole) of 6-bromo-α-(piperidyl)-9-phenanthrenemethanol (**5a**) in 75 ml of pyridine was added dropwise 2.2 g (0.02 mole) of ethyl chloroformate. The solid gradually dissolved as the reaction mixt became warm. After the addn, the reaction mixt was allowed to stand for 3 hr at room temp, during which time a solid slowly pptd. It was collected by filtration (3 g) and was found to be the HCl salt of 6-bromo-α-(2-piperidyl)-9-phenanthrenemethanol. The filtrate was poured into 250 ml of H_2O and after 1 hr the resulting ppt was collected by filtration. The solid was recrystd from 2-methoxyethanol to give 3.2 g (36% yield) of **5c** as buff needles, mp 207-209°. An analytical sample was prepd by another recrystn from the same solvent: mp 209-211°; ir, 2.9 (OH) and 6.05 μ (C=O). *Anal.* ($C_{23}H_{24}BrNO_3$) C, H, N.

The use of a large vol of Et_3N as an acid scavenger in the preceding reaction in order to improve the yield of **5c** was attempted. 6-Bromo-α-(2-piperidyl)-9-phenanthrenemethanol hydrochloride was again isolated but the yield of **5c** was essentially the same.

6-Bromo-α-[2-(1-butyrylpiperidyl)]-9-phenanthrenemethanol Butyrate (6). To a stirred slurry of 7.4 g (0.02 mole) of 6-bromo-α-(2-piperidyl)-9-phenanthrenemethanol (**5a**) in 210 ml of dry pyridine was added 7.5 g of PrCOCl. The clear yellow soln was stirred for 48 hr and a small amt of insol solid was removed by filtration. The filtrate was evapd under reduced pressure to a semisolid. It was stirred with 200 ml of H_2O and extd with three 50-ml

portions of $CHCl_3$. The exts were washed with two 50-ml portions of 3 *N* HCl and 50 ml of H_2O, dried, and evapd to a syrup, which crystd on standing. The solid was recrystd from EtOH to give 5.8 g (57% yield) of product, mp 153–155°. *Anal.* ($C_{28}H_{32}BrNO_3$) C, H, N.

6-Bromo-α-[2-(1-butylpiperidyl)]-9-phenanthrenemethanol Hydrochloride (7). Compd **6** (7.7 g, 0.015 mole) was reduced with 3 g (0.075 mole) of LAH in the following manner. The butyrate was placed in a thimble in a Soxhlet extractor and the hydride was suspended in 1 l. of anhyd Et_2O in the distn flask. The butyrate was extd continuously, under N_2, for 24 hr. To avoid "hot spots" and overheating the solid in the flask, the Et_2O mixt was stirred magnetically throughout the operation. The resulting mixt was cooled and excess hydride was hydrolyzed by slow addn of 3 ml of H_2O, 3 ml of 20% NaOH, and then 9 ml of H_2O. The hydrolyzed mixt was stirred for 1 hr, and the salts were removed by filtration. The filtrate was then reduced to *ca.* 150 ml, cooled in ice-bath, and treated by dropwise addn of ethanolic HCl until the pptn of the HCl salt was complete. The mixt was stirred for 1 hr and the crude solid (5 g, mp 251–252° dec) was sepd and recrystd from *i*-PrOH–EtOH (20:80) to give 4.2 g (61% yield) of the desired product: mp 252–253° dec; $\lambda_{max}^{pH\ 1}$ 229 (ε 31,000), 265 (61,500), 290 (11,600), 302 mμ (ε 13,200); $\lambda_{max}^{pH\ 11}$ 231 (ε 25,500), 257 (37,500), 308 mμ (13,200). *Anal.* ($C_{24}H_{28}BrNO \cdot HCl$) C, H, N.

9-(6-Bromophenanthryl) 2-Pyridyl Ketone Methiodide (8). A soln of 1.5 g (0.004 mole) of **4a** and 25 ml of MeI in 40 ml of THF was heated in a stainless steel pressure vessel at 110° for 16 hr. Filtration of the cooled contents gave 1.6 g (80% yield) of the yellow methiodide: mp 211–212°; λ_{max}^{EtOH} 256 mμ (ε 53,700). *Anal.* ($C_{21}H_{15}BrINO$) C, H, N.

6-Bromo-α-(2-pyridyl)-9-phenanthrenemethanol (11). To a stirred mixt of 3.0 g (0.008 mole) of 9-(6-bromophenanthryl) 2-pyridyl ketone in 50 ml of THF and 100 ml of EtOH was added, in 5 min, a soln of 0.5 g of $NaBH_4$ in 25 ml of EtOH. The mixt was heated under reflux with stirring for 3 hr, cooled, and poured into 400 ml of H_2O. After 30 min the solid product was removed by filtration, washed with H_2O, and dried. There was obtd 2.8 g (93% yield) of **11**, mp 235–236°. A small sample was recrystd from THF: mp 236–237°; $\lambda_{max}^{pH\ 1}$ 255 mμ (ε 36,000); $\lambda_{max}^{pH\ 11}$ 255 mμ (ε 21,100); $\lambda_{max}^{pH\ 1,11}$ 300 mμ (ε 15,600). *Anal.* ($C_{20}H_{14}BrNO$) C, H, N.

6-Bromo-α-(2-pyridyl)-9-phenanthrenemethanol Methiodide (12). A soln of 1.5 g (0.004 mole) of **11** and 25 ml of MeI in 50 ml of THF was heated in a stainless steel pressure vessel at 110° for 16 hr. Filtration of the cooled contents gave 1.5 g (75% yield) of the tan-colored methiodide **12**: mp 218–220° dec; $\lambda_{max}^{pH\ 1,11}$ 225 mμ (ε 66,000), 290 (sh) (12,100), 301 mμ (11,600). *Anal.* ($C_{21}H_{17}BrINO$) C, H, N.

6-Bromo-α-[2-(1-methylpiperidyl)]-9-phenanthrenemethanol Hydrochloride (10). Method 1. A suspension of 6 g (0.012 mole) of **12** in 250 ml of abs EtOH was hydrogenated in the presence of 0.4 g of PtO_2 at 4.2 kg/cm² for 3 hr. The theoretical amt of H_2 was absorbed at the end of this period. The mixt was filtered to remove the catalyst and the filtrate was concd to 50 ml. It was made basic (pH 9) with 10% ethanolic KOH and dild with 50 ml of H_2O. The free base was extd with three 50-ml portions of $CHCl_3$ and the combined exts were dried and evapd to a syrup. The residue was dissolved in 50 ml of EtOH and treated with ethanolic HCl. After being allowed to stand overnight, the solid was filtered to give 1.5 g of crude product, mp 252–254° dec. Recrystn of the solid from 25 ml of abs EtOH gave 1.3 g (25% yield) of **10a** · HCl · H_2O: mp 272–274° dec; $\lambda_{max}^{pH\ 1}$ 230 (ε 32,800), 255 (63,500), 290 (12,300), 301 mμ (14,000); $\lambda_{max}^{pH\ 11}$ 230 (26,000), 255 (43,900), 301 mμ (12,700). *Anal.* ($C_{21}H_{22}BrNO \cdot HCl \cdot H_2O$) C, H, N.

The mother liquor was evapd to dryness to leave a pale yellow solid residue. Recrystn of the solid from anhyd EtOH and then from BuOH gave 40% yield of a white solid **10b**: mp 191–193° dec. Its ir and uv are identical with those of the higher melting substance mentioned above. *Anal.* ($C_{21}H_{22}BrNO \cdot HCl \cdot 0.5H_2O$) C, H, N.

An attempt to hydrogenate the pyridylmethanol **12** in the presence of MeI to the desired compd was not successful.

Method 2. A mixt of 4.0 g (0.008 mole) of **8**, 0.2 g of PtO_2, and 250 ml of EtOH was shaken under H_2 at 4.2 kg/cm² for 20 hr. The catalyst was removed by filtration and the filtrate evapd to dryness. Ir spectrum of the yellow solid residue showed residual C=O absorption at 6.0 μ. The solid product **9** was dissolved in 100 ml of EtOH and a soln of 1.5 g of $NaBH_4$ in 75 ml of EtOH was added in 5 min. The mixt was stirred under reflux for 2 hr and allowed to cool overnight. It was poured into 500 ml of H_2O, stirred for 30 min, and filtered. The solid product was recrystd from EtOH to afford the free base of **10**: mp 130–132°; ν_{max} 3.4 μ (OH); $\lambda_{max}^{pH\ 1}$ 230 (ε 32,600), 255 (61,500), 290 (11,100), 302 mμ (13,200); $\lambda_{max}^{pH\ 11}$ 230 (ε 24,600), 255 (40,000), 300 mμ (sh) (15,300). The nmr spectrum is consistent with the structure. *Anal.* ($C_{21}H_{22}BrNO$) C, H, N.

The free base thus obtd was dissolved in 50 ml of warm EtOH, filtered, and treated with ethanolic HCl. After being allowed to stand for 3 hr, the solid was filtered to give 1.6 g (50% yield) of crude HCl salt: mp 161–163° dec. Recrystn from EtOH gave 1.2 g of **10a** · HCl: mp 272–274° dec. The ir and uv are identical with those of the compd prepared in method 1.

9-(6-Bromophenanthryl) 2-Quinolyl Ketone (13a). To a soln of 50 ml of BuLi (1.6 *M* in hexane) in 30 ml of anhyd Et_2O was added, at −40° to −50° under N_2, a soln of 14.7 g (0.072 mole) of 2-bromoquinoline in 50 ml of anhyd Et_2O. The mixt was stirred at −40° for 30 min and cooled to −60°, and a soln of 7.3 g (0.024 mole) of **1a** in 150 ml of THF was added at this temp over 40 min. The reaction mixt was kept at −60° for 2 hr, and then allowed to warm to room temp. About 5 ml of H_2O was added and the mixt was allowed to stand overnight. The solid was collected by filtration, the filtrate was evapd *in vacuo* to 0.5 of its original vol, and the solid was again collected by filtration. The filtrate was extd with H_2O and the org layer was discarded. The combined solid product was washed with warm H_2O, the washings were combined with the aforementioned aq ext, and the aq soln was acidified with HCl. The resulting solid was collected by filtration and dried to give 3.2 g of unreacted **1a**, identified by its ir spectrum. The recovery was 45%.

The combined solid product was recrystd twice from THF–EtOH and once from C_6H_6 to give 3.7 g of pale yellow solid, mp 238–240°. All mother liquors were combined from which an addl 1.9 g of purified yellow solid, mp 235–238°, was recovered. These solid products were combined and recrystd from C_6H_6 to afford 4.6 g (47% yield) of **13a** as light yellow needles: mp 238–240°. Another recrystn from C_6H_6 gave an analytical sample: mp 239–241°. *Anal.* ($C_{24}H_{14}BrNO$) C, H, N.

9-[3,6-Bis(trifluoromethyl)phenanthryl] 2-Quinolyl Ketone (13b) was prepd from **3a** and 2-lithioquinoline in a similar fashion as for the prepn of **13a** in 73% yield: mp 227–228° (C_6H_6–hexane). *Anal.* ($C_{26}H_{13}F_6NO$) C, H, N.

6-Bromo-α-[2-(1,2,3,4-tetrahydroquinolyl)]-9-phenanthrenemethanol (14). To a soln of 2.0 g (0.005 mole) of **13a** in 200 ml of EtOH and 15 ml of concd HCl was added 200 mg of PtO_2 and 2 g of charcoal. The mixt was hydrogenated (3.5 kg/cm²) for 15 hr. Catalyst and charcoal were removed by filtration and the filtrate was evapd to dryness *in vacuo*. The residue was triturated with cold EtOH and filtered. The filtrate was reduced to 0.5 of its original vol and kept overnight at room temp. On filtration there was obtd 1.1 g of buff crystals: mp 255–261°. These were recrystd from EtOH contg concd HCl to give 0.9 g of solid, mp 263–265°, which was identified as **14** · HCl. Since purification of the salt presented some difficulty, the solid was dissolved in EtOH and added to 100 ml of 10% aq NaOH. The pptd free base was removed by filtration, washed, dried, and recrystd twice from EtOH to give 0.5 g (24% yield) of **14** as buff needles: mp 160–162°. An analytical sample was obtd on recrystn from MeOH: mp 163–164°. *Anal.* ($C_{24}H_{20}BrNO$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(2-decahydroquinolyl)-9-phenanthrenemethanol (15). A soln of 7 g (0.015 mole) of **13b** in 150 ml of hot THF was treated with a soln of 1.1 g (0.03 mole) of $NaBH_4$ in 50 ml of EtOH. After standing at room temp for 30 min, the reaction mixt was boiled on a steam bath for 30 min while solvent was permitted to escape. At the end of this time the vol of the reaction mixt had been reduced to *ca.* 75 ml. To this was added 250 ml of EtOH, and the mixt was chilled in an ice bath. The resulting white needles were collected by filtration, washed with H_2O and EtOH, and dried to give 6.2 g (89% yield) of the intermediate 3,6-bis(trifluoromethyl)-α-(2-quinolyl)-9-phenanthrenemethanol: mp 215–218°. This material was used in the next step without further purification.

To a soln of 1 g (0.002 mole) of the aforementioned phenanthrenemethanol in 300 ml of EtOH contg 15 ml of concd HCl was added 1 g of charcoal and 100 mg of PtO_2. The mixt was hydrogenated at 3.5 kg/cm² for 4 hr. Suspended solids were then collected by filtration and extd three times with 50-ml portions of boiling EtOH. The combined filtrate and exts were evapd *in vacuo* to dryness. The residue was redissolved in 100 ml of hot EtOH. To the soln was added 100 ml of 10% aq Na_2CO_3. After standing overnight, the pptd free base was collected by filtration, washed with H_2O, and dried. On recrystn from C_6H_6 there was obtd 0.8 g (79% yield) of **15** as white needles, mp 218–220°. *Anal.* ($C_{26}H_{25}F_6NO$) C, H, N.

6-Bromo-α-[3-(3-azabicyclo[3.2.2]nonyl)]-9-phenanthrenemethanol Hydrochloride (16a). NaH dispersion in oil (50%) (2.0 g,

0.04 mole) was washed with hexane 3 times by decantation. DMSO (25 ml) was added and the suspension was heated at 70° for 2 hr under N_2 until H_2 evoln ceased. To the clear soln thus obtd was added 25 ml of THF and the mixt was cooled in ice. A soln of 8.6 g (0.04 mole) of trimethylsulfonium iodide in 40 ml of DMSO was added. The reaction mixt was then treated with a soln of 2.85 g (0.01 mole) of 1c in 25 ml of THF and stirred for 1 hr at room temp under N_2. H_2O (150 ml) was added and the reaction mixt extd with Et_2O. The Et_2O ext was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residual 6-bromo-9-phenanthryloxirane was heated with 3.8 g (0.03 mole) of 3-azabicyclo[3.2.2]nonane at 100° until the reactants began to melt. The temp of the reaction mixt was then raised to 150° and heating was contd for 4 hr under N_2. The amine which tended to sublime onto the cooler portions of the reaction flask was dislodged from time to time with a spatula and returned to the reaction mixt. Toward the end of this period the excess amine was permitted to escape while the reaction mixt was heated under reduced pressure (H_2O aspirator). The residue was dissolved in EtOH and treated with ethanolic HCl. On removal of solvent *in vacuo* and recrystn from EtOH of the remaining solid there was obtd 3.2 g (70% yield) of **16a** as white plates: mp 207–209°. An analytical sample was prepd by an addl recrystn from EtOH: mp 207–209°. *Anal.* ($C_{24}H_{26}BrNO \cdot HCl$) C, H, N.

6-Bromo-α-(*N*,*N*-octamethyleneaminomethyl)-9-phenanthrenemethanol Hydrochloride (16b). A mixt of 3 g (0.01 mole) of the aforementioned 6-bromo-9-phenanthryloxirane and 3.8 g (0.03 mole) of octamethyleneimine was heated at 150° under N_2 for 4 hr. Excess amine was then removed and the residue was dissolved in EtOH and treated with ethanolic HCl. Solvent was removed *in vacuo* and the residue redissolved in warm EtOH. Et_2O was added to induce crystn. The mixt was cooled and filtered. The crude solid product was recrystd from EtOH to give 1.8 g (39% yield) of **16b** as white plates: mp 255–257°. An analytical sample was prepd by recrystn from EtOH, mp 256–258°. *Anal.* ($C_{24}H_{28}BrNO \cdot HCl$) C, H, N.

α-[*N*-(5-Amino-2-methoxybenzyl)-*N*-ethyl]aminomethyl-6-bromo-9-phenanthrenemethanol Dihydrochloride (16c). *N*-α-Ethyl α,3-diamino-6-methoxytoluene dihydrochloride was converted to the free base by treating its aq soln with 10% aq NaOH. The free amine was isolated *via* Et_2O extn, and evapn of the solvent. The product thus obtd was used without further purification.

To 3.0 g (0.01 mole) of 6-bromo-9-phenanthryloxirane was added 5.4 g (0.03 mole) of the aforementioned base. The mixt was heated at 150° under N_2 for 4 hr. Excess amine was removed by heating *in vacuo* and the resulting residual gum was triturated with MeOH. The solid product thus obtd (as the free base) was collected by filtration and then added to boiling EtOH. To the boiling mixt was slowly added concd HCl until soln was attained. The solvents were then removed *in vacuo* and the solid residue recrystd from EtOH contg a small amt of concd HCl to afford 3.8 g of analytically pure **16c** as tan crystals, mp 250–252°. *Anal.* ($C_{26}H_{27}BrN_2O_2 \cdot 2HCl$) C, H, N.

6-Bromo-α-(*endo*-2-norbornylamino)-9-phenanthrenemethanol hydrochloride (16d) was prepd in a similar manner from 6-bromo-9-phenanthryloxirane and *endo*-2-aminonorbornane as white needles: mp 277–278° (EtOH). *Anal.* ($C_{23}H_{24}BrNO \cdot HCl$) C, H, N.

The following compds were prepd from the appropriate phenanthryloxirane and amine by procedures similar to those described.

α-[(1-Methyl-2-piperidinylmethyl)aminomethyl]-6-bromo-9-phenanthrenemethanol dihydrochloride (16e) was obtained as tan crystals: mp 159–161° (*i*-PrOH). *Anal.* ($C_{23}H_{27}BrN_2O$) C, H, N.

α-[4-(Dimethylaminopropyl)piperazinylmethyl]-6-bromo-9-phenanthrenemethanol trihydrochloride (16f) was obtained as buff crystals: mp 248–250° (EtOH). *Anal.* ($C_{25}H_{32}BrN_3O \cdot 3HCl$) C, H, N.

α-{*N*,*N*-Bis[2-(diethylamino)ethyl]aminomethyl}-6-bromo-9-phenanthrenemethanol trihydrochloride (16g) was obtained as white crystals: mp 214–215° (BuOH). *Anal.* ($C_{28}H_{40}BrN_3O \cdot 3HCl$) C, H, N.

3,6-Dichloro-α-(dibutylaminomethyl)-9-phenanthrenemethanol hydrochloride (16h) was obtained as white needles: mp 221–223° (MeOH–Me_2CO). *Anal.* ($C_{24}H_{29}Cl_2NO \cdot HCl$) C, H, N.

3,6-Dichloro-α-(diheptylaminomethyl)-9-phenanthrenemethanol hydrochloride (16i) was obtained as white crystals: mp 187–189° (Me_2CO) (lit.[§] mp 187–188.5°).

3,6-Dichloro-α-(cyclohexylaminomethyl)-9-phenanthrenemethanol hydrochloride (16j) was obtained as white plates: mp 266–268° (MeOH). *Anal.* ($C_{22}H_{23}Cl_2NO \cdot HCl$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(cyclohexylaminomethyl)-9-phenanthrenemethanol hydrochloride (16k) was obtained as white plates: mp 285–287° dec (MeOH). *Anal.* ($C_{24}H_{23}F_6NO \cdot HCl$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(isopropylaminomethyl)-9-phenanthrenemethanol hydrochloride (16l) was obtained as white needles: mp 265–267° (EtOH–HCl). *Anal.* ($C_{21}H_{19}F_6NO \cdot HCl$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(1-ethylpropylaminomethyl)-9-phenanthrenemethanol hydrochloride (16m) was obtained as white needles: mp 233–234° dec (Me_2CO). *Anal.* ($C_{23}H_{23}F_6NO \cdot HCl$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(1-propylbutylaminomethyl)-9-phenanthrenemethanol hydrochloride (16n) was obtained as white needles: mp 243–245° dec (Me_2CO). *Anal.* ($C_{25}H_{27}F_6NO \cdot HCl$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(propylaminomethyl)-9-phenanthrenemethanol hydrochloride (16o) was prepd by a similar method except that the reactants were heated in an autoclave at 140° for 15 hr: white crystals; mp 254–256° (MeOH–Me_2CO). *Anal.* ($C_{21}H_{19}F_6NO \cdot HCl$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(butylaminomethyl)-9-phenanthrenemethanol hydrochloride (16p) was obtained as a white solid: mp 248–250° dec (MeOH–Me_2CO). *Anal.* ($C_{22}H_{21}F_6NO \cdot HCl$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(4-diethoxybutylaminomethyl)-9-phenanthrenemethanol (16q) was obtained as white crystals: mp 130–132° (MeOH). *Anal.* ($C_{26}H_{29}F_6NO_3$) C, H, N.

3,6-Bis(trifluoromethyl)-α-(DL-1-carbomethoxy-2-methylpropylaminomethyl)-9-phenanthrenemethanol hydrochloride (16ra) was obtained as white crystals: mp 220–222° (MeOH). *Anal.* ($C_{24}H_{23}F_6NO_3 \cdot HCl$) C, H, N. **16rb** was obtained as white crystals: mp 243–245° (MeOH). *Anal.* ($C_{24}H_{23}F_6NO_3 \cdot HCl$) C, H, N.

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