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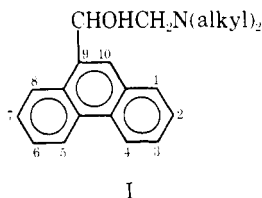
Antimalarial Phenanthrene Amino Alcohols. 3. Halogen-Containing 9-Phenanthrenemethanols¹

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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 berghoi* in the mouse. Some structural requirements for optimal efficacy are considered.

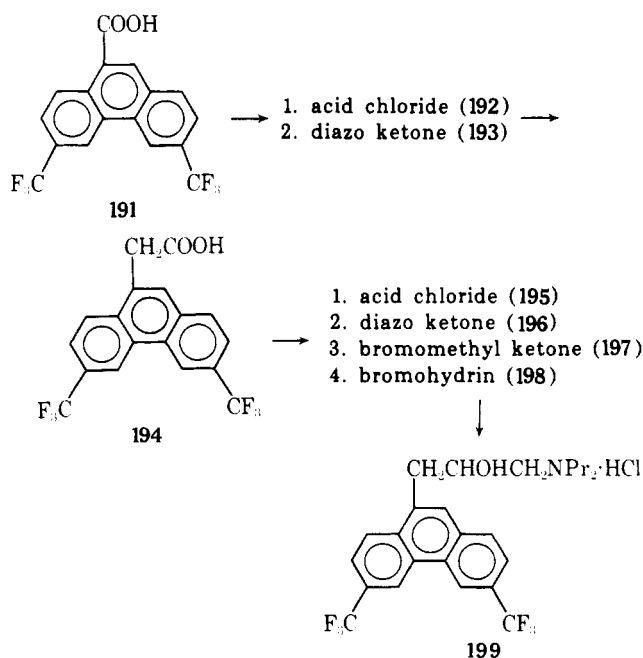
The recent emergence of drug-refractory *falciparum* malaria²⁻⁴ sparked various promising chemotherapeutic leads, dormant since World War II. Prominent among these early leads was the significant avian antiplasmodial activity of the 9-phenanthrenemethanols (I) and particularly those with a nuclear chlorine or bromine atom.^{2b,5,6}



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.

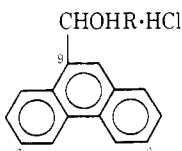
Introduction of a second halogen atom produced a much improved group of compounds, some of which were curative (1/5) at 20 mg/kg and most of which were active at 10 mg/kg. The favored positions were 2,4 and 2,6. The dibromo compounds were a bit more active than the corresponding dichloro derivatives.

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 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.

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).

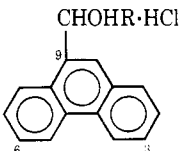
Table II has collected, from the three papers in this series, all of the compounds which are curative at concentrations of 20 mg/kg or less. These compounds are presented in order of decreasing activity so that an optimal substitution pattern begins to emerge from the upper portion of the table. Thus, 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)

<div style="text-align: center;">  </div>			Δ MST or C ^c at dose, mg/kg							
No.	Substituents	R ^b	5	10	20	40	80	160	320	640
153	1-Cl	CH ₂ NBu ₂			2.1	4.7	5.7	10.9	1C	2C
154	1-Cl	CH ₂ NHep ₂			0.5	1.5	2.1	5.3	7.3	8.7
155	2-Cl	CH ₂ NBu ₂			1.1	3.3	7.5	13.3	1C	5C
156	2-Cl	CH ₂ NHep ₂			2.2	5.6	6.2	11.0	12.6	5C
157	2-Br	CH ₂ NBu 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 ₂ NHep ₂			0.7	3.1	3.3	4.3	7.3	2C
159	5-Cl	CH ₂ NBu ₂			0.3	0.5	1.5	4.9	9.1	2C
160	5-Cl	CH ₂ NHep ₂			1.3	4.9	7.1	8.9	13.2	5C
161	6-Cl	CH ₂ NBu ₂			0.3	0.7	4.7	8.1	10.1	2C
162	6-Cl	CH ₂ NHep 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 ₂ NBu ₂			0.3	0.7	1.1	7.1	7.9	14.1
164	7-Cl	CH ₂ NHep ₂			2.1	4.7	7.5	9.3	1C	3C
165	8-Cl	CH ₂ NBu 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 ₂ NBu ₂	1.9	9.5	11.5	4C	5C	5C	5C	5C
167	2,6-Cl ₂	CH ₂ NEt ₂	1.3	9.7	1C	3C	5C	5C	5C	5C
168	2,6-Cl ₂	CH ₂ NPr ₂	1.9	9.3	13.5	3C	5C	5C	5C	5C
169	2,6-Cl ₂	CH ₂ NBu ₂		2.9	10.7	1C	3C	5C	5C	5C
170	2,6-Cl ₂	CH ₂ NAm 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 ₂ NPr ₂		6.5	1C	5C	5C	5C	5C	5C
172	2,6-Br ₂	CH ₂ NBu 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 ₂ NHep 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 ₂ NBu ₂			0.3	0.5	0.5	1.1	6.9	10.1
175	3-Cl, 6-OCH ₃	CH ₂ NHep 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 ₂ NEt ₂	5.7	8.8	1C	1C	5C	5C	5C	5C
177	1,3,6-Cl ₃	CH ₂ NPr ₂	4.1	12.1	2C	5C	5C	5C	5C	5C
178	1,3,6-Cl ₃	CH ₂ NBu 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 ₂ NBu 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 ₂ NBu 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 ₂ NBu 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 ₂ NBu ₂	4.5	8.1	12.1	3C	5C	5C	5C	5C
183	2,5,7-Cl ₃	CH ₂ NBu 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 ₂ NBu ₂		5.3	11.7	5C	5C	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 ₂ O ⁻	Pip		0.1	0.3	0.3	0.5	3.9	9.5	3C
185	2,3,5,6-Cl ₄	CH ₂ NBu ₂		7.5	1C	3C	5C	5C	5C	5C
186	2,3,6,7-Cl ₄	CH ₂ NBu ₂		7.7	2C	5C	5C	5C	5C	5C
187	1,2,6,7-Cl ₄	CH ₂ NBu ₂		3.3	4.9	6.9	11.9	15.1	5C	5C
188	1,3,5,7-Cl ₄	CH ₂ NBu ₂	3.9	8.7	14.1	2C	5C	5C		
189	2,4-(CF ₃) ₂	CH ₂ NMe ₂	0.7	9.5	15.1	2C	4C	5C	5C	5C
190	2,4-(CH ₃) ₂	CH ₂ NPr 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		

^aTests 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. ^bPip = 2-piperidyl. ^c Δ MST, mean survival time over controls (6.2 \pm 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)

		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

^aTable I, footnote a. ^bPip = 2-piperidyl. ^cΔMST at 2.5 and 1.25 mg/kg = 12.1 and 6.9 days, respectively. ^dOne and two toxic deaths at 320 and 640 mg/kg, respectively. ^eTable I, footnote c. ^fE. L. May and E. Mosettig, *J. Org. Chem.*, 11, 10 (1946).

Table IV. Nitro-α-phenylcinnamic Acids^a

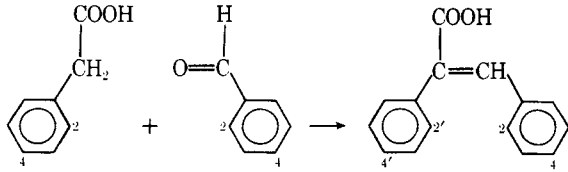
									
No.	Phenylcinnamic acid	Phenylacetic acid	Benz-aldehyde	Meth-od	Temp, °C	Mp, °C (solvent)	Yield, %	Formula	Analyses ^c
1	2-Cl, 2'-NO ₂	2-NO ₂ ^b	2-Cl ^b	B	100	216–218 (EtOH)	76	C ₁₅ H ₁₀ ClNO ₄	C, H
2	5-Cl, 2'-NO ₂	Unsubstituted	5-Cl, 2-NO ₂ ^b	B	100	191–192.5 ^d (EtOH)	79	C ₁₅ H ₁₀ ClNO ₄	C, H

Table IV (Continued)

No.	Phenylcinnamic acid	Phenylacetic acid	Benzaldehyde	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 ^c (EtOH)	45	C ₁₅ H ₁₀ ClNO ₄	<i>h</i>
6	2'-Cl, 2-NO ₂	2-Cl ^c	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 ^e	2-NO ₂ ^b	A	65	192-200 (crude)	80	C ₁₆ H ₁₃ NO ₄	<i>h</i>
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 ^e	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 ⁱ	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	<i>h</i>
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 ⁱ	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 ⁱ	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 , ⁱ 2-NO ₂	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 ^e	4,5-Cl ₂ , ⁱ 2-NO ₂	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 ^e	4,5-Br ₂ , ⁱ 2-NO ₂	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 ⁱ	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 , ⁱ 2-NO ₂	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, ^b 2-NO ₂	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 ^e	4,5-Cl ₂ , ⁱ 2-NO ₂	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 , ⁱ 2-NO ₂	2,3-Cl ₂ ⁱ	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 , ⁱ 2-NO ₂	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 ⁱ	B	80	197-200 (Et ₂ O-petr ether)	81	C ₁₇ H ₅ F ₆ NO ₄	<i>h</i>

^aThe 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 Et₃N (method A), K₂CO₃ (method B), or a mixture of K₂CO₃ and pyridine (method C).

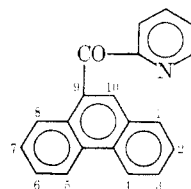
Table IV (Continued)

^bAldrich Chemical Co., Milwaukee, Wis. ^cAnalyses of the indicated elements were within $\pm 0.4\%$ of theory except as noted. ^dLit. mp 183–184° [K. Schofield and T. Swain, *J. Chem. Soc.*, 2393 (1949)]. ^eLit. mp 186–186.5° [P. Nylen, *Ber.*, 53, 158 (1920)]. ^fL. C. Behr, *J. Am. Chem. Soc.*, 76, 3678 (1954). ^gResearch Organic/Inorganic Chemical Corp., Sun Valley, Calif. ^hUsed without analysis. ⁱDistillation Products Industries, Rochester, N.Y. ^jB. Bogoslovskii and T. Yakovenko, *Zh. Obshch. Khim.*, 24, 1043 (1954). ^kD. P. Spalding, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, 68, 1598 (1946). ^lReference 10. ^mReference 9. ⁿN: calcd, 4.14; found, 4.63. ^oPrepared from 3,5-dichlorobenzoic acid (Aldrich) via the method described for 4-trifluoromethoxyphenylacetic acid in ref 9: mp 113–114° (ligroine). Anal. (C₈H₆Cl₂O₂) C, H, Cl. ^pL. Simet, *J. Org. Chem.*, 28, 3580 (1963). ^qPrepared 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. (C₇H₂Cl₄O) Cl.

Table V. Phenanthrene-9-carboxylic Acids

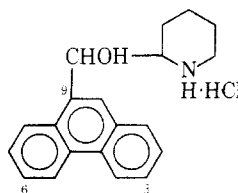
No.	Starting material ^a	Substituents	Mp, °C (solvent)	Yield, %	Formula ^b
33	1	1-Cl	316–317 (AcOH)	64	C ₁₅ H ₉ ClO ₂
34	2	2-Cl	240–241.5 (MeOH) ^{c, d}	83	C ₁₅ H ₉ ClO ₂
34	3	2-Cl	240–241.5 (MeOH) ^{c-e}	12	C ₁₅ H ₉ ClO ₂
35	3	4-Cl	244–246 (MeOH) ^e	24	C ₁₅ H ₉ ClO ₂
36	4	5-Cl	276–278 (EtOH) ^f	25	C ₁₅ H ₉ ClO ₂
37	5	6-Cl	295–296 (aq EtOH) ^g	94	C ₁₅ H ₉ ClO ₂
38	4	7-Cl	273–274.5 (EtOH) ^f	13	C ₁₅ H ₉ ClO ₂
39	6	8-Cl	188–190 (aq EtOH)	79	C ₁₅ H ₉ ClO ₂
40	7	2-Br	294–296 (C ₆ H ₆ –EtOH)	61	C ₁₅ H ₉ BrO 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 ₈ Cl ₂ O ₂
43	10	2,4-Br ₂	266–268 (C ₆ H ₆) ^j	70	C ₁₅ H ₈ Br ₂ O ₂
44	11	2,6-Cl ₂	253–254 (EtOH)	66	C ₁₅ H ₈ Cl ₂ O ₂
45	12	2,6-Br ₂	267–268 (dioxane–MeOH)	75	C ₁₅ H ₈ Br ₂ O ₂
46	13	3,6-Cl ₂	287.5–288.5 (AcOH)	71	C ₁₅ H ₈ Cl ₂ O ₂ ^k
47	14	5,7-Cl ₂	288 (C ₆ H ₆ –EtOH)	52	C ₁₅ H ₈ Cl ₂ O 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 ₆ H ₆)	62	C ₁₅ H ₇ Cl ₃ O ₂
50	17	6-Br, 1,3-Cl ₂	324–326 (dioxane–EtOH)	44 ^m	C ₁₅ H ₇ BrCl ₂ O ₂
51	18	1,3,6-Br ₃	338–339 (dioxane)	48	C ₁₅ H ₇ Br ₃ O ₂
52	19	1,3,7-Cl ₃	> 300 (THF–hexane)	37	C ₁₅ H ₇ Cl ₃ O ₂
53	20	2,3,6-Cl ₃	296–298 (EtOH–Me ₂ CO)	60	C ₁₅ H ₇ Cl ₃ O ₂
54	21	6-Br, 2,3-Cl ₂	297–299 (Me ₂ CO)	53	C ₁₅ H ₇ BrCl ₂ O ₂
55	22	2,3,6-Br ₃	307–308 (dioxane)	51	C ₁₅ H ₇ Br ₃ O ₂ ⁿ
56	23	2,4,6-Cl ₃	291–292 (C ₆ H ₆ –EtOH)	31	C ₁₅ H ₇ Cl ₃ O ₂
57	24	2,4,7-Cl ₃	294–296 (AcOH)	55	C ₁₅ H ₇ Cl ₃ O ₂
58	25	2,5,7-Cl ₃	305–308 (dioxane)	50	C ₁₅ H ₇ Cl ₃ O ₂
59	26	3,5,7-Cl ₃	305–306.5 (C ₆ H ₆)	70	C ₁₅ H ₇ Cl ₃ O ₂
60	27	3,6,7-Cl ₃	342 (dioxane)	41	C ₁₅ H ₇ Cl ₃ O ₂
61	28	6-Cl, 2,3-OCH ₂ O–	305–306 (aq dioxane)	67	C ₁₆ H ₉ ClO ₄
62	29	2,3,6,7-Cl ₄	o		C ₁₅ H ₆ Cl ₄ O ₂
63	29	2,3,5,6-Cl ₄	o		C ₁₅ H ₆ Cl ₄ O ₂
64	30	1,2,6,7-Cl ₄	337–338 (AcOH)	51	C ₁₅ H ₆ Cl ₄ O ₂
65	31	1,3,5,7-Cl ₄	310 (EtOH–C ₆ H ₆)	45	C ₁₅ H ₆ Cl ₄ O ₂
66	32	1,2,3,4-Cl ₄ , 6-CF ₃	268.5–269 (AcOH)	55	C ₁₆ H ₅ Cl ₄ F ₃ O ₂
66a	32a	2,4-(CF ₃) ₂	257–258 (AcOH)	67	C ₁₇ H ₈ F ₆ NO ₂

^aThe nitrocinnamic acids (Table IV) were reduced with alkaline FeSO₄ (ref 9) and the resulting amino derivatives were subjected to Pschorr cyclization without purification. ^bAll compounds were analyzed for C and H. ^cLit. mp 233–234° (footnote d, Table IV). ^dThe 2-Cl derivatives obtained unambiguously from 2, and as part of an isomer mixture from 3, displayed identical IR spectra. ^eThese isomeric acids were separated by fractional crystallization from MeOH, the 4-isomer 35 being the less soluble fraction. ^fIsomer separation effected by fractional crystallization from EtOH with the 5-isomer less soluble. Structural assignment was based on NMR analysis. ^gLit. mp 291–292° (footnote e, Table IV). ^hLit. mp 238° [R. Pschorr, *Ber.*, 39, 3106 (1906)]. ⁱAlso isolated was 3-(2',4'-dichlorobenzylidene)-2-coumaranone, mp 182–182.5°. Anal. (C₁₅H₈Cl₂O₂) C, H, Cl, O. ^jUsed without analysis. ^kC: calcd, 61.88; found, 61.41. ^lH: calcd, 3.87; found, 4.30. ^mIsolated as a by-product was 3-(2',4'-dichlorobenzylidene)-6-bromocoumarone, mp 262–263° (C₆H₆–petr ether). Anal. (C₁₅H₇BrCl₂NO) C, H, N. ⁿH: calcd, 1.52; found, 1.03. ^oThe 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 ₂ NO	C, H, N
72	2,6-Cl ₂	194–195 (C ₆ H ₆ –hexane)	60	C ₂₀ H ₁₁ Cl ₂ NO	C, H, N
73	2,6-Br ₂	214–215 (dioxane–MeOH)	68	C ₂₀ H ₁₁ Br ₂ NO	C, H, N
74	3,6-Cl ₂	205–206 (EtOH)	61	C ₂₀ H ₁₁ Cl ₂ NO	C, H, N
75	5,7-Cl ₂	182–183 (C ₆ H ₆)	25	C ₂₀ H ₁₁ Cl ₂ NO	C, H, N
76	1,3,6-Cl ₃	218–223 (crude)	32	C ₂₀ H ₁₀ Cl ₃ NO	<i>b</i>
77	6-Br, 1,3-Cl ₂	226–234 (crude)	23	C ₂₀ H ₁₀ BrCl ₂ NO	<i>b</i>
78	1,3,7-Cl ₃	208–210 (C ₆ H ₆ –hexane)	26	C ₂₀ H ₁₀ Cl ₃ NO	C, H, N
79	2,3,6-Cl ₃	253–257 (C ₆ H ₆)	78	C ₂₀ H ₁₀ Cl ₃ NO	C, H, N
80	6-Br, 2,3-Cl ₂	273–276 (C ₆ H ₆)	55	C ₂₀ H ₁₀ BrCl ₂ NO	C, H, N
81	2,4,6-Cl ₃	229–233 (EtOH–C ₆ H ₆)	84	C ₂₀ H ₁₀ Cl ₃ NO	<i>c</i>
82	2,5,7-Cl ₃	Indefinite (crude)	59	C ₂₀ H ₁₀ Cl ₃ NO	<i>b</i>
83	3,6,7-Cl ₃	242–247 (crude)	55	C ₂₀ H ₁₀ Cl ₃ NO	<i>b</i>
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 ₈ Cl ₄ F ₃ NO	<i>b</i>
84b	2,4-(CF ₃) ₂	143–146 (crude)	24	C ₂₂ H ₁₁ F ₆ NO	<i>b</i>

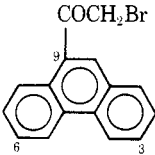
^aThe starting material, 9-phenanthroic acid, was made by heating commercial 9-cyanophenanthrene with aqueous-methanolic KOH, under reflux for 10 hr. ^bUsed without purification. ^cUsed without analysis.

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 ₃ NO	H; C ^b
90	2,6-Cl ₂	>320 (MeOH)	56	C ₂₀ H ₂₀ Cl ₃ NO	C, H, N
91	2,6-Br ₂	309–310 (EtOH)	45	C ₂₀ H ₂₀ Br ₂ ClNO	C, H, N
92	3,6-Cl ₂	298–300 (MeOH)	40	C ₂₀ H ₂₀ Cl ₃ NO	C, H, N
93	5,7-Cl ₂	312 (C ₆ H ₆ –EtOH)	76	C ₂₀ H ₂₀ Cl ₃ NO	C, H, N
94	1,3,6-Cl ₃	339–342 (EtOH)	37	C ₂₀ H ₁₉ Cl ₄ NO	C, H, N
95	6-Br, 1,3-Cl ₂	334–336 (dioxane–EtOH)	33	C ₂₀ H ₁₉ BrCl ₃ NO	C, H, N
96	1,3,7-Cl ₃	346–348 (MeOH)	41	C ₂₀ H ₁₉ Cl ₄ NO	C, H, N
97	2,3,6-Cl ₃	332–333 (MeOH)	62	C ₂₀ H ₁₉ Cl ₄ NO	C, H, N
98	6-Br, 2,3-Cl ₂	340–342 (MeOH)	58	C ₂₀ H ₁₉ BrCl ₃ NO	C, H, N
99	2,4,6-Cl ₃	324–326 (MeOH–10% HCl)	40	C ₂₀ H ₁₉ Cl ₄ NO	C, H, N
100	2,5,7-Cl ₃	326–327 (EtOH)	36	C ₂₀ H ₁₉ Cl ₄ NO ^c	C, H, Cl, N
101	3,6,7-Cl ₃	341–342 (EtOH)	68	C ₂₀ H ₁₉ Cl ₄ NO	C, H, Cl, N
102	6-Cl, 2,3-OCH ₂ O–	315 (MeOH)	67	C ₂₁ H ₂₁ Cl ₂ NO 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 ₅ F ₃ NO	C, H, Cl, N
104	2,4-(CF ₃) ₂	330–331 (EtOH)	62	C ₂₂ H ₂₀ ClF ₆ NO	C, H, F, N

^aNo attempts were made to isolate the two possible racemates. ^bC: calcd, 60.52; found, 61.20. ^cAnalyzed as the hemihydrate.

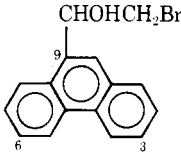
Table VIII. 9-Bromoacetylphenanthrenes



No.	Substituents	Mp, °C (solvent)	Yield, ^b %	Formula	Analyses
105	1-Cl	96-98 (EtOH)	88	C ₁₆ H ₁₀ BrClO	C, H
106	2-Cl	97.5-98.5 (ligroine)	66	C ₁₆ H ₁₀ BrClO	C, H
107	2-Br	Indefinite		C ₁₆ H ₁₀ Br ₂ O	<i>a</i>
108	4-Cl	112-113 (ligroine)	74	C ₁₆ H ₁₀ BrClO	C, H
109	5-Cl	102-104 (EtOH)	62	C ₁₆ H ₁₀ BrClO	C, H
110	6-Cl	125-128 (C ₆ H ₆) ^b	72	C ₁₆ H ₁₀ BrClO	
111	7-Cl	132.5-134 (CCl ₄)	45	C ₁₆ H ₁₀ BrClO	C, H
112	8-Cl	Viscous yellow oil	72	C ₁₆ H ₁₀ BrClO	<i>a</i>
113	2,4-Br ₂	152-153 (C ₆ H ₆ -hexane)	45	C ₁₆ H ₈ Br ₃ O	<i>c</i>
114	2,6-Cl ₂	168-169 (C ₆ H ₆ -hexane)	82	C ₁₆ H ₈ BrCl ₂ O	<i>c</i>
115	2,6-Br ₂	145-148 (C ₆ H ₆ -hexane)	39	C ₁₆ H ₈ Br ₃ O	<i>c</i>
116	3,6-Cl ₂	150-152 (crude)	87	C ₁₆ H ₈ BrCl ₂ O	<i>a</i>
117	3-Cl, 6-OCH ₃	159-160 (EtOAc)	87	C ₁₇ H ₁₂ BrClO ₂	C, H
118	1,3,6-Cl ₃	179.5-180.5 (C ₆ H ₆ -hexane)	86	C ₁₆ H ₈ BrCl ₃ O	C, H
119	1,3,6-Br ₃	220-221 (C ₆ H ₆)	74	C ₁₆ H ₈ Br ₄ O	C, H
120	2,3,6-Br ₃	235-236 (C ₆ H ₆)	73	C ₁₆ H ₈ Br ₄ O	C, H
121	2,4,6-Cl ₃	152-157 (crude)	57	C ₁₆ H ₈ BrCl ₃ O	<i>a</i>
122	2,4,7-Cl ₃	164-167 (crude)	54	C ₁₆ H ₈ BrCl ₃ O	<i>a</i>
123	2,5,7-Cl ₃	164-166 (EtOH-ligroine)	30	C ₁₆ H ₈ BrCl ₃ O	C, H
124	3,5,7-Cl ₃	169-170 (EtOH-ligroine)	61	C ₁₆ H ₈ BrCl ₃ O	<i>c</i>
125	2,3,5,6-Cl ₄ ^d	148-150 (C ₆ H ₆)	17	C ₁₆ H ₇ BrCl ₄ O	<i>c</i>
126	2,3,6,7-Cl ₄ ^d	202 (C ₆ H ₆)	25	C ₁₆ H ₇ BrCl ₄ O	<i>c</i>
127	1,2,6,7-Cl ₄	190-191 (crude)	66	C ₁₆ H ₇ BrCl ₄ O	<i>a</i>
128	1,3,5,7-Cl ₄	Indefinite		C ₁₆ H ₇ BrCl ₄ O	<i>a</i>
129	2,4-(CF ₃) ₂	100-103 (Et ₂ O-petr ether)	80	C ₁₆ H ₈ BrF ₆ O	<i>c</i>

^aUsed without purification. ^bLit. mp 126.5-127° [E. May and E. Mosettig, *J. Org. Chem.*, 11, 441 (1946)]. ^cUsed without analysis.^dIsomers 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

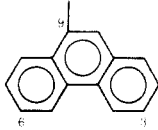


No.	Substituents	Mp, °C (solvent)	Yield, %	Formula	Analyses
130	2-Cl	175-177 (EtOH)	97	C ₁₆ H ₁₂ BrClO	<i>a</i>
131	2-Br	Indefinite		C ₁₆ H ₁₂ Br ₂ O	<i>b</i>
132	4-Cl	149-150 (EtOH)	93	C ₁₆ H ₁₂ BrClO	<i>a</i>
133	5-Cl	138-141 (EtOH)	63	C ₁₆ H ₁₂ BrClO	<i>a</i>
134	7-Cl	139-141.5 (EtOH)	91	C ₁₆ H ₁₂ BrClO	C, H
135	8-Cl	Oil (crude)	90	C ₁₆ H ₁₂ BrClO	<i>b</i>
136	2,4-Br ₂	172-174 (aq EtOH)	90	C ₁₆ H ₁₁ Br ₃ O	C, H
137	2,6-Cl ₂	154-156 (C ₆ H ₆ -hexane)	76	C ₁₆ H ₁₁ BrCl ₂ O	<i>a</i>
138	2,6-Br ₂	139-141 (C ₆ H ₆ -hexane)	93	C ₁₆ H ₁₁ Br ₃ O	<i>a</i>
139	3,6-Cl ₂	198-199 (EtOH)	100	C ₁₆ H ₁₁ BrCl ₂ O	C, H
140	3-Cl, 6-OCH ₃	173.5-174.5 (EtOH)	82	C ₁₇ H ₁₄ BrClO ₂	C, H
141	1,3,6-Cl ₃	181-182 (C ₆ H ₆ -hexane)	69	C ₁₆ H ₁₀ BrCl ₃ O	<i>a</i>
142	1,3,6-Br ₃	195-200 (H ₂ O wash)	89	C ₁₆ H ₁₀ Br ₄ O	<i>b</i>
143	2,3,6-Br ₃	212-213 (aq EtOH)	84	C ₁₆ H ₁₀ Br ₄ O	<i>a</i>
144	2,4,6-Cl ₃	170-174 (H ₂ O wash)	68	C ₁₆ H ₁₀ BrCl ₃ O	<i>b</i>
145	2,4,7-Cl ₃	190-197 (H ₂ O wash)	40	C ₁₆ H ₁₀ BrCl ₃ O	<i>b</i>

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	<i>b</i>
147	3,5,7-Cl ₃	170–172 (H ₂ O wash)	90	C ₁₆ H ₁₀ BrCl ₃ O	<i>b</i>
148	2,3,5,6-Cl ₄	162–165 (H ₂ O wash)	100	C ₁₆ H ₈ BrCl ₄ O	<i>b</i>
149	2,3,6,7-Cl ₄	200–202 (H ₂ O wash)	97	C ₁₆ H ₈ BrCl ₄ O	<i>b</i>
150	1,2,6,7-Cl ₄	200–202 (EtOH)	70	C ₁₆ H ₈ BrCl ₄ O	<i>a</i>
151	1,3,5,7-Cl ₄	148 (C ₆ H ₆ –hexane)	85	C ₁₆ H ₈ BrCl ₄ O	<i>a</i>
152	2,4-(CF ₃) ₂	120–125 (H ₂ O wash)	100	C ₁₈ H ₈ BrF ₆ O	<i>b</i>

^aUsed without analysis. ^bUsed without purification.**Table X.** α -(Di-*n*-alkylaminomethyl)-9-phenanthrenemethanol Hydrochlorides

<div style="text-align: center;"> $\text{CHOHCH}_2\text{N(R)}_2 \cdot \text{HCl}$  </div>							
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

^aMethods A and B used bromohydrins (Table VII) and bromo ketones (Table VI), respectively, as starting materials. ^bAnalyzed as free base. ^cLit. mp 184–186° (footnote *b*, Table VI). ^dAnalyzed as the tartrate monohydrate. ^eAnalyzed as the hemihydrate. ^fH: 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 = CH₂NPr₂.

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 Section¹¹

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 SOCl₂) and 800 ml of ethereal CH₂N₂ (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 Ag₂O, 9 g of Na₂S₂O₃, 15 g of Na₂CO₃, and 350 ml of H₂O 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. (C₁₈H₁₀F₆O₂) 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 Me₂CO 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 Et₂O. The extract was washed with 10% K₂CO₃, dried (MgSO₄), 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 Pr₂NH was heated at 110–115°, under N₂, overnight, and allowed to cool. Pr₂NH·HBr was filtered and excess Pr₂NH 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 Et₂O, with Et₂O·HCl provided 0.9 g (54%) of 199 as white solid, mp 205–207° (Me₂CO-ligroine). Anal. (C₂₅H₂₈ClF₆NO) C, H, F, N.

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Supplementary Material Available. Table III which lists the blood schizonticidal antimalarial activities of the phenanthrene amino alcohols synthesized in this study against *P. gallinaceum* (chick) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St. N.W., Washington, D.C. 20036. Remit check or money order for \$4.00 for photocopy or \$2.50 for microfiche, referring to code number JMED-75-1011.

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