Antimalarial Phenanthrene Amino Alcohols. 1. Fluorine-Containing 3- and 6-Substituted 9-Phenanthrenemethanols[1]

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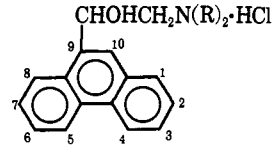
A number of the title compounds are quite effective against *Plasmodium berghei* in mice. The most active members of this group are disubstituted and bear CF_3 groups or a combination of CF_3 and halogen at positions 3 and 6. Many of these compds are curative at 40 mg/kg and some at 20 mg/kg. None of the 9-phenanthrenemethanols caused photosensitization in the test animals.

The appearance of drug-resistant *falciparum* malaria has stimulated the search for new antimalarials. In their monograph Coatney, *et al.*,[2] discussed the efficacy of many simple 9-phenanthrenemethanols against *Plasmodium gallinaceum* in chicks. The most active com-



pounds in this group were those which contained Cl or Br atom in positions 3 or 6 and in which R was an unbranched alkyl 4–7 C long. The best of these, 6-bromo-α-(di-*n*-heptylaminomethyl)-9-phenanthrenemethanol·HCl,[3] was used as our standard for comparison.

The value of substituting F or F-containing groups for halogen or H in prototype medicinals has been demonstrated repeatedly in the past two decades.[4] In a logical extension of this work we have prepared a series of 9-phenanthrenemethanols with F or F-containing groups at positions 3 and/or 6. A number of these compds are considerably more effective than the standard.

Biological Data. Table X includes comparison data (Rane mouse screen[5]) for the standard and our F-containing analogs. The most active members of this group are disubstituted and bear CF_3 groups or a combination of CF_3 and halogen at positions 3 and 6. Most of these compds are curative at 40 mg/kg and a number are curative at 20 mg/kg.

Among the monosubstituted compds only the 6-CF_3 derivative (IXd) is significantly more potent than the standard. None of the phenanthrenemethanols caused photosensitization[6] in the test animals. The intermediates listed in Tables I to VII and in Table VIII were all inactive.

Chemistry.—The antimalarials in Table X were prepd by standard sequences. Thus, the Perkin reaction between the appropriate phenylacetic acids and benzaldehydes in the presence of Et_3N (method A)[7-9] or K_2CO_3 (method B)[8] provided the nitrocinnamic acids (I). Reduction to the corresponding amino acids (II) was effected with ammoniacal $FeSO_4$ (method A)[8,9] or $FeSO_4$ and NaOH (method B). In the latter method the Na salt was often isolated rather than the free acid. This expedient permitted simpler work-up and in the case of the 2′-amino derivatives minimized concomitant lactam (IIA) formation. Pschorr cyclization[8,9] of the amino acids or amino acid salts gave the phenanthroic acids (III). Sequential conversion of these acids to the acid chlorides (IV), the diazomethyl ketones (not isolated), and the bromomethyl ketones (V) was routine.[3] Reaction of the ketones with alkaline methanolic $NaBH_4$[10] and treatment of the resulting ethylene oxides (VI) with the appropriate dialkylamines produced the α-(di-*n*-alkylaminomethyl)-9-phenanthrenemethanols (VII) (method A).[11,12] In another approach to VII the bromomethyl ketones (V) were converted to the amino ketones (VA, not isolated) and reduced [$Al(O\text{-}i\text{-}Pr)_3$ (method B)[13] or $NaBH_4$ (method C)].[10] The α-(2-piperidyl)-9-phenanthrenemethanols (IX) were made from the acids (III) *via* the pyridyl ketones (VIII) by the Boykin procedure.[14,15]

Experimental Section[16]

4-Trifluoromethoxyphenylacetic Acid.—The reaction between 4-$F_3COC_6H_4COCl$ (from 25 g of commercial 4-$F_3COC_6H_4CO_2H$, 60

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(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract DADA 17-67-C-7067 and is Contribution No. 903 from the Army Research Program on Malaria.

(2) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, Washington, D. C., 1953.

(3) E. L. May and E. Mosettig, *J. Org. Chem.*, **11**, 627 (1946).

(4) The pharmacology of F-contg compds has been reviewed by F. Herr in "Aromatic Fluorine Compounds," A. Pavlath and A. Leffler, Ed., Reinhold, N.Y., 1962, p 682.

(5) Tests were carried out in five mice, infected with a lethal dose of *P. berghei*, by Dr. L. Rane and coworkers, Malaria Screening Laboratory, University of Miami, Miami, Florida. For details of test procedure, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). Test data were supplied by Drs. T. R. Sweeney and R. E. Strube of Walter Reed Army Institute of Research.

(6) Phototoxicity evaluation was carried out by Col. William E. Rothe, Division of Medicinal Chemistry, WRAIR, Walter Reed Army Medical Center, Washington, D. C. 20012. For details of the test procedure see W. E. Rothe and D. P. Jacobus, *J. Med. Chem.*, **11**, 366 (1968).

(7) M. Pailer, A. Schleppnik, and A. Meller, *Monatsh. Chem.*, **89**, 211 (1958).

(8) D. F. DeTar, *Org. React.*, **9**, 409 (1957).

(9) P. H. Leake, *Chem. Rev.*, **56**, 27 (1956).

(10) S. W. Chaikin and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 122 (1949).

(11) R. E. Lutz, *et al.*, *ibid.*, **68**, 1813 (1946).

(12) S. Winstein, T. L. Jacobs, R. B. Henderson, J. H. Robson, and B. F. Day, *J. Org. Chem.*, **11**, 157 (1946).

(13) E. L. May and E. Mosettig, *ibid.*, **11**, 1 (1946).

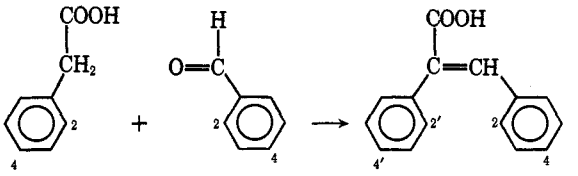
(14) R. M. Pinder and A. Burger, *J. Med. Chem.*, **11**, 267 (1968).

(15) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *ibid.*, **11**, 273 (1968).

(16) Melting points were determined with an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Microanalysis, Inc., Wilmington, Del. Where analyses are indicated only by symbols of the elements anal. results were within ±0.4% of the theor values.

TABLE I

NITRO α-PHENYLCINNAMIC ACIDS



No.	Phenylcinnamic acid	Phenylacetic acid	Benzaldehyde	Method	Temp, °C	Mp, °C (solvent)	Yield, %	Formula[a]
Ia	4-F, 2′-NO_2	2-NO_2[b]	4-F[c]	A	45	194–195 (HOAc)	77	$C_{15}H_{10}FNO_4$
Ib	2′-NO_2, 4-CF_3	2-NO_2[b]	4-CF_3[d]	A	20	177.5–178 (aq EtOH)	76	$C_{16}H_{10}F_3NO_4$
Ic	4′-F, 2-NO_2	4-F[c]	2-NO_2[b]	A	70	179.5–181 (EtOH)	82	$C_{15}H_{10}FNO_4$
Id	2-NO_2, 4′-CF_3[e]	4-CF_3[c]	2-NO_2[b]	A	85	155.5–158 (C_6H_6)	63	$C_{16}H_{10}F_3NO_4$[f]
Ie	2′-NO_2, 4′-CF_3[e]	2-NO_2, 4-CF_3[g]	Unsubst	B	20	176–179 (ligroin–C_6H_6)	58	$C_{14}H_{10}F_3NO_4$
If	2-NO_2, 4′-CF_3O	4-CF_3O[h]	2-NO_2[b]	B	45	141–142.5 (aq MeOH)	73	$C_{16}H_{10}F_3NO_5$[i]
Ig	4-Br, 2′-NO_2, 4′-CF_3	2-NO_2, 4-CF_3[g]	4-Br[b]	B	40[j]	185–186.5 (aq HOAc)	83[j]	$C_{16}H_9BrF_3NO_4$
Ih	4-Cl, 2′-NO_2, 4′-CF_3	2-NO_2, 4-CF_3[g]	4-Cl[b]	B	100	201–202 (aq EtOH)	69	$C_{16}H_9ClF_3NO_4$
Ii	4-I, 2′-NO_2, 4′-CF_3	2-NO_2, 4-CF_3[g]	4-I[k]	B	65	193–194 (ligroin–C_6H_6)	80	$C_{16}H_9F_3INO_4$
Ij	4′-Br, 2′-NO_2, 4-CF_3	4-Br, 2-NO_2[l]	4-CF_3[d]	B	100	194–195 (C_6H_6)	60	$C_{16}H_9BrF_3NO_4$[m]
Ik	4′-Cl, 2′-NO_2, 4-CF_3	4-Cl, 2-NO_2[n]	4-CF_3[d]	B	45[o]	203–205 (aq EtOH)	82[o]	$C_{16}H_9ClF_3NO_4$
Il	2′-NO_2, 4,4′-$(CF_3)_2$	2-NO_2, 4-CF_3[g]	4-CF_3[d]	B	100	176–178 (C_6H_6)	71	$C_{17}H_9F_6NO_4$

[a] All compds were analyzed for C, H, N. [b] Aldrich Chemical Co., Milwaukee, Wis. [c] Pierce Chemical Co., Rockford, Ill. [d] British Patent 870,541 (June 14, 1961). [e] Compounds Id and Ie are both intermediates in the prepn of IIId. Use of Ie instead of Id eliminates the need for expensive *p*-trifluoromethylphenylacetic acid. [f] C: calcd, 57.00; found, 57.54. [g] L. Simet, *J. Org. Chem.*, **28**, 3580 (1963). [h] Experimental. [i] N: calcd, 3.97; found, 3.35. [j] At 20, 50, and 80°, the yields were 58, 66, and 41%, resp. [k] Sapon Laboratories, Oceanside, N. Y. [l] From 2,5-dibromonitrobenzene (Aldrich) *via* adaptation of method of Simet (footnote *g*). [m] Used without anal. [n] From commercial 2,5-dichloronitrobenzene as in ref 1. [o] At 23 and 80° the yields were 65 and 55%, resp.

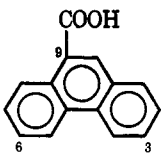
TABLE II

No.	Substituents	Mp, °C (solvent)	Method	Yield, %	Formula	Analyses
		A. AMINO α-PHENYLCINNAMIC ACIDS				
IIa	2′-NH_2, 4-F	*a*, *b* (EtOH)	A	69	$C_{15}H_{12}FNO_2$	C, H, N
IIb	2′-NH_2, 4-CF_3	*b* (EtOH)	A	72	$C_{16}H_{12}F_3NO_2$	C, H, N
IIc	2-NH_2, 4′-F	202.5–203.5 (EtOH)	A	87	$C_{15}H_{12}FNO_2$	C, H, N
IId	2-NH_2, 4′-CF_3	208–210 (C_6H_6)	A	67	$C_{16}H_{12}F_3NO_2$	C, H, N
IIe	2′-NH_2, 4′-CF_3	*b* (C_6H_6–ligroin)	A	67	$C_{16}H_{12}F_3NO_2$	C, H, N
IIf	2-NH_2, 4′-CF_3O		B	91	$C_{16}H_{12}F_3NO_3$	*c*
IIg	2′-NH_2, 4-Br, 4′-CF_3		B	98	$C_{16}H_{11}BrF_3NO_2$	*c*
IIh	2′-NH_2, 4-Cl, 4′-CF_3	*b* ($CHCl_3$)	B	88	$C_{16}H_{11}ClF_3NO_2$	C, H, N
IIi	2′-NH_2, 4-I, 4′-CF_3	*b*	B	92	$C_{16}H_{11}F_3INO_2$	*d*
IIj	2′-NH_2, 4′-Br, 4-CF_3		B	63	$C_{16}H_{11}BrF_3NO_2$	*c*
IIk	2′-NH_2, 4′-Cl, 4-CF_3		B	79	$C_{16}H_{11}ClF_3NO_2$	*c*
IIl	2′-NH_2, 4,4′-$(CF_3)_2$	*b*	B	80	$C_{17}H_{11}F_6NO_2$	*d*
		B. 3-Benzaloxindoles[e]				
IIAa	4′-F	193–194 (EtOH)			$C_{15}H_{10}FNO$	C, H, N
IIAb	4′-CF_3	235–236 (EtOH)			$C_{16}H_{10}F_3NO$	C, H, N
IIAg	4′-Br, 6-CF_3	234–235 (EtOH)			$C_{16}N_9BrF_3NO$	C, H, N
IIAh	4′-Cl, 6-CF_3	211–213 (EtOH)			$C_{16}H_9ClF_3NO$	C, H, N
IIAk	6-Cl, 4′-CF_3	231–232 (EtOH)			$C_{16}H_9ClF_3NO$	C, H, N

[a] On a large scale this material was used without crystn because boiling in EtOH caused cyclodehydration and formation of IIAa. [b] Rapid conversion of this compd to the corresponding lactam, on heating, made the mp indefinite. [c] Isolated as Na salt. [d] Used as free amino acid without purification. [e] Isolated as by-products in the synthesis of the corresponding 2′-amino-α-phenylcinnamic acids.

TABLE III

PHENANTHRENE-9-CARBOXYLIC ACIDS



No.	Substituents	Mp, °C (solvent)	Yield, %	Formula[a]
IIIa	3-F	267 (EtOH)	67	$C_{15}H_9FO_2$
IIIb	3-CF_3	234–235 (aq EtOH)	37	$C_{16}H_9F_3O_2$
IIIc	6-F	270–272 (EtOH)	34	$C_{15}H_9FO_2$
IIId	6-CF_3[b,d]	259–260 (C_6H_6)	30	$C_{16}H_9F_3O_2$
IIId	6-CF_3[c,d]	259–260 (aq EtOH)	41	$C_{16}H_9F_3O_2$
IIIf	6-CF_3O	234–235 (aq HOAc)	57	$C_{16}H_9F_3O_3$
IIIg	3-Br, 6-CF_3	280–281 (dioxane)	67	$C_{16}H_8BrF_3O_2$
IIIh	3-Cl, 6-CF_3	268–270 (EtOAc)	61	$C_{16}H_8ClF_3O_2$
IIIi	3-I, 6-CF_3	285–286 (EtOH)	54	$C_{16}H_8F_3IO_2$
IIIj	6-Br, 3-CF_3	264–267 (C_6H_6)	69	$C_{16}H_8BrF_3O_2$
IIIk	6-Cl, 3-CF_3	256–257 (EtOH)	52	$C_{16}H_8ClF_3O_2$
IIIl	3,6-$(CF_3)_2$	272–273 (aq EtOH)	42	$C_{17}H_8F_6O_2$

[a] All compds were analyzed for C, H. [b] From IId. [c] From IIe. [d] The ir spectra of IIId obtd from IId and IIe were identical.

TABLE IV

9-PHENANTHROYL CHLORIDES

p-COCl

No.	Substituents	Mp, °C (solvent)	Formula[a]
IVa	3-F	136 (C_6H_6)	$C_{15}H_8ClFO$
IVb	3-CF_3	146–147 (C_6H_6–petr ether)	$C_{16}H_8ClF_3O$
IVc	6-F	130–132 (sublimation)	$C_{15}H_8ClFO$
IVd	6-CF_3	127–130 (C_6H_6)	$C_{16}H_8ClF_3O$

[a] IVa was used without anal. The remaining compds were analyzed for C, H.

ml of C_6H_6, and 250 ml of $SOCl_2$) and 750 ml of ethereal CH_2N_2 (from 50 g of *N*-nitrosomethylurea) carried out in the usual manner[17] gave 20 g of 2-diazo-4′-trifluoromethoxyacetophenone as pale yellow crystals, mp 48–49° (petr ether). *Anal.* ($C_9H_5F_3N_2O_2$) C, H. To a mixt of 2 g of Ag_2O, 3 g of $Na_2S_2O_3$, 5 g of Na_2CO_3, and 200 ml of H_2O, at 50–60°, was added 5 g (0.022 mole) of the diazoacetophenone in 30 ml of dioxane.[17] After 1 hr at 50–60° the mixt was maintained at reflux until N_2 evoln ceased (*ca.* 2.5 hr). A small quantity of black solid was filtered from the cooled mixt and the filtrate was acidified with dil HCl to give 3.3 g (70%) of the phenylacetic acid as off-white solid, mp 82–84°. A colorless anal. sample was obtained by vac sublimation. *Anal.* ($C_9H_7F_3O_3$) C, H.

Nitro α-Phenylcinnamic Acids (Table I). Method A.—A mixt of 0.3 mole of the phenylacetic acid, 0.3 mole of the benzaldehyde, 300 g of Ac_2O, and 30 g of Et_3N was stirred at the listed temp for 24 hr, poured into 1.8 l. of warm H_2O and stirred. The resulting crystals were washed, dried, and recrystd.

Method B.—A mixt of 0.3 mole of phenylacetic acid, 0.3 mole of benzaldehyde, 0.17 mole of K_2CO_3, and 0.75 mole of Ac_2O was slowly raised to the listed temp and maintained at this temp for 24 hr. To the hot soln were added 400 ml of H_2O and 200 ml of 10% HCl. The mixt was stirred at room temp for 2 hr and filtered.

Amino α-Phenylcinnamic Acids (Table II). Method A.—To a mixt of 70 g of $FeSO_4 \cdot 7H_2O$, 146 ml of H_2O, and 146 ml of concd NH_4OH, at 70–80°, was added a soln of 0.03 mole of the nitro acid (Table I) in 70 ml of warm dil NH_4OH (1:1). The mixt was maintained at 70–80° for 2 hr, filtered, and acidified with AcOH.

Method B.—To a soln of 0.5 mole of $FeSO_4 \cdot 7H_2O$ in 150 ml of H_2O was added a soln of 1.5 moles of NaOH in 600 ml of H_2O. To this mixt at 80° was added a soln of 0.05 mole of the nitro acid (Table I) in 0.075 mole of warm 2% NaOH. The mixt was maintained at 100° for 30 min and filtered hot. On cooling, the Na salt of the amino acid either sepd spontaneously or was forced out by addition of solid NaCl or solid NaOH.

(17) E. W. Bachman and W. S. Struve, *Org. React.*, **1**, 38 (1942).

TABLE V

9-BROMOACETYLPHENANTHRENES

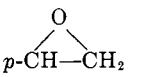
p-$COCH_2Br$

No.	Substituents	Mp, °C (solvent)	Yield,[b] %	Formula[a]
Va	3-F	144–145 (EtOAc)	71	$C_{16}H_{10}BrFO$
Vb	3-CF_3	119–120[a]	61	$C_{17}H_{10}BrF_3O$
Vc	6-F	104–106 (C_6H_6)	51	$C_{16}H_{10}BrFO$
Vd	6-CF_3	133–135 (C_6H_6–ligroin)	50	$C_{17}H_{10}BrF_3O$
Vh	3-Cl, 6-CF_3	147–149 (EtOH)	77	$C_{17}H_9BrClF_3O$
Vi	3-I, 6-CF_3	173–174 (EtOH)	92	$C_{17}H_9BrF_3IO$
Vk	6-Cl, 3-CF_3	142–144[a]	82	$C_{17}H_9BrClF_3O$
Vl	3,6-$(CF_3)_2$	166–168 (EtOH)	50	$C_{18}H_9BrF_6O$

[a] All compds were analyzed for C, H except Vb and Vk which were used in the next step without crystn. [b] Based on the corresponding phenanthroic acid (Table III).

TABLE VI

9-PHENANTHRYL ETHYLENE OXIDES[a]



No.	Substituents	Mp, °C (solvent)	Yield, %
VId	6-CF_3	120–125 (crude)	64
VIi	3-I, 6-CF_3	151–152.5 (MeOH)	60[b]
VIk	6 Cl, 3-CF_3	150 (ligroin)	66

[a] These compds were generally used without analysis. [b] Isolated as a by-product was a compd whose elemental [($C_{17}H_{12}F_3IO$) C, H] and ir analyses indicated that it was most probably the methyl carbinol (9-$CHOHCH_3$)(VIi′); mp, 178–179.5° (C_6H_6–ligroin).

Phenanthrene-9-carboxylic Acids (Table III).—A mixt of 0.05 mole of the Na salt of the aminophenylcinnamic acid (Table II), suspended in 200 ml of EtOH and 0.17 mole of *i*-AmONO, was treated at −5° with 160 ml of 15% ethanolic HCl during 60 min. The mixt was maintained at −5 to 0° for an additional 2 hr and slowly poured into a mixt of 0.5 mole of NaH_2PO_2, 2.3 g of Cu bronze, 3 drops of concd H_2SO_4, and 80 ml of H_2O at 40°. After 1 hr the resulting crystals were collected.

The free amino acids in Table II were cyclized to the corresponding phenanthroic acids in an identical manner.

9-Bromoacetylphenanthrenes (Table V).—A mixt of 0.03 mole of phenanthrene-9-carboxylic acid (Table III), 150 ml of dry C_6H_6, and 150 ml of $SOCl_2$ was heated under reflux for 3 hr. The solvent and excess $SOCl_2$ were removed, and the residual acid chloride (quant) was used without further purification. (Data for some of the acid chlorides are included in Table IV.)

To a mixt of 90 ml of 40% KOH and 400 ml of Et_2O, at 0–5°, was added, in portions, 30 g of *N*-nitrosomethylurea. The yellow, ethereal CH_2N_2 layer was sepd, dried over KOH pellets (4 hr), and dild with 50 ml of C_6H_6. To this soln at 5° was added, during 15 min, 0.03 mole of the acid chloride. The mixt was stirred at 5° for 2 hr and at room temp overnight. The resulting pale yellow diazo ketone was suspended in 75 ml of dioxane at room temp and treated with 30 ml of a 1:1 mixture of 48% HBr and dioxane. After 0.5 hr, the brown soln was stirred with a mixt of 20 g of Na_2CO_3 in 150 ml of H_2O to give the bromoacetyl deriv.

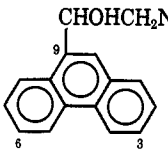
9-Phenanthryl Ethylene Oxides (Table VI).—To a suspension of 0.015 mole of the bromomethyl ketone (Table V) in 525 ml of MeOH was added at room temp, during 15 min, 0.03 mole of $NaBH_4$. The mixt was stirred at room temp for 10 min, treated with 10 ml of 12% NaOH, allowed to stand overnight, and evapd to dryness. The epoxide was extd with C_6H_6.

α-(Di-*n*-alkylaminomethyl)-9-phenanthrenemethanol Hydrochlorides (Table VII). Method A.—A mixt of 0.008 mole of the epoxide (Table VI) and 0.024 mole of the R_2NH was heated at 110° overnight. The cooled mixt was dild with 400 ml of Et_2O and treated with ethereal HCl to remove $R_2NH \cdot HCl$. Continued addn of Et_2O–HCl gave the target compd.

Method B.—A mixt of 0.023 mole of the bromo ketone (Table V), 200 ml of Et_2O, 50 ml of Me_2CO, and 0.046 mole of R_2NH

TABLE VII

α-(DI-*n*-ALKYLAMINOMETHYL)-9-PHENANTHRENEMETHANOL HYDROCHLORIDES

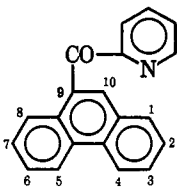


No.	Substituents	R	Mp, °C (solvent)	Method	Yield, %	Formula	Analyses
VIIa	3-F	C_4H_9	188–189 (EtOAc)	C	55	$C_{24}H_{31}ClFNO$	C, H, Cl, N
VIIa′	3-F	C_7H_{15}	145–146 (EtOAc)	B	73	$C_{30}H_{43}ClFNO$	C, H, Cl; N[a]
VIIb	3-CF_3	C_4H_9	180–181 (C_6H_6–ligroin)	B	36	$C_{25}H_{31}ClF_3NO$	C, H, Cl, N
VIIb′	3-CF_3	C_7H_{15}	149–151 (ligroin)	B	34	$C_{31}H_{43}ClF_3NO$	C, H, Cl, N
VIIc	6-F	C_4H_9	187–188 (EtOAc–$CHCl_3$)	B	17	$C_{24}H_{31}ClFNO$	C, H, Cl, N
VIIc′	6-F	C_7H_{15}	157–159 (EtOAc–$CHCl_3$)	B	40	$C_{30}H_{43}ClFNO$	C, H, N
VIId	6-CF_3	C_4H_9	223–226 (EtOAc)	B	50	$C_{25}H_{31}ClF_3NO$	C, H, N
VIId′	6-CF_3	C_7H_{15}	195–197 (EtOAc–$CHCl_3$)	A	27	$C_{31}H_{43}ClF_3NO$	C, H, N
VIIh	3-Cl, 6-CF_3	C_4H_9	229–230 (EtOH)	C	43	$C_{25}H_{30}Cl_2F_3NO$	C, H, Cl, N
VIIh′	3-Cl, 6-CF_3	C_7H_{15}	185–186 (EtOH)	C	58	$C_{31}H_{42}Cl_2F_3NO$	C, H, Cl, N
VIIi	3-I, 6-CF_3	C_4H_9	215.5–216.5 (ligroin–C_6H_6)	A	56	$C_{25}N_{30}ClF_3INO$	C, H, F, N
VIIi′	3-I, 6-CF_3	C_7H_{15}	160–163 (aq EtOH)	A	82	$C_{31}H_{42}ClF_3INO$	C, H, F, N
VIIk	6-Cl, 3-CF_3	C_4H_9	225–226 (EtOH–Et_2O)	A	28	$C_{25}H_{30}Cl_2F_3NO$	C, H, N
VIIk′	6-Cl, 3-CF_3	C_7H_{15}	182–184 (Me_2CO–Et_2O)	A	28	$C_{31}H_{42}Cl_2F_3NO$	C, H, N
VIIl	3,6-$(CF_3)_2$	C_3H_7	243–244 (EtOH)	B	17	$C_{24}H_{26}ClF_6NO$	C, H, F, N
VIIl′	3,6-$(CF_3)_2$	C_4H_9	221–223.5 (C_6H_6)	B	19	$C_{26}H_{30}ClF_6NO$	C, H, F, N

[a] N: calcd, 2.87; found, 3.29.

TABLE VIII

2-PYRIDYL 9-PHENANTHRYL KETONES



No.	Substituents	Mp, °C (solvent)	Yield, %	Formula[a]
VIIIb	3-CF_3[b]	153–154 (EtOH)	70	$C_{21}H_{12}F_3NO$
VIIId	6-CF_3	164–166 (EtOH–Me_2CO)	55	$C_{21}H_{12}F_3NO$
VIIIf	6-CF_3O	151–152 (EtOH)	47	$C_{21}H_{12}F_3NO_2$
VIIIg	3-Br, 6-CF_3	198–199 (aq Me_2CO)	47	$C_{21}H_{11}BrF_3NO$
VIIIh	3-Cl, 6-CF_3	193–195 (aq EtOH)	32	$C_{21}H_{11}ClF_3NO$[c]
VIIIi	3-I, 6-CF_3	209–210.5 (aq Me_2CO)	56	$C_{21}H_{11}F_3INO$
VIIIj	6-Br, 3-CF_3	260–263 (C_6H_6)	41	$C_{21}H_{11}BrF_3NO$
VIIIk	6-Cl, 3-CF_3	230–231 (dioxane–MeOH)	82	$C_{21}H_{11}ClF_3NO$[d]
VIIIl	3,6-$(CF_3)_2$	243–245 (EtOH)	74	$C_{22}H_{11}F_6NO$

[a] All compds analyzed for C, H, N. [b] Reduction of VIIIb with $NaBH_4$ gave 39% of α-(2-pyridyl)-3-trifluoromethyl-9-phenanthrenemethanol (VIIIb′), mp 168–169° (MeOH). *Anal.* ($C_{21}H_{14}F_3NO$) C, H, N. [c] C: calcd, 65.38; found, 64.85. [d] C: calcd, 65.38; found, 64.68.

was stirred at room temp for 4 hr and $R_2NH \cdot HBr$ was removed. The filtrate was concd to a syrup and dild with 200 ml of Et_2O, and addl $R_2NH \cdot HBr$ was removed. The filtrate was concd to an oil and treated with a mixt of 30 g of freshly dist $Al(i\text{-}OPr)_3$ and 300 ml of *i*-PrOH. The mixt was gently heated under reflux for 0.5 hr and the solvent was then slowly distd (Vigreux column, bath temp 100°) until Me_2CO was no longer evident in the distillate (0.75 hr). The bath temp was raised to 110° and dist was contd for 0.5 hr. The remainder of the solvent was removed under reduced pressure and the residue was extd with 2 l. of Et_2O. The ext was washed with H_2O, dried ($MgSO_4$), and treated with 500 ml of Et_2O satd with HCl gas. The pale brown soln was filtered and concd.

Method C.—A mixt of 0.01 mole of the bromo ketone (Table V), 0.02 mole of the R_2NH, 15 ml of dry Et_2O, and 3 ml of Me_2CO was stirred at room temp for 5 hr. The mixt was filtered to remove $R_2NH \cdot HBr$ and the filtrate was evapd to dryness *in vacuo*. The residue was dissolved in 50 ml of MeOH and treated with 0.01 mole of $NaBH_4$. Two ml of 0.2 *N* NaOH was added and the mixt was stirred for 1.5 hr. The MeOH was removed under reduced pressure, and the residue was made alk with 2 *N* NaOH and extd with Et_2O. The ext was dried ($MgSO_4$) and treated with Et_2O–HCl.

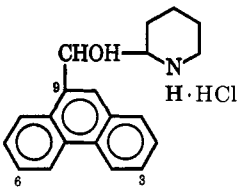
2-Pyridyl 9-Phenanthryl Ketones (Table VIII).—To a vigorously stirred mixt of 32 ml (0.05 mole) of 15% BuLi in hexane (Foote Mineral Co., Exton, Pa.) and 50 ml of dry Et_2O, cooled to −60°, was added 0.05 mole of 2-bromopyridine (Aldrich Chemical Co.). The brown soln was stirred at −60° for 1 hr and a suspension of 0.02 mole of the phenanthrene-9-carboxylic acid (Table III) in 150 ml of Et_2O, cooled to −60°, was added all at once. The mixt was stirred at −60° for 2 hr, allowed to warm to room temp, and hydrolyzed with H_2O. The Et_2O layer was dried ($MgSO_4$) and evapd.

α-(2-Piperidyl)-9-phenanthrenemethanol Hydrochlorides (Table IX).—A mixt of 0.01 mole of the ketone (Table VIII), 250 ml of EtOH, and 2 ml of concd HCl was hydrogenated for 1 hr over 0.2 g of PtO_2, at 40 psig. The mixt was filtered and concd.

An attempt to reduce the iodo pyridyl ketone (VIIIi) in this

TABLE IX

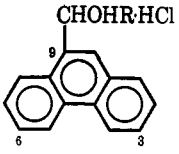
α-(2-PIPERIDYL)-9-PHENANTHRENEMETHANOL HYDROCHLORIDES



No.	Substituents	Mp, °C (solvent)	Yield, %	Formula	Analyses
IXb	3-CF_3	314–316 (EtOH)	37	$C_{21}H_{21}ClF_3NO$	C, H, N
IXd	6-CF_3	311–313 (aq EtOH)	30	$C_{21}H_{21}ClF_3NO$	C, H, F, N
IXf	6-CF_3O	298.5–299.5 (MeOH)	80	$C_{21}H_{21}ClF_3NO_2$	C, H, N
IXg	3-Br, 6-CF_3	317–319 (Me_2CO–5% HCl)	45	$C_{21}H_{20}BrClF_3NO$	C, H, F, N
IXh	3-Cl, 6-CF_3	312–315 (aq Me_2CO)	40	$C_{21}H_{20}Cl_2F_3NO$	C, H, N
IXj	6-Br, 3-CF_3	348–352 (MeOH)	60	$C_{21}H_{20}BrClF_3NO$	C, H, F, N
IXk	6-Cl, 3-CF_3	314–315 (aq EtOH)	77	$C_{21}H_{20}Cl_2F_3NO$	C, H, N
IXl	3,6-$(CF_3)_2$	324–327 (aq EtOH)	67	$C_{22}H_{20}ClF_6NO$	C, H, F, N

TABLE X

ANTIMALARIAL ACTIVITY[a]



			ΔMST or C[b]						
			Dose, mg/kg						
No.	Substituents	R	10	20	40	80	160	320	640
Standard	6-Br	$CH_2N(C_7H_{15})_2$	2.1	4.5	6.7	1 C	3 C	4 C	4 C
VIIa	3-F	$CH_2N(C_4H_9)_2$		0.2	0.2	1.2	4.6	5.2	6.4
VIIa′	3-F	$CH_2N(C_7H_{15})_2$		0.6	2.8	3.6	5.6	7.6	12.2
VIIb	3-CF_3	$CH_2N(C_4H_9)_2$	0.4	2.4	7.8	8.4	11.0	13.2	2 C
VIIb′	3-CF_3	$CH_2N(C_7H_{15})_2$		0.5	5.9	13.3	14.5	1 C	5 C
IXb	3-CF_3	2-Piperidyl		5.5	12.9	16.9	3 C	5 C	5 C
VIIc	6-F	$CH_2N(C_4H_9)_2$		1.1	2.1	3.3	7.7	9.3	13.3
VIIc′	6-F	$CH_2N(C_7H_{15})_2$		4.7	4.9	8.7	10.9	15.1	5 C
VIId	6-CF_3	$CH_2N(C_4H_9)_2$			9.4		1 C		5 C
VIId′	6-CF_3	$CH_2N(C_7H_{15})_2$		4.7	10.4	13.0	3 C	4 C	5 C
IXd	6-CF_3	2-Piperidyl	0.3	4.7	2 C	2 C	4 C	5 C	5 C
IXf	6-CF_3O	2-Piperidyl		0.2	1.8	11.2	1 C	2 C	5 C
IXg	3-Br, 6-CF_3	2-Piperidyl	3.9	1 C	2 C	2 C	5 C	5 C	5 C
VIIh	3-Cl, 6-CF_3	$CH_2N(C_4H_9)_2$		3.4	1 C	1 C	5 C	5 C	5 C
VIIh′	3-Cl, 6-CF_3	$CH_2N(C_7H_{15})_2$			7.8		3 C		5 C
IXh	3-Cl, 6-CF_3	2-Piperidyl	5.0	1 C	3 C	5 C	5 C	5 C	5 C
VIIi	3-I, 6-CF_3	$CH_2N(C_4H_9)_2$	6.5	8.1	11.9	1 C	5 C	5 C	5 C
VIIi′	3-I, 6-CF_3	$CH_2N(C_7H_{15})_2$		0.2	4.6	9.8	1 C	2 C	5 C
IXj	6-Br, 3-CF_3	2-Piperidyl	0.2	1.4	4.8	4 C	5 C		
VIIk	6-Cl, 3-CF_3	$CH_2N(C_4H_9)_2$	2.7	7.3	1 C	5 C	5 C	5 C	5 C
VIIk′	6-Cl, 3-CF_3	$CH_2N(C_7H_{15})_2$		0.3	0.5	5.3	8.3	10.7	2 C
IXk	6-Cl, 3-CF_3	2-Piperidyl	1.5	2 C	5 C	5 C	5 C	5 C	5 C
VIIl	3,6-$(CF_3)_2$	$CH_2N(C_3H_7)_2$	5.0	11.0	2 C	2 C	5 C	5 C	5 C
VIIl′	3,6-$(CF_3)_2$	$CH_2N(C_4H_9)_2$	5.9	1 C	3 C	3 C	5 C	5 C	5 C
IXl	3,6-CF_3	2-Piperidyl	9.1	18.9	2 C	5 C	5 C	5 C	5 C

[a] See ref 5. [b] ΔMST, mean survival time over controls (6.2 ± 0.49 days); C, number of cures (mice surviving to 60 days).

manner gave only the corresponding pyridyl carbinol (VIIIi′), mp 219–220° (aq EtOH). *Anal.* ($C_{21}H_{13}F_3INO$) C, H; ir as expected. The same compd (VIIIi′) was obtained on reduction of VIIIi with methanolic $NaBH_4$.

No attempts were made to isolate the two possible racemates of the α-(2-piperidyl) analogs. For IX1 this was subsequently accomplished by Dr. Edward E. Hamel, Aerojet Solid Propulsion Company, who will publish his results shortly.