Notes

Antimalarial Phenanthrene Amino Alcohols. 3. Halogen-Containing 9-Phenanthrenemethanols[1]

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A series of new 9-phenanthrene amino alcohols has been prepared in which each compound bears from one to five halogen or halogen-containing moieties. A number of these compounds are extremely active against *Plasmodium berghei* in the mouse. Some structural requirements for optimal efficacy are considered.

The recent emergence of drug-refractory *falciparum* malaria[2-4] sparked various promising chemotherapeutic leads, dormant since World War II. Prominent among these early leads was the significant avian antiplasmodial activity of the 9-phenanthrenemethanols (I) and particularly those with a nuclear chlorine or bromine atom.[2b,5,6]

I
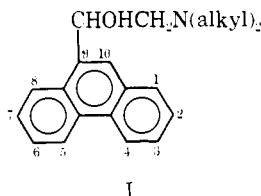
The enhancement of prototype medicinals by substituting fluorine or fluorine-containing groups for halogen or hydrogen has been demonstrated repeatedly during the past two decades.[7,8] It was therefore a logical extension of this work which led us to a series of extremely potent fluorine-containing 9-phenanthrenemethanol antimalarials.[9,10]

The present paper completes our fluoro series and details a congeneric group, almost as active, comprised of 9-phenanthrenemethanols substituted with halogens other than fluorine.

Scheme I
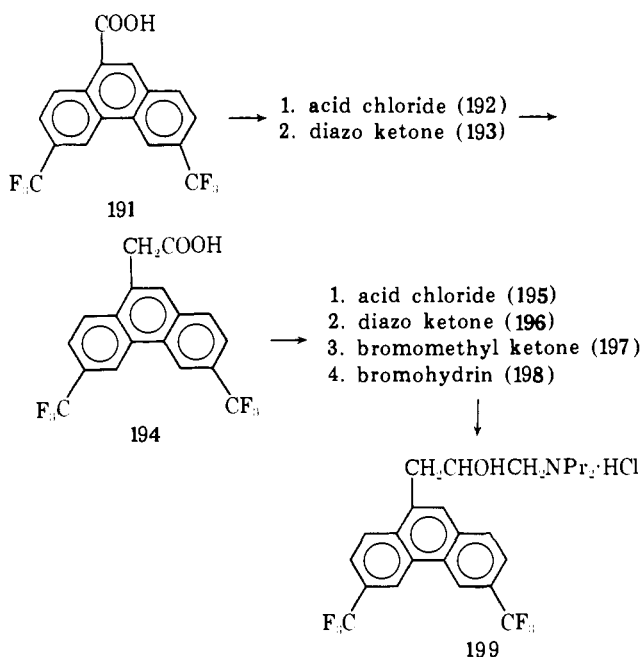
Chemistry. The preparative routes were essentially those described in paper 1.[9] Details have been tabulated in the Experimental Section. The synthesis of the phenanthreneethanol (199) was effected as indicated in Scheme I.

Biology. Table I provides murine antimalarial data for 15 monohalo-, 13 dihalo-, 17 trihalo-, and 4 tetrahalo-9-phenanthrenemethanols. Also included are data for a single methyl derivative, three compounds in which halogen is combined with ether moieties, and four additional trifluoromethyl analogs (189, 190, 104, 103). A 9-phenanthreneethanol derivative (199) was prepared to test the effect of homologizing the side chain of an active 9-phenanthrenemethanol in the position adjacent to the nucleus. The result was complete loss of activity.

All of the monochloro derivatives were relatively unimpressive, providing multiple cures only at the highest concentrations. 2-Cl (155) held a slight edge over the others while 8-Cl (165) was unique in its complete inactivity even at 640 mg/kg.

By contrast, the monobromo derivatives (157, 86, 87) were active or curative at 80 mg/kg with 157 and 86 showing some activity as low as 40 mg/kg.

Those compounds which contained no halogen (88) or in which halogen was combined with nonhalogenic groups (174, 175, 102) were not curative below 640 mg/kg.

Introduction of a second halogen atom produced a much improved group of compounds, some of which were curative (1/5) at 20 mg/kg and most of which were active at 10 mg/kg. The favored positions were 2,4 and 2,6. The dibromo compounds were a bit more active than the corresponding dichloro derivatives.

Peak activity among the unfluorinated 9-phenanthrenemethanols was achieved with the trisubstituted derivatives. Thus, the 2,4,6 and 2,5,7 analogs (99, 100) produced 5/5 cures at 20 mg/kg with the latter providing an additional cure at 10 mg/kg.

The best of the tetrachloro derivatives (186), with 5/5 cures at 40 mg/kg, 2/5 cures at 20 mg/kg, and some activity at 10 mg/kg, was about as active as the best of the dihalo series (171).

Table II has collected, from the three papers in this series, all of the compounds which are curative at concentrations of 20 mg/kg or less. These compounds are presented in order of decreasing activity so that an optimal substitution pattern begins to emerge from the upper portion of the table. Thus, nine of the topmost ten compounds (80–100% curative at 20 mg/kg) are polysubstituted with Cl or a combination of Cl and CF₃. (The lone exception, the monosubstituted 2-CF₃ analog, was also anomalous in being the only toxic compound in the entire series.) The top ten com-

Table I. Blood Schizonticidal Antimalarial Activity[a] (*P. berghei*, Mouse)

CHOHR·HCl

			ΔMST or C[c] at dose, mg/kg							
No.	Substituents	R[b]	5	10	20	40	80	160	320	640
153	1-Cl	CH_2NBu_2			2.1	4.7	5.7	10.9	1C	2C
154	1-Cl	CH_2NHep_2			0.5	1.5	2.1	5.3	7.3	8.7
155	2-Cl	CH_2NBu_2			1.1	3.3	7.5	13.3	1C	5C
156	2-Cl	CH_2NHep_2			2.2	5.6	6.2	11.0	12.6	5C
157	2-Br	CH_2NBu_2		1.9	5.9	7.3	11.9	3C	5C	5C
86	2-Br	Pip			3.1	12.7	2C	2C	3C	5C
158	4-Cl	CH_2NHep_2			0.7	3.1	3.3	4.3	7.3	2C
159	5-Cl	CH_2NBu_2			0.3	0.5	1.5	4.9	9.1	2C
160	5-Cl	CH_2NHep_2			1.3	4.9	7.1	8.9	13.2	5C
161	6-Cl	CH_2NBu_2			0.3	0.7	4.7	8.1	10.1	2C
162	6-Cl	CH_2NHep_2			0.7	3.9	5.9	7.9	9.9	11.9
87	6-Br	Pip			0.6	1.8	9.6	2C	3C	5C
88	6-CH_3	Pip				0.4	1.2	5.8	11.4	4C
163	7-Cl	CH_2NBu_2			0.3	0.7	1.1	7.1	7.9	14.1
164	7-Cl	CH_2NHep_2			2.1	4.7	7.5	9.3	1C	3C
165	8-Cl	CH_2NBu_2			0.7			0.7		0.9
89	1,3-Cl_2	Pip		2.5	4.1	12.9	3C	5C	5C	5C
166	2,4-Br_2	CH_2NBu_2	1.9	9.5	11.5	4C	5C	5C	5C	5C
167	2,6-Cl_2	CH_2NEt_2	1.3	9.7	1C	3C	5C	5C	5C	5C
168	2,6-Cl_2	CH_2NPr_2	1.9	9.3	13.5	3C	5C	5C	5C	5C
169	2,6-Cl_2	CH_2NBu_2		2.9	10.7	1C	3C	5C	5C	5C
170	2,6-Cl_2	CH_2NAm_2		5.5	8.3	2C	5C	5C	5C	5C
90	2,6-Cl_2	Pip	0.5	3.9	14.9	5C	5C	5C		
171	2,6-Br_2	CH_2NPr_2		6.5	1C	5C	5C	5C	5C	5C
172	2,6-Br_2	CH_2NBu_2		6.3	11.5	3C	5C	5C	5C	5C
91	2,6-Br_2	Pip	0.6	6.2	15.6	3C	5C	5C	5C	5C
173	3,6-Cl_2	CH_2NHep_2			0.3	2.5	3.1	9.5	16.1	5C
92	3,6-Cl_2	Pip		0.3	9.1	12.3	13.5	4C	5C	5C
174	3-Cl, 6-OCH_3	CH_2NBu_2			0.3	0.5	0.5	1.1	6.9	10.1
175	3-Cl, 6-OCH_3	CH_2NHep_2			0.5	1.5	3.9	13.7	16.7	3C
93	5,7-Cl_2	Pip			0.7	12.5	14.9	5C	5C	
176	1,3,6-Cl_3	CH_2NEt_2	5.7	8.8	1C	1C	5C	5C	5C	5C
177	1,3,6-Cl_3	CH_2NPr_2	4.1	12.1	2C	5C	5C	5C	5C	5C
178	1,3,6-Cl_3	CH_2NBu_2		4.9	11.3	14.1	2C	5C	5C	5C
94	1,3,6-Cl_3	Pip		0.3	3.9	4C	4C	5C	5C	5C
179	1,3,6-Br_3	CH_2NBu_2		6.1	6.9	2C	3C	5C	5C	
95	6-Br, 1,3-Cl_2	Pip		0.5	2.1	11.9	3C	3C	5C	
96	1,3,7-Cl_3	Pip	0.3	0.3	0.5	1C	3C			
97	2,3,6-Cl_3	Pip		0.3	4.9	15.3	1C	5C	5C	
180	2,3,6-Br_3	CH_2NBu_2	1.9	5.9	9.9	1C	3C	5C		
98	6-Br, 2,3-Cl_2	Pip		0.5	3.1	13.5	3C	5C	5C	5C
181	2,4,6-Cl_3	CH_2NBu_2		8.1	2C	3C	5C	5C	5C	5C
99	2,4,6-Cl_3	Pip	3.1	10.1	5C	5C	5C	5C	5C	5C
182	2,4,7-Cl_3	CH_2NBu_2	4.5	8.1	12.1	3C	5C	5C	5C	5C
183	2,5,7-Cl_3	CH_2NBu_2	6.3	8.5	10.9	13.1	5C	5C	5C	5C
100	2,5,7-Cl_3	Pip	0.7	1C	5C	5C	5C	5C	5C	5C
184	3,5,7-Cl_3	CH_2NBu_2		5.3	11.7	2C	3C	5C	5C	5C
101	3,6,7-Cl_3	Pip		1.3	11.9	2C	3C	5C	5C	5C
102	6-Cl, 2,3-OCH_2O^-	Pip		0.1	0.3	0.3	0.5	3.9	9.5	3C
185	2,3,5,6-Cl_4	CH_2NBu_2		7.5	1C	3C	5C	5C	5C	5C
186	2,3,6,7-Cl_4	CH_2NBu_2		7.7	2C	5C	5C	5C	5C	5C
187	1,2,6,7-Cl_4	CH_2NBu_2		3.3	4.9	6.9	11.9	15.1	5C	5C
188	1,3,5,7-Cl_4	CH_2NBu_2	3.9	8.7	14.1	2C	5C	5C		
189	2,4-$(CF_3)_2$	CH_2NMe_2	0.7	9.5	15.1	2C	4C	5C	5C	5C
190	2,4-$(CH_3)_2$	CH_2NPr_2	5.9	14.1	2C	5C	5C	5C	5C	5C
104	2,4-$(CF_3)_2$	Pip	0.9	4.3	5.9	5C	5C	5C		
103	1,2,3,4-Cl_4, 6-CF_3	Pip	0.5	4C	5C	5C	5C	5C		

[a] Tests were carried out by the Rane Laboratory, University of Miami, Miami, Fla., using blood induced *P. berghei* infected mice (five animals/group) by the method described by Osdene et al.[13] Test data were supplied by Drs. T. R. Sweeney and R. E. Strube of Walter Reed Army Institute of Research. [b] Pip = 2-piperidyl. [c] ΔMST, mean survival time over controls (6.2 ± 0.49 days); C, number of cures (mice surviving to 60 days); a compound is considered to be "active" when the MST of the treated group is more than twice that of the control group.

Table II. Blood Schizonticidal Antimalarial Activity, Curative at 20 mg/kg[a] (*P. berghei*, Mouse)

CHOHR·HCl

		Cures (C) or ΔMST[e] at dose, mg/kg				
Substituents	R[b]	5	10	20	40	80
6,7-Cl$_2$, 2,4-(CF$_3$)$_2$[c]	CH$_2$NPr$_2$	5C	5C	5C	5C	5C
7-Cl, 2,4-(CF$_3$)$_2$	Pip	4.1	5C	5C	5C	5C
6-Cl, 2,4-(CF$_3$)$_2$	Pip	10.3	3C	5C	5C	5C
2,4-Cl$_2$, 6-CF$_3$	Pip	5.5	3C	4C	5C	5C
1,2,3,4-Cl$_4$, 6-CF$_3$	Pip	0.5	3C	5C	5C	
2,5,7-Cl$_3$	Pip	0.7	1C	5C	5C	5C
6,7-Cl$_2$, 2,4-(CF$_3$)$_2$	Pip	7.9	1C	4C	5C	5C
2,4,6-Cl$_3$	Pip	3.1	10.1	5C	5C	5C
1,2-Cl$_2$, 6-CF$_3$	Pip	0.7	13.5	4C	5C	5C
2-CF$_3$[d]	Pip		6.5	4C	5C	5C
5,7-Cl$_2$, 3-CF$_3$	Pip	0.5	1C	2C	5C	5C
1,3-Cl$_2$, 6-CF$_3$	CH$_2$NBu$_2$	7.1	12.5	2C	5C	5C
2,4-(CF$_3$)$_2$	CH$_2$NPr$_2$	5.9	14.1	2C	5C	5C
3,4-Cl$_2$, 6-CF$_3$	Pip	1.3	11.5	3C	5C	5C
2,4,6-(CF$_3$)$_3$	Pip		1.9	3C	5C	5C
6,7-Cl$_2$, 3-CF$_3$	CH$_2$NPr$_2$		13.1	2C	4C	5C
2,3,6,7-Cl$_4$	CH$_2$NBu$_2$		7.7	2C	5C	5C
6-Cl, 3-CF$_3$	Pip	0.6	1.5	2C	5C	5C
7-Cl, 2-CF$_3$	Pip	1.1	1C	1C	5C	5C
2,6-Br$_2$	CH$_2$NPr$_2$		6.5	1C	5C	5C
2,4,6-Cl$_3$	CH$_2$NBu$_2$		8.1	2C	3C	5C
1,3,6-Cl$_3$	CH$_2$NPr$_2$		7.9	2C	3C	5C
1,3,6-Br$_3$	CH$_2$NBu$_2$	6.1	6.9	2C	3C	5C
2,3-Cl$_2$, 6-CF$_3$	Pip	0.6	7.0	1C	4C	5C
2,6-Cl$_2$	CH$_2$NEt$_2$	1.3	9.5	1C	3C	5C
2,3,5,7-Cl$_4$	CH$_2$NBu$_2$		7.5	1C	3C	5C
3-Cl, 6-CF$_3$	Pip		5.0	1C	3C	5C
1,3-Br$_2$, 6-CF$_3$	Pip		0.3	1C	3C	5C
2-Br, 6-CF$_3$	Pip	1.8	17.5	1C	3C	4C
2-Cl, 6-CF$_3$	Pip	0.3	0.3	1C	3C	4C
2-Cl, 5-CF$_3$	Pip	3.8	17.3	2C	2C	4C
3,6-(CF$_3$)$_2$	CH$_2$NBu$_2$	4.7	5.9	1C	3C	3C
2-Br, 6-CF$_3$	CH$_2$NBu$_2$			1C	3C	3C
2-Cl, 6-CF$_3$	CH$_2$NBu$_2$	5.3	7.5	1C	2C	2C
3,4-Cl$_2$, 6-CF$_3$	CH$_2$NPr$_2$		5.5	1C	2C	5C
3-Br, 6-CF$_3$	Pip		3.9	1C	2C	2C
1,3,6-Cl$_3$	CH$_2$NEt$_2$	5.7	8.7	1C	1C	5C
Unsubstituted	Pip			0.3	0.3	0.5
Unsubstituted[f]	CH$_2$NHex$_2$			0.2	1.2	1.6
Unsubstituted[f]	CH$_2$NHep$_2$			4.0	4.2	5.2

[a]Table I, footnote *a*. [b]Pip = 2-piperidyl. [c]ΔMST at 2.5 and 1.25 mg/kg = 12.1 and 6.9 days, respectively. [d]One and two toxic deaths at 320 and 640 mg/kg, respectively. [e]Table I, footnote *c*. [f]E. L. May and E. Mosettig, *J. Org. Chem.*, 11, 10 (1946).

Table IV. Nitro-α-phenylcinnamic Acids[a]

No.	Phenylcinnamic acid	Phenylacetic acid	Benz-aldehyde	Meth-od	Temp, °C	Mp, °C (solvent)	Yield, %	Formula	Analyses[c]
1	2-Cl, 2'-NO$_2$	2-NO$_2$[b]	2-Cl[b]	B	100	216–218 (EtOH)	76	C$_{15}$H$_{10}$ClNO$_4$	C, H
2	5-Cl, 2-NO$_2$	Unsubstituted	5-Cl, 2-NO$_2$[b]	B	100	191–192.5[d] (EtOH)	79	C$_{15}$H$_{10}$ClNO$_4$	C, H

Table IV *(Continued)*

No.	Phenylcinnamic acid	Phenylacetic acid	Benz-aldehyde	Meth-od	Temp, °C	Mp, °C (solvent)	Yield, %	Formula	Analyses[c]
3	3-Cl, 2'-NO$_2$	2-NO$_2$[b]	3-Cl[b]	B	100	192–194 (50% EtOH)	79	C$_{15}$H$_{10}$ClNO$_4$	C, H, N
4	3'-Cl, 2-NO$_2$	3-Cl[b]	2-NO$_2$[b]	B	100	160–162 (50% EtOH)	65	C$_{15}$H$_{10}$ClNO$_4$	C, H, N
5	4'-Cl, 2-NO$_2$	4-Cl[b]	2-NO$_2$[b]	B	100	185–187[e] (EtOH)	45	C$_{15}$H$_{10}$ClNO$_4$	h
6	2'-Cl, 2-NO$_2$	2-Cl[g]	2-NO$_2$[b]	B	100	181.5–183.5 (EtOH)	67	C$_{15}$H$_{10}$ClNO$_4$	C, H, N
7	5-Br, 2-NO$_2$	Unsubstituted	5-Br, 2-NO$_2$[f]	B	65	179–181 (C$_6$H$_6$)	60	C$_{15}$H$_{10}$BrNO$_4$	C, H, N
8	4'-CH$_3$, 2-NO$_2$	4-CH$_3$[g]	2-NO$_2$[b]	A	65	192–200 (crude)	80	C$_{16}$H$_{13}$NO$_4$	h
9	2,4-Cl$_2$, 2'-NO$_2$	2-NO$_2$[b]	2,4-Cl$_2$[i]	B	80	198–199 (C$_6$H$_6$)	71	C$_{15}$H$_9$Cl$_2$NO$_4$	C, H, N
10	3,5-Br$_2$, 2'-NO$_2$	2-NO$_2$[b]	3,5-Br$_2$[j]	B	80	232–233 (AcOH)	73	C$_{15}$H$_9$Br$_2$NO$_4$	C, H, N
11	4',5-Cl$_2$, 2-NO$_2$	4-Cl[b]	5-Cl, 2-NO$_2$[b]	C	75	200.5–201.5 (C$_6$H$_6$–hexane)	81	C$_{15}$H$_9$Cl$_2$NO$_4$	C, H, N
12	4',5-Br$_2$, 2-NO$_2$	4-Br[g]	5-Br, 2-NO$_2$[f]	B	95	218–219 (MeOH)	69	C$_{15}$H$_9$Br$_2$NO$_4$	C, H, N
13	4,4'-Cl$_2$, 2-NO$_2$	4-Cl[b]	4-Cl, 2-NO$_2$[k]	B	100	179.5–180.5 (EtOH)	77	C$_{15}$H$_9$Cl$_2$NO$_4$	C, H, N[n]
14	3',5'-Cl$_2$, 2'-NO$_2$	3,5-Cl$_2$, 2-NO$_2$[l]	Unsubstituted	B	55	202–203 (C$_6$H$_6$)	62	C$_{15}$H$_9$Cl$_2$NO$_4$	C, H, N
15	4-Cl, 4'-OCH$_3$, 2-NO$_2$	4-OCH$_3$[b]	4-Cl, 2-NO$_2$[k]	B	100	167.5–168.5 (EtOH)	76	C$_{16}$H$_{12}$ClNO$_5$	C, H, N
16	2,4,4'-Cl$_3$, 2'-NO$_2$	4-Cl, 2-NO$_2$[m]	2,4-Cl$_2$[i]	C	75	241–243 (dioxane–aq EtOH)	98	C$_{15}$H$_8$Cl$_3$NO$_4$	h
17	4'-Br, 2,4-Cl$_2$, 2'-NO$_2$	4-Br, 2-NO$_2$[m]	2,4-Cl$_2$[i]	C	85	241–243 (aq EtOH)	88	C$_{15}$H$_8$Cl$_2$BrNO$_4$	C, H, N
18	2,4,4'-Br$_3$, 2'-NO$_2$	4-Br, 2-NO$_2$[m]	2,4-Br$_2$[l]	C	75	243–244 (AcOH)	48	C$_{15}$H$_8$Br$_3$NO$_4$	C, H, N
19	2,4,5'-Cl$_3$, 2'-NO$_2$	5-Cl, 2-NO$_2$[l]	2,4-Cl$_2$[i]	C	75	191.5–192.5 (C$_6$H$_6$–hexane)	78	C$_{15}$H$_8$Cl$_3$NO$_4$	C, H, N
20	4,4',5-Cl$_3$, 2-NO$_2$	4-Cl[b]	4,5-Cl$_2$, 2-NO$_2$[l]	B	80	186–189 (C$_6$H$_6$)	58	C$_{15}$H$_8$Cl$_3$NO$_4$	C, H, N
21	4'-Br, 4,5-Cl$_2$, 2-NO$_2$	4-Br[g]	4,5-Cl$_2$, 2-NO$_2$[l]	B	60	211–213 (C$_6$H$_6$)	64	C$_{15}$H$_8$Cl$_2$BrNO$_4$	C, H, N
22	4,4',5-Br$_3$, 2-NO$_2$	4-Br[g]	4,5-Br$_2$, 2-NO$_2$[l]	B	70	219–220 (AcOH)	56	C$_{15}$H$_8$Br$_3$NO$_4$	C, H, N
23	3,4',5-Cl$_3$, 2'-NO$_2$	4-Cl, 2-NO$_2$[m]	3,5-Cl$_2$[b]	B	90	252–254 (C$_6$H$_6$)	78	C$_{15}$H$_8$Cl$_3$NO$_4$	C, H, N
24	3,5,5'-Cl$_3$, 2'-NO$_2$	5-Cl, 2-NO$_2$[l]	3,5-Cl$_2$[b]	B	90	235–237 (C$_6$H$_6$)	44	C$_{15}$H$_8$Cl$_3$NO$_4$	C, H, N
25	3',5',5-Cl$_3$, 2-NO$_2$	3,5-Cl$_2$[o]	5-Cl, 2-NO$_2$[b]	B	90	181–182 (aq EtOH)	81	C$_{15}$H$_8$Cl$_3$NO$_4$	C, H
26	3',4,5'-Cl$_3$, 2-NO$_2$	3,5-Cl$_2$[o]	4-Cl, 2-NO$_2$[k]	C	75	205–207 (EtOH)	38	C$_{15}$H$_8$Cl$_3$NO$_4$	C, H
27	4,4',5'-Cl$_3$, 2'-NO$_2$	4,5-Cl$_2$, 2-NO$_2$[l]	4-Cl[b]	B	50	212–213 (AcOH)	88	C$_{15}$H$_8$Cl$_3$NO$_4$	C, H, Cl
28	4'-Cl, 4,5-OCH$_2$O–, 2-NO$_2$	4-Cl[b]	4,5-OCH$_2$O, 2-NO$_2$[b]	B	55	206–207 (C$_6$H$_6$)	70	C$_{16}$H$_{10}$ClNO$_6$	C, H, N
29	3',4',4,5-Cl$_4$, 2-NO$_2$	3,4-Cl[g]	4,5-Cl$_2$, 2-NO$_2$[l]	B	50	184 (C$_6$H$_6$)	47	C$_{15}$H$_7$Cl$_4$NO$_4$	C, H, N
30	2,3,4',5'-Cl$_4$, 2'-NO$_2$	4,5-Cl$_2$, 2-NO$_2$[l]	2,3-Cl$_2$[l]	B	80	223–225 (AcOH)	48	C$_{15}$H$_7$Cl$_4$NO$_4$	C, H, N
31	2,3',4,5'-Cl$_4$, 2'-NO$_2$	3,5-Cl$_2$, 2-NO$_2$[l]	2,4-Cl$_2$[i]	B	55	197–198 (C$_6$H$_6$)	76	C$_{15}$H$_7$Cl$_4$NO$_4$	C, H, N
32	2,3,4,5-Cl$_4$, 2'-NO$_2$, 4'-CF$_3$	2-NO$_2$, 4-CF$_3$[p]	2,3,4,5-Cl$_4$[q]	B	80	230–232 (AcOH)	67	C$_{16}$H$_6$Cl$_4$F$_3$NO$_4$	C, H, N
32a	2'-NO$_2$, 3,5-(CF$_3$)$_2$	2-NO$_2$[b]	3,5-(CF$_3$)$_2$[l]	B	80	197–200 (Et$_2$O–petr ether)	81	C$_{17}$H$_9$F$_6$NO$_4$	h

[a]The compounds in this table were made via the usual Perkin reaction (ref 9) between the appropriate phenylacetic acids and benzaldehydes, at the listed temperatures, in the presence of Et$_3$N (method A), K$_2$CO$_3$ (method B), or a mixture of K$_2$CO$_3$ and pyridine (method C).

Table IV *(Continued)*

[b]Aldrich Chemical Co., Milwaukee, Wis. [c]Analyses of the indicated elements were within ±0.4% of theory except as noted. [d]Lit. mp 183–184° [K. Schofield and T. Swain, *J. Chem. Soc.*, 2393 (1949)]. [e]Lit. mp 186-186.5° [P. Nylen, *Ber.*, **53**, 158 (1920)]. [f]L. C. Behr, *J. Am. Chem. Soc.*, **76**, 3678 (1954). [g]Research Organic/Inorganic Chemical Corp., Sun Valley, Calif. [h]Used without analysis. [i]Distillation Products Industries, Rochester, N.Y. [j]B. Bogoslovskii and T. Yakovenko, *Zh. Obshch. Khim.*, 24, 1043 (1954). [k]D. P. Spalding, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, 68, 1598 (1946). [l]Reference 10. [m]Reference 9. [n]N: calcd, 4.14; found, 4.63. [o]Prepared from 3,5-dichlorobenzoic acid (Aldrich) via the method described for 4-trifluromethoxyphenylacetic acid in ref 9: mp 113-114° (ligroine). Anal. ($C_8H_6Cl_2O_2$) C, H, Cl. [p]L. Simet, *J. Org. Chem.*, 28, 3580 (1963). [q]Prepared in 46% yield by reduction of 2,3,4,5-tetrachlorobenzoyl chloride [B. W. Nordlander and W. E. Cass, *J. Am. Chem. Soc.*, 69, 2679 (1947)] with LATBH (Alfa Inorganics Co.) as described for the preparation of 3,5-bis(trifluoromethyl)benzaldehyde in ref 10: mp 106-107.5° (EtOH). Anal. ($C_7H_2Cl_4O$) Cl.

Table V. Phenanthrene-9-carboxylic Acids

| No.	Starting material[a]	Substituents	Mp, °C (solvent)	Yield, %	Formula[b]
33	1	1-Cl	316–317 (AcOH)	64	$C_{15}H_9ClO_2$
34	2	2-Cl	240–241.5 (MeOH)[c,d]	83	$C_{15}H_9ClO_2$
34	3	2-Cl	240–241.5 (MeOH)[c-e]	12	$C_{15}H_9ClO_2$
35	3	4-Cl	244–246 (MeOH)[e]	24	$C_{15}H_9ClO_2$
36	4	5-Cl	276–278 (EtOH)[f]	25	$C_{15}H_9ClO_2$
37	5	6-Cl	295–296 (aq EtOH)[g]	94	$C_{15}H_9ClO_2$
38	4	7-Cl	273–274.5 (EtOH)[f]	13	$C_{15}H_9ClO_2$
39	6	8-Cl	188–190 (aq EtOH)	79	$C_{15}H_9ClO_2$
40	7	2-Br	294–296 (C_6H_6–EtOH)	61	$C_{15}H_9BrO_2$
41	8	6-CH$_3$	236–237 (AcOH)[h]	51	$C_{16}H_{12}O_2$
42	9	1,3-Cl$_2$	307–310 (AcOH)	46[i]	$C_{15}H_8Cl_2O_2$
43	10	2,4-Br$_2$	266–268 (C_6H_6)[j]	70	$C_{15}H_8Br_2O_2$
44	11	2,6-Cl$_2$	253–254 (EtOH)	66	$C_{15}H_8Cl_2O_2$
45	12	2,6-Br$_2$	267–268 (dioxane–MeOH)	75	$C_{15}H_8Br_2O_2$
46	13	3,6-Cl$_2$	287.5–288.5 (AcOH)	71	$C_{15}H_8Cl_2O_2$[k]
47	14	5,7-Cl$_2$	288 (C_6H_6–EtOH)	52	$C_{15}H_8Cl_2O_2$
48	15	3-Cl, 6-OCH$_3$	252.5–253.5 (AcOH)	47	$C_{16}H_{11}ClO_3$[l]
49	16	1,3,6-Cl$_3$	311–313 (dioxane–C_6H_6)	62	$C_{15}H_7Cl_3O_2$
50	17	6-Br, 1,3-Cl$_2$	324–326 (dioxane–EtOH)	44[m]	$C_{15}H_7BrCl_2O_2$
51	18	1,3,6-Br$_3$	338–339 (dioxane)	48	$C_{15}H_7Br_3O_2$
52	19	1,3,7-Cl$_3$	>300 (THF–hexane)	37	$C_{15}H_7Cl_3O_2$
53	20	2,3,6-Cl$_3$	296–298 (EtOH–Me$_2$CO)	60	$C_{15}H_7Cl_3O_2$
54	21	6-Br, 2,3-Cl$_2$	297–299 (Me$_2$CO)	53	$C_{15}H_7BrCl_2O_2$
55	22	2,3,6-Br$_3$	307–308 (dioxane)	51	$C_{15}H_7Br_3O_2$[n]
56	23	2,4,6-Cl$_3$	291–292 (C_6H_6–EtOH)	31	$C_{15}H_7Cl_3O_2$
57	24	2,4,7-Cl$_3$	294–296 (AcOH)	55	$C_{15}H_7Cl_3O_2$
58	25	2,5,7-Cl$_3$	305–308 (dioxane)	50	$C_{15}H_7Cl_3O_2$
59	26	3,5,7-Cl$_3$	305–306.5 (C_6H_6)	70	$C_{15}H_7Cl_3O_2$
60	27	3,6,7-Cl$_3$	342 (dioxane)	41	$C_{15}H_7Cl_3O_2$
61	28	6-Cl, 2,3-OCH$_2$O–	305–306 (aq dioxane)	67	$C_{16}H_9ClO_4$
62	29	2,3,6,7-Cl$_4$	[o]		$C_{15}H_6Cl_4O_2$
63	29	2,3,5,6-Cl$_4$	[o]		$C_{15}H_6Cl_4O_2$
64	30	1,2,6,7-Cl$_4$	337–338 (AcOH)	51	$C_{15}H_6Cl_4O_2$
65	31	1,3,5,7-Cl$_4$	310 (EtOH–C_6H_6)	45	$C_{15}H_6Cl_4O_2$
66	32	1,2,3,4-Cl$_4$, 6-CF$_3$	268.5–269 (AcOH)	55	$C_{16}H_5Cl_4F_3O_2$
66a	32a	2,4-(CF$_3$)$_2$	257–258 (AcOH)	67	$C_{17}H_8F_6NO_2$

[a]The nitrocinnamic acids (Table IV) were reduced with alkaline $FeSO_4$ (ref 9) and the resulting amino derivatives were subjected to Pschorr cyclization without purification. [b]All compounds were analyzed for C and H. [c]Lit. mp 233-234° (footnote d, Table IV). [d]The 2-Cl derivatives obtained unambiguously from 2, and as part of an isomer mixture from 3, displayed identical ir spectra. [e]These isomeric acids were separated by fractional crystallization from MeOH, the 4-isomer 35 being the less soluble fraction. [f]Isomer separation effected by fractional crystallization from EtOH with the 5-isomer less soluble. Structural assignment was based on NMR analysis. [g]Lit. mp 291-292° (footnote e, Table IV). [h]Lit. mp 238° [R. Pschorr, *Ber.*, 39, 3106 (1906)]. [i]Also isolated was 3-(2',4'-dichlorobenzylidene)-2-coumaranone. mp 182-182.5°. Anal. ($C_{15}H_8Cl_2O_2$) C, H, Cl, O. [j]Used without analysis. [k]C: calcd, 61.88; found, 61.41. [l]H: calcd, 3.87; found, 4.30. [m]Isolated as a by-product was 3-(2',4'-dichlorobenzylidene-6-bromooxindole, mp 262-263° (C_6H_6-petr ether). Anal. ($C_{15}H_8BrCl_2NO$) C, H, N. [n]H: calcd, 1.52; found, 1.03. [o]The mixture of isomers (**62 and 63**) which resulted from the cyclization of 29 was difficult to separate and was carried through to the bromoacetyl stage (Table VI).

Table VI. 2-Pyridyl 9-Phenanthryl Ketones
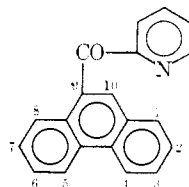
No.	Substituents	Mp, °C (solvent)	Yield, %	Formula	Analyses
67	Unsubstituted[a]	120–120.5 (EtOH)	52	$C_{20}H_{13}NO$	C, H, N
68	2-Br	164–166 (MeOH–Me$_2$CO)	30	$C_{20}H_{12}BrNO$	C, H, N
69	6-Br	182–185 (EtOH)	42	$C_{20}H_{12}BrNO$	C, H, N
70	6-CH$_3$	164.5–166.5 (EtOH)	52	$C_{21}H_{15}NO$	C, H, N
71	1,3-Cl$_2$	202–204 (C$_6$H$_6$–hexane)	42	$C_{20}H_{11}Cl_2NO$	C, H, N
72	2,6-Cl$_2$	194–195 (C$_6$H$_6$–hexane)	60	$C_{20}H_{11}Cl_2NO$	C, H, N
73	2,6-Br$_2$	214–215 (dioxane–MeOH)	68	$C_{20}H_{11}Br_2NO$	C, H, N
74	3,6-Cl$_2$	205–206 (EtOH)	61	$C_{20}H_{11}Cl_2NO$	C, H, N
75	5,7-Cl$_2$	182–183 (C$_6$H$_6$)	25	$C_{20}H_{11}Cl_2NO$	C, H, N
76	1,3,6-Cl$_3$	218–223 (crude)	32	$C_{20}H_{10}Cl_3NO$	*b*
77	6-Br, 1,3-Cl$_2$	226–234 (crude)	23	$C_{20}H_{10}BrCl_2NO$	*b*
78	1,3,7-Cl$_3$	208–210 (C$_6$H$_6$–hexane)	26	$C_{20}H_{10}Cl_3NO$	C, H, N
79	2,3,6-Cl$_3$	253–257 (C$_6$H$_6$)	78	$C_{20}H_{10}Cl_3NO$	C, H, N
80	6-Br, 2,3-Cl$_2$	273–276 (C$_6$H$_6$)	55	$C_{20}H_{10}BrCl_2NO$	C, H, N
81	2,4,6-Cl$_3$	229–233 (EtOH–C$_6$H$_6$)	84	$C_{20}H_{10}Cl_3NO$	*c*
82	2,5,7-Cl$_3$	Indefinite (crude)	59	$C_{20}H_{10}Cl_3NO$	*b*
83	3,6,7-Cl$_3$	242–247 (crude)	55	$C_{20}H_{10}Cl_3NO$	*b*
84	6-Cl, 2,3-OCH$_2$O–	240–241 (dioxane–hexane)	75	$C_{21}H_{12}ClNO_3$	C, H, N
84a	1,2,3,4-Cl$_4$, 6-CF$_3$	178–183 (crude)	50	$C_{21}H_8Cl_4F_3NO$	*b*
84b	2,4-(CF$_3$)$_2$	143–146 (crude)	24	$C_{22}H_{11}F_6NO$	*b*

[a]The starting material, 9-phenanthroic acid, was made by heating commercial 9-cyanophenanthrene with aqueous-methanolic KOH. under reflux for 10 hr. [b]Used without purification. [c]Used without analysis.

Table VII. α-(2-Piperidyl)-9-phenanthrenemethanol Hydrochlorides[a]
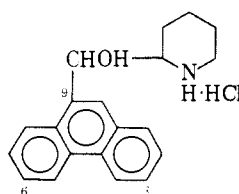
No.	Substituents	Mp, °C (solvent)	Yield, %	Formula	Analyses
85	Unsubstituted	282–283 (EtOH)	50	$C_{20}H_{22}ClNO$	C, H, Cl, N
86	2-Br	303–305 (MeOH–10% HCl)	48	$C_{20}H_{21}BrClNO$	C, H, N
87	6-Br	320–322 (aq EtOH)	43	$C_{20}H_{21}BrClNO$	C, H, N
88	6-CH$_3$	302–303 (MeOH)	56	$C_{21}H_{24}ClNO$	C, H, Cl, N
89	1,3-Cl$_2$	320–322 (MeOH–10% HCl)	36	$C_{20}H_{20}Cl_3NO$	H; C[b]
90	2,6-Cl$_2$	>320 (MeOH)	56	$C_{20}H_{20}Cl_3NO$	C, H, N
91	2,6-Br$_2$	309–310 (EtOH)	45	$C_{20}H_{20}Br_2ClNO$	C, H, N
92	3,6-Cl$_2$	298–300 (MeOH)	40	$C_{20}H_{20}Cl_3NO$	C, H, N
93	5,7-Cl$_2$	312 (C$_6$H$_6$–EtOH)	76	$C_{20}H_{20}Cl_3NO$	C, H, N
94	1,3,6-Cl$_3$	339–342 (EtOH)	37	$C_{20}H_{19}Cl_4NO$	C, H, N
95	6-Br, 1,3-Cl$_2$	334–336 (dioxane–EtOH)	33	$C_{20}H_{18}BrCl_3NO$	C, H, N
96	1,3,7-Cl$_3$	346–348 (MeOH)	41	$C_{20}H_{19}Cl_4NO$	C, H, N
97	2,3,6-Cl$_3$	332–333 (MeOH)	62	$C_{20}H_{19}Cl_4NO$	C, H, N
98	6-Br, 2,3-Cl$_2$	340–342 (MeOH)	58	$C_{20}H_{19}BrCl_3NO$	C, H, N
99	2,4,6-Cl$_3$	324–326 (MeOH–10% HCl)	40	$C_{20}H_{19}Cl_4NO$	C, H, N
100	2,5,7-Cl$_3$	326–327 (EtOH)	36	$C_{20}H_{19}Cl_4NO^c$	C, H, Cl, N
101	3,6,7-Cl$_3$	341–342 (EtOH)	68	$C_{20}H_{19}Cl_4NO$	C, H, Cl, N
102	6-Cl, 2,3-OCH$_2$O–	315 (MeOH)	67	$C_{21}H_{21}Cl_2NO_3$	C, H, N
103	1,2,3,4-Cl$_4$, 6-CF$_3$	316–317 (EtOH–10% HCl)	9	$C_{21}H_{17}Cl_5F_3NO$	C, H, Cl, N
104	2,4-(CF$_3$)$_2$	330–331 (EtOH)	62	$C_{22}H_{20}ClF_6NO$	C, H, F, N

[a]No attempts were made to isolate the two possible racemates. [b]C: calcd, 60.52; found, 61.20. [c]Analyzed as the hemihydrate.

Table VIII. 9-Bromoacetylphenanthrenes

COCH₂Br structure

No.	Substituents	Mp, °C (solvent)	Yield,[b] %	Formula	Analyses
105	1-Cl	96–98 (EtOH)	88	C₁₆H₁₀BrClO	C, H
106	2-Cl	97.5–98.5 (ligroine)	66	C₁₆H₁₀BrClO	C, H
107	2-Br	Indefinite		C₁₆H₁₀Br₂O	a
108	4-Cl	112–113 (ligroine)	74	C₁₆H₁₀BrClO	C, H
109	5-Cl	102–104 (EtOH)	62	C₁₆H₁₀BrClO	C, H
110	6-Cl	125–128 (C₆H₆)[b]	72	C₁₆H₁₀BrClO	
111	7-Cl	132.5–134 (CCl₄)	45	C₁₆H₁₀BrClO	C, H
112	8-Cl	Viscous yellow oil	72	C₁₆H₁₀BrClO	a
113	2,4-Br₂	152–153 (C₆H₆–hexane)	45	C₁₆H₉Br₃O	c
114	2,6-Cl₂	168–169 (C₆H₆–hexane)	82	C₁₆H₉BrCl₂O	c
115	2,6-Br₂	145–148 (C₆H₆–hexane)	39	C₁₆H₉Br₃O	c
116	3,6-Cl₂	150–152 (crude)	87	C₁₆H₉BrCl₂O	a
117	3-Cl, 6-OCH₃	159–160 (EtOAc)	87	C₁₇H₁₂BrClO₂	C, H
118	1,3,6-Cl₃	179.5–180.5 (C₆H₆–hexane)	86	C₁₆H₈BrCl₃O	C, H
119	1,3,6-Br₃	220–221 (C₆H₆)	74	C₁₆H₈Br₄O	C, H
120	2,3,6-Br₃	235–236 (C₆H₆)	73	C₁₆H₈Br₄O	C, H
121	2,4,6-Cl₃	152–157 (crude)	57	C₁₆H₈BrCl₃O	a
122	2,4,7-Cl₃	164–167 (crude)	54	C₁₆H₈BrCl₃O	a
123	2,5,7-Cl₃	164–166 (EtOH–ligroine)	30	C₁₆H₈BrCl₃O	C, H
124	3,5,7-Cl₃	169–170 (EtOH–ligroine)	61	C₁₆H₈BrCl₃O	c
125	2,3,5,6-Cl₄[d]	148–150 (C₆H₆)	17	C₁₆H₇BrCl₄O	c
126	2,3,6,7-Cl₄[d]	202 (C₆H₆)	25	C₁₆H₇BrCl₄O	c
127	1,2,6,7-Cl₄	190–191 (crude)	66	C₁₆H₇BrCl₄O	a
128	1,3,5,7-Cl₄	Indefinite		C₁₆H₇BrCl₄O	a
129	2,4-(CF₃)₂	100–103 (Et₂O–petr ether)	80	C₁₈H₉BrF₆O	c

[a]Used without purification. [b]Lit. mp 126.5–127° [E. May and E. Mosettig, *J. Org. Chem.*, 11, 441 (1946)]. [c]Used without analysis. [d]Isomers **125** and **126** were separated by fractional crystallization from Et₂O with **126** the less soluble isomer. Structural assignment was based on NMR analysis.

Table IX. α-Bromomethyl-9-phenanthrenemethanols

CHOHCH₂Br structure

No.	Substituents	Mp, °C (solvent)	Yield, %	Formula	Analyses
130	2-Cl	175–177 (EtOH)	97	C₁₆H₁₂BrClO	a
131	2-Br	Indefinite		C₁₆H₁₂Br₂O	b
132	4-Cl	149–150 (EtOH)	93	C₁₆H₁₂BrClO	a
133	5-Cl	138–141 (EtOH)	63	C₁₆H₁₂BrClO	a
134	7-Cl	139–141.5 (EtOH)	91	C₁₆H₁₂BrClO	C, H
135	8-Cl	Oil (crude)	90	C₁₆H₁₂BrClO	b
136	2,4-Br₂	172–174 (aq EtOH)	90	C₁₆H₁₁Br₃O	C, H
137	2,6-Cl₂	154–156 (C₆H₆–hexane)	76	C₁₆H₁₁BrCl₂O	a
138	2,6-Br₂	139–141 (C₆H₆–hexane)	93	C₁₆H₁₁Br₃O	a
139	3,6-Cl₂	198–199 (EtOH)	100	C₁₆H₁₁BrCl₂O	C, H
140	3-Cl, 6-OCH₃	173.5–174.5 (EtOH)	82	C₁₇H₁₄BrClO₂	C, H
141	1,3,6-Cl₃	181–182 (C₆H₆–hexane)	69	C₁₆H₁₀BrCl₃O	a
142	1,3,6-Br₃	195–200 (H₂O wash)	89	C₁₆H₁₀Br₄O	b
143	2,3,6-Br₃	212–213 (aq EtOH)	84	C₁₆H₁₀Br₄O	a
144	2,4,6-Cl₃	170–174 (H₂O wash)	68	C₁₆H₁₀BrCl₃O	b
145	2,4,7-Cl₃	190–197 (H₂O wash)	40	C₁₆H₁₀BrCl₃O	b

Table IX (*Continued*)

No.	Substituents	Mp, °C (solvent)	Yield, %	Formula	Analyses
146	2,5,7-Cl$_3$	Indefinite	70	C$_{16}$H$_{10}$BrCl$_3$O	b
147	3,5,7-Cl$_3$	170–172 (H$_2$O wash)	90	C$_{16}$H$_{10}$BrCl$_3$O	b
148	2,3,5,6-Cl$_4$	162–165 (H$_2$O wash)	100	C$_{16}$H$_9$BrCl$_4$O	b
149	2,3,6,7-Cl$_4$	200–202 (H$_2$O wash)	97	C$_{16}$H$_9$BrCl$_4$O	b
150	1,2,6,7-Cl$_4$	200–202 (EtOH)	70	C$_{16}$H$_9$BrCl$_4$O	a
151	1,3,5,7-Cl$_4$	148 (C$_6$H$_6$–hexane)	85	C$_{16}$H$_9$BrCl$_4$O	a
152	2,4-(CF$_3$)$_2$	120–125 (H$_2$O wash)	100	C$_{18}$H$_9$BrF$_6$O	b

[a]Used without analysis. [b]Used without purification.

Table X. α-(Di-n-alkylaminomethyl)-9-phenanthrenemethanol Hydrochlorides

CHOHCH$_2$N(R)$_2$·HCl

No.	Substituents	R	Mp, °C (solvent)	Method[a]	Yield, %	Formula	Analyses
153	1-Cl	Bu	97.5–99.5 (MeOH)	B	34	C$_{24}$H$_{30}$ClNO	C, H, N[b]
154	1-Cl	Hep	166–168 (Me$_2$CO)	B	25	C$_{30}$H$_{43}$Cl$_2$NO	C, H, N
155	2-Cl	Bu	158–159 (Me$_2$CO–Et$_2$O)	A	86	C$_{24}$H$_{31}$Cl$_2$NO	C, H, N
156	2-Cl	Hep	153–155 (Me$_2$CO–petr ether)	A	40	C$_{30}$H$_{43}$Cl$_2$NO	C, H, N
157	2-Br	Bu	217–218 (C$_6$H$_6$–EtOH)	A	41	C$_{24}$H$_{31}$BrClNO	C, H, N
158	4-Cl	Hep	136.5–138 (Me$_2$CO–ligroine)	A	40	C$_{30}$H$_{43}$Cl$_2$NO	C, H, N
159	5-Cl	Bu	164–166 (C$_6$H$_6$–petr ether)	A	36	C$_{24}$H$_{31}$Cl$_2$NO	C, H, N
160	5-Cl	Hep	122–123.5 (Me$_2$CO–petr ether)	A	33	C$_{30}$H$_{43}$Cl$_2$NO	C, H, N
161	6-Cl	Bu	226–227 (EtOH)	B	51	C$_{24}$H$_{31}$Cl$_2$NO	C, H, N
162	6-Cl	Hep	187–188 (EtOH)[c]	B	22	C$_{30}$H$_{43}$Cl$_2$NO	
163	7-Cl	Bu	212–214 (MeOH–petr ether)	A	58	C$_{24}$H$_{31}$Cl$_2$NO	C, H, N
164	7-Cl	Hep	141–143 (Me$_2$CO–petr ether)	A	32	C$_{30}$H$_{43}$Cl$_2$NO	C, H, N
165	8-Cl	Bu	45–46 (C$_6$H$_6$–ligroine)	A	81	C$_{28}$H$_{38}$ClNO$_8$	C, H, N[d]
166	2,4-Br$_2$	Bu	228–230 (aq EtOH)	A	22	C$_{24}$H$_{30}$Br$_2$ClNO	C, H, N
167	2,6-Cl$_2$	Et	220–221 (MeOH–Et$_2$O)	A	41	C$_{20}$H$_{22}$Cl$_3$NO	C, H, N
168	2,6-Cl$_2$	Pr	250–251 (MeOH–Et$_2$O)	A	62	C$_{22}$H$_{26}$Cl$_3$NO	C, H, N
169	2,6-Cl$_2$	Bu	244–245 (MeOH)	A	52	C$_{24}$H$_{30}$Cl$_3$NO	C, H, N
170	2,6-Cl$_2$	Am	235.5–236.5 (MeOH)	A	46	C$_{26}$H$_{34}$Cl$_3$NO	C, H, N[e]
171	2,6-Br$_2$	Pr	249–250 (EtOH)	A	30	C$_{22}$H$_{26}$Br$_2$ClNO	C, H, N
172	2,6-Br$_2$	Bu	249.5–250 (EtOH)	A	31	C$_{24}$H$_{30}$Br$_2$ClNO	C, H, N
173	3,6-Cl$_2$	Hep	187–187.5 (Me$_2$CO)	A	96	C$_{30}$H$_{42}$Cl$_3$NO	C, H, Cl, N
174	3-Cl, 6-OCH$_3$	Bu	194–196 (EtOH)	A	46	C$_{25}$H$_{33}$Cl$_2$NO$_2$	C, H, Cl, N
175	3-Cl, 6-OCH$_3$	Hep	147.5–148.5 (ligroine–Me$_2$CO)	A	40	C$_{31}$H$_{45}$Cl$_2$NO$_2$	C, Cl, N; H[f]
176	1,3,6-Cl$_3$	Et	263.5–265 (EtOH)	A	20	C$_{20}$H$_{21}$Cl$_4$NO	C, H, N
177	1,3,6-Cl$_3$	Pr	268.5–269.5 (EtOH)	A	41	C$_{22}$H$_{25}$Cl$_4$NO	C, H, N
178	1,3,6-Cl$_3$	Bu	267–267.5 (EtOH–hexane)	A	18	C$_{24}$H$_{29}$Cl$_4$NO	C, H, N
179	1,3,6-Br$_3$	Bu	273–273.5 (EtOH)	A	23	C$_{24}$H$_{29}$Br$_3$ClNO	C, H, N
180	2,3,6-Br$_3$	Bu	252–253.5 (EtOH)	A	20	C$_{24}$H$_{29}$Br$_3$ClNO	C, H, N
181	2,4,6-Cl$_3$	Bu	231–234 (C$_6$H$_6$)	A	22	C$_{24}$H$_{29}$Cl$_4$NO	C, H, N
182	2,4,7-Cl$_3$	Bu	250–252 (C$_6$H$_6$)	A	41	C$_{24}$H$_{29}$Cl$_4$NO	C, H, N
183	2,5,7-Cl$_3$	Bu	241–242 (Me$_2$CO)	A	46	C$_{24}$H$_{29}$Cl$_4$NO	C, H, N
184	3,5,7-Cl$_3$	Bu	224–225 (aq EtOH)	A	50	C$_{24}$H$_{29}$Cl$_4$NO	C, H, N
185	2,3,5,6-Cl$_4$	Bu	253–254 (EtOH–C$_6$H$_6$)	A	63	C$_{24}$H$_{28}$Cl$_5$NO	C, H, N
186	2,3,6,7-Cl$_4$	Bu	278 (EtOH–C$_6$H$_6$)	A	42	C$_{24}$H$_{28}$Cl$_5$NO	C, H, N
187	1,2,6,7-Cl$_4$	Bu	254–255 (EtOH–2% HCl)	A	54	C$_{24}$H$_{28}$Cl$_5$NO	C, H, N
188	1,3,5,7-Cl$_4$	Bu	264–265 (EtOH–C$_6$H$_6$)	A	76	C$_{24}$H$_{28}$Cl$_5$NO	C, H, N
189	2,4-(CF$_3$)$_2$	Me	263–264 (EtOH)	B	40	C$_{20}$H$_{18}$ClF$_6$NO	C, H, F, N
190	2,4-(CF$_3$)$_2$	Pr	237–238 (C$_6$H$_6$)	A	54	C$_{24}$H$_{26}$ClF$_6$NO	C, H, F, N

[a]Methods A and B used bromohydrins (Table VII) and bromo ketones (Table VI), respectively, as starting materials. [b]Analyzed as free base. [c]Lit. mp 184–186° (footnote b, Table VI). [d]Analyzed as the tartrate monohydrate. [e]Analyzed as the hemihydrate. [f]H: calcd, 8.48; found, 7.89.

pounds have a 2-substituent in common and seven of them are substituted at both 2 and 4. All seven, including the best five (60–100% curative at 10 mg/kg), have at least one other moiety at positions 6 and/or 7. Nine of the compounds have R = 2-piperidyl although the most effective derivative of all has R = CH$_2$NPr$_2$.

The difference between the compounds at the top of Table II and the unsubstituted prototypes, added to the bottom for comparison, is quite dramatic.

A number of our 9-phenanthrenemethanols were also evaluated in the *Plasmodium gallinaceum* chick screen. Although several were curative and most were active (Table III), they were considerably less impressive in this test than in the *P. berghei* screen (see paragraph at end of paper regarding supplementary material).

Experimental Section[11]

Details of the preparation of compounds 1–199 are given in Tables IV–X.

3,6-Bis(trifluoromethyl)phenanthrene-9-acetic Acid (194). The reaction between 3,6-bis(trifluoromethyl)phenanthrene-9-carboxylic acid chloride (**192**) (from 5 g of the corresponding phenanthroic acid and 50 ml of SOCl$_2$) and 800 ml of ethereal CH$_2$N$_2$ (from 42.5 g of *N*-nitrosomethylurea), carried out in the usual manner,[12] gave 4.5 g (88%) of the diazo ketone **193**, mp 151–152°. A solution of the latter (used without purification) in 60 ml of warm dioxane was added, in a single portion, to a stirred mixture of 6 g of Ag$_2$O, 9 g of Na$_2$S$_2$O$_3$, 15 g of Na$_2$CO$_3$, and 350 ml of H$_2$O at 40°. The mixture was heated under reflux overnight, filtered hot, and allowed to cool. The resulting solid was crystallized from HOAc to give 4.2 g (95%) of **194** as a white solid, mp 248–250°. An additional crystallization from HOAc provided an analytical sample, mp 255–256°. Anal. (C$_{18}$H$_{10}$F$_6$O$_2$) C, H.

3,6-Bis(trifluoromethyl)-α-(di-*n*-propylaminomethyl)-9-phenanthreneethanol Hydrochloride (199). 194 was converted, via the usual sequence, to acid chloride **195** (93%, mp 154–156°), diazo ketone **196** (not isolated), and bromomethyl ketone **197** (78%, mp 196–198°).

A mixture of 2 g (0.0044) of **197**, 150 ml of *i*-PrOH, and 25 ml of molten Al(*i*-OPr)$_3$ was slowly distilled until Me$_2$CO was no longer evident in the distillate (ca. 5 hr). The solvent was removed under reduced pressure and the residue was treated with 200 ml of 10% HCl and extracted with Et$_2$O. The extract was washed with 10% K$_2$CO$_3$, dried (MgSO$_4$), concentrated, and diluted with petroleum ether (bp 20–40°) to give 1.65 g (83%) of the bromohydrin **198** as pale yellow solid, mp 115–120°.

A mixture of 1.5 g (0.0033 mol) of **198** and 10 g of Pr$_2$NH was heated at 110–115°, under N$_2$, overnight, and allowed to cool. Pr$_2$NH·HBr was filtered and excess Pr$_2$NH was distilled off under reduced pressure. The residue was extracted with petroleum ether (bp 20–40°) and the extract was evaporated to dryness. Treatment of the residue, in Et$_2$O, with Et$_2$O–HCl provided 0.9 g (54%) of **199** as white solid, mp 205–207° (Me$_2$CO–ligroine). Anal. (C$_{25}$H$_{28}$ClF$_6$NO) C, H, F, N.

References and Notes

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(11) Satisfactory spectra were obtained where required for structural confirmation: ir as Nujol mulls on Perkin-Elmer 137B Infracord; NMR (by Sadtler Research Laboratories, Phila., Pa.) on Varian A-60A. Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. Where analyses (Micro-Analysis, Inc., Wilmington, Del.) are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

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