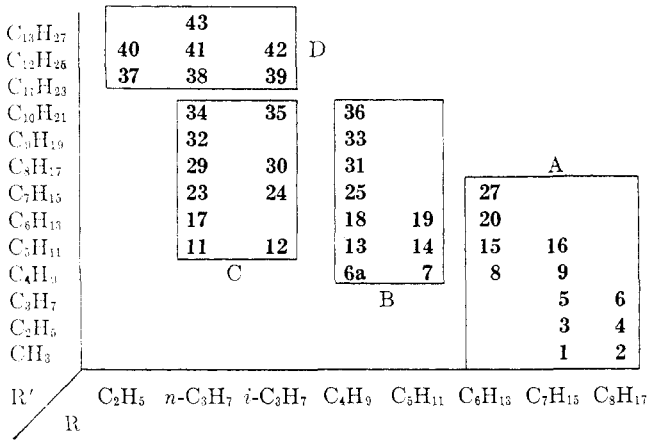

Figure 1.—Compounds arranged according to systematic position and grouped according to activity.

porary looseness, regardless of whether the dog had been treated or not. The majority of dogs in these trials had normal bowel movements or were somewhat constipated.

Discussion

After bunamidine hydrochloride was selected as the best of the naphthamidines made prior to 1965, a number of papers have appeared concerning its activity against 14 species of tapeworms of mice, dogs, cats, sheep, horses, and poultry. These papers are listed in a prior article.[3] In addition to the various papers dealing with the effect of bunamidine on different cestode species, one article[10] dealt with the effect of 8 naphthamidines against *Echinococcus granulosus* in Argentine dogs. All 8 of these compounds fell into groups A and B, 6 had moderate activity, 2 had good activity, and bunamidine hydrochloride was considered the better of the 2 good ones.

Hatton[7b] tested 3 different salts of bunamidine: hydrochloride, hydroxynaphthoate, and *p*-chlorobenzenesulfonate. He reported that the hydroxynaphthoate produced fewer side effects than either of the others, but was rather inactive when given on an empty stomach. When mixed with food it was quite active. On the other hand, Burrows and Lillis[5] found the hydrochloride more effective against *T. pisiformis* when given on an empty stomach than when given at or near mealtime.

The most effective group of naphthamidines made to date are those in group C, which contains the compounds in which OR ranges from pentyloxy to decyloxy and R′ is either *n*-Pr or *i*-Pr. Differences between compounds having $(n\text{-Pr})_2$ or $(i\text{-Pr})_2$ are minor and not consistently favorable to either.

Now that the most active group of the naphthamidines appears to be pinpointed, several other problems must be attacked. These involve additional trials at various dose levels of most of the compounds of the group, the relation of dosage time to feeding time, the testing of different particle sizes, the preparation of the hydroxynaphthoate salt of the better compounds, and the evaluation of several different types of formulations of the better drugs.

(10) B. D. Blood, V. Moya, and J. L. Lelijveld, *Bull. W. H. O.*, **39**, 67 (1968).

Syntheses of Halogenated Phenanthrene Amino Alcohols as Antimalarials[1]

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A series of phenanthrene-1-amino alcohols has been prepared and evaluated against *Plasmodium berghei* in mice. The target compounds contain halogen at the 2, 6, 6,7, 6,7,9, or 10 positions, and were made through sequences beginning with chlorobenzene, *o*-dichlorobenzene, methyl 1-phenanthrylate, or methyl 3,4-dihydro-1-phenanthrylate. Some of these halogen-substituted phenanthrene-1-amino alcohols showed moderate curative activity against *P. berghei* in mice.

As part of the current U. S. Army Research Program on Malaria, we undertook the syntheses of phenanthrene aminomethylmethanols. The aim was activity against the drug-resistant strain of *Plasmodium falciparum*. In a similar program during World War II, a considerable number of phenanthrene aminomethylmethanols had been prepared, and some showed considerable activity against other types of malaria.[2] Most of the earlier phenanthrene derivatives had the dialkylamino alcohol group at the 3 or 9 position, a few were located at the 2 position, and one[3] was found[4] to be at the 1 position. We have described our earlier syntheses of basic phenanthrenemethanols with the dialkylamino alcohol side chain attached at the 1 and at the 4 position, and with H, Cl, or Br at the 9 or 10 position.[4] We now report the syntheses of phenanthrene-1-amino alcohols substituted with Cl or Br at the 2, 6, or 6 and 7 positions, and with Cl, Br, or H at the 9 or 10 positions.

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(1) This is contribution No. 819 from the Army Research Program on Malaria. The investigation was conducted under Contract No. DADA17-68-C-8025-P-901, U. S. Army Medical Research and Development Command, Report AD862199L.

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

(3) J. Schultz, M. A. Goldberg, E. P. Ordas, and G. Carsch, *J. Org. Chem.*, **11**, 329 (1946).

(4) L. O. Krbechek, R. R. Riter, R. G. Wagner, and C. W. Huffman, *J. Med. Chem.*, **13**, 234 (1970).

Aromatization of 3,4-dihydro-1-phenanthrylate with NBS is preferable to the classical high-temp reaction with S. The yields for the latter procedure were about 10% higher, but the product from the NBS reaction was easier to purify. While phenanthrenes[5] as well as a variety of other compds[6] have been prepared by this aromatization reaction, few examples in which the aromatized ring contains a deactivating group such as carbomethoxy are recorded.[7] The reaction proceeds satisfactorily with NBS in refluxing CH_2Cl_2, $CHCl_3$, or CCl_4, or with *N*-chlorosuccinimide in CCl_4. In the former case, an induction period was noted, the duration of which was inversely proportional to the temp of the refluxing mixture.

Experimental Section[8]

β-(4-Chlorobenzoyl)propionic acid was prepared by the procedure described by Rioult and Vialle;[9] mp 125–127°, lit.[10] mp 131° (84%).

β-(3,4-Dichlorobenzoyl)propionic Acid.—Succinic anhydride was allowed to react with *o*-$Cl_2C_6H_4$ in the presence of $AlCl_3$ according to the usual procedure.[11] As an alternative to steam distillation, however, the reaction mixture was poured over ice, and the organic layer was sepd. The crude acid was pptd by the addition of an equal vol of CH_2Cl_2, collected, and triturated with C_6H_6 to give crude product, mp 150–155° (87%). Recrystn from petr ether gave mp 161–163°, lit.[12] mp 166–166.7°.

γ-(4-Chlorophenyl)- and γ-(3,4-dichlorophenyl)butyric acids were prepared in 75–95% yield from the corresponding β-benzoylpropionic acids by the Huang-Minlon modification of the Wolff–Kishner reduction as described by Wilds and Werth,[13] except that ethylene glycol was substituted for diethylene glycol. Crude γ-(3,4-dichlorophenyl)butyric acid was recrystd from *n*-C_7H_{16}, mp 64–68°, and then sublimed at 75° (0.1 mm) to give mp 66–68°. *Anal.* ($C_{10}H_{10}Cl_2O_2$) C, H.

7-Chloro- and 6,7-Dichloro-3,4-dihydro-1(2*H*)-naphthalenone.—The cyclization of the γ-phenylbutyric acids by the procedure of Newman and Seshadri[14] was carried out by heating with polyphosphoric acid at 70–85° to give 72% of 7-chloro-3,4-dihydro-1(2*H*)-naphthalenone, mp 89–91°, lit.[15] mp 94°. 6,7-Dichloro-3,4-dihydro-1(2*H*)-naphthalenone was extd with CH_2Cl_2 and distd, bp 155–160° (0.25 mm), to give 91%, mp 102–104°. *Anal.* ($C_{10}H_8Cl_2O$) C, H.

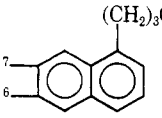
Ethyl 4-(7-Chloro-3,4-dihydro-1-naphthyl)butyrate.[16]—The structure of these compounds is based only on precedent; we have not attempted to establish whether the double bond is exocyclic or endocyclic. The exptl procedure is given in some detail since reaction conditions have been shown[17] to be a structural determinant in some cases. A mixture of 154 g (2.4 moles) of activated granular Zn, 0.5 g of $HgCl_2$, and 3 l. of Et_2O was refluxed for 5 min, and 396 g (2.2 moles) of 7-chloro-3,4-dihydro-1(2-*H*)-naphthalenone was added. After an additional 5 min of reflux, 502 g (2.1 moles) of ethyl γ-bromocrotonate was added dropwise over 5 hr. The mixture was stirred under reflux for 18 hr and about 1.5 l. of cold dil (*ca.* 6 *N*) HCl was added. The Et_2O layer was sepd, dried, and concd. The residue dissolved in 300 ml of C_6H_6 was added to a large excess (*ca.* 250 g) of Raney Ni and reduced in a Paar low-pressure hydrogenator. The catalyst was removed and the product dehydrated using a Dean–Stark separator. The soln was concd and the residue was distd to give 478 g (78%), bp 157–165° (0.7 mm). *Anal.* ($C_{16}H_{19}ClO_2$) C, H.

Ethyl 4-(6,7-dichloro-3,4-dihydro-1-naphthyl)butyrate[16] was prepd by the Reformatsky procedure outlined above in a yield of 77%, bp 155–160° (0.2 mm). *Anal.* ($C_{16}H_{18}Cl_2O_2$) C, H. In this case, the dehydration step required the presence of catalytic amounts of *p*-TosOH.

Halogenated 4-Naphthylbutyric Acids and Esters (Table I).

TABLE I

HALOGENATED NAPHTHYLBUTYRIC ACIDS AND ESTERS



6	7	R	Method	Mp, °C	Formula[a]
H	Cl	Me	A	45–47	$C_{15}H_{13}ClO_2$
H	Cl	Et	B	[b]	$C_{16}H_{17}ClO_2$
Cl	Cl	Et	B	38–39[c]	$C_{16}H_{16}Cl_2O_2$
H	Cl	H	C	165–168	$C_{14}H_{13}ClO_2$
Cl	Cl	H	C	123–127	$C_{14}H_{12}Cl_2O_2$

[a] Correct C and H analyses were obtained for all compounds. [b] Bp 166–170° (0.75 mm). [c] Bp 175–180° (0.20 mm).

Method A.—This ester was obtained by treatment of the corresponding acid with MeOH–HCl, followed by recrystn from EtOH.

Method B.—The corresponding ethyl 3,4-dihydro-1-naphthylbutyrates were heated at *ca.* 230° with equimolar amounts of S until evoln of H_2S was complete (*ca.* 3 hr). The reaction was quenched by addition of a small amount of powdered Zn, and the product was distd and recrystd from EtOH.

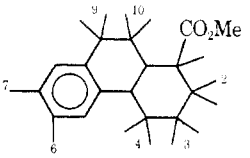
Method C.—The acids were obtd by hydrolysis of the corresponding ethyl esters with aq KOH, followed by recrystn from EtOH.

Methyl Halodihydro-1-phenanthrylates (Table II). Method A.—Methyl 1,2-dibromo-1,2,3,4-tetrahydrophenanthrylate was heated at *ca.* 150° until the evoln of HBr subsided (2 hr) and the crude product was recrystd from EtOH.

Method B.—The condensation of diethyl oxalate with the corresponding ethyl 4-(halo-1-naphthyl)butyrate was as described,[18] except that KO-*t*-Bu was substituted for KOEt. Attempted cyclization of the ketosuccinate resulting from ethyl 4-(7-chloro-1-naphthyl)butyrate in boiling 20% H_2SO_4[19,20] resulted in the recovery of 4-(7-chloro-1-naphthyl)butyric acid. Treatment of ethyl 4-(6,7-dichloro-1-naphthyl)butyrate with boiling 65% H_2SO_4 gave a 30% yield of 6,7-dichloro-3,4-dihydrophenanthrene-1,2-dicarboxylic anhydride, mp >300° (from HOAc): ir (KBr) 1830 and 1750 (C=O), 1580 (aryl), 1240 (COC), and 886 cm^{-1}. *Anal.* ($C_{16}H_8Cl_2O_3$) C, H. Use of 45–50% H_2SO_4 followed by esterification in MeOH–HCl gave satisfactory overall

(5) R. A. Barnes, *J. Amer. Chem. Soc.*, **70**, 145 (1948).
(6) M. Mousseron and G. Manon, *C. R. Acad. Sci.*, **227**, 533 (1948).
(7) R. Filler, *Chem. Rev.*, **63**, 21 (1963).
(8) The chemicals employed in this investigation were used as obtained from chemical supply houses without purification unless otherwise noted. Melting points were determined with a Thomas-Hoover melting point apparatus or, for mp >260°, with a SGA Van der Kamp Cu block, and boiling points were determined by distillation; neither have been corrected. Glc analyses were carried out on an F&M Model 720 dual column programmed temp gas chromatograph with thermal conductivity detection. Most reactions and purification procedures were followed by tlc on Gelman SG sheets; a convenient general-purpose solvent system for these compounds on this medium is 4–6% Me_2CO in heptane. Target hydrochlorides, however, were sepd by reversed-phase partition chromatography on SG sheets impregnated with mineral oil using 85–95:5:10–0; MeOH–Et_2NH–H_2O as mobile phase. Visualization was accomplished with shortwave uv, 0.2% disodium fluoresceinate in MeOH or 0.2% $KMnO_4$ in 1.0% Na_2CO_3. Routine ir spectra were detd on a Beckman IR5A prism instrument; some ir anal. were carried out with the aid of a Perkin-Elmer Model 521 spectrometer. Nmr spectra were detd at 60 or 100 MHz by Sadtler Research Laboratories (Philadelphia, Pa.) or Midwest Research Institute (Kansas City, Mo.), with, in a few cases, consultation with Varian Associates (Palo Alto, Calif.). The Midwest Research Institute also obtained the mass spectral data. Elemental analyses were carried out with a Hewlitt-Packard Model 185 CHN analyzer by the IMC Organic Analysis Group under the supervision of Mr. Steve Weger. Where analyses were indicated only by symbols of the elements, the results were within ±0.4% of the theoretical values. Thermal gravimetric analyses were made by IMC Physical–Inorganic Group under the supervision of Dr. J. W. Currier.
(9) P. Rioult and J. Vialle, *Bull. Soc. Chim. Fr.*, **11**, 3312 (1965).
(10) S. Skraup and E. Schwanberger, *Justus Liebigs Ann. Chem.*, **462**, 135 (1928).
(11) E. Berliner, *Org. React.*, **5**, 229 (1949).
(12) E. A. Steck, R. Brundage, and L. Fletcher, *J. Amer. Chem. Soc.*, **75**, 1117 (1953).
(13) A. Wilds and R. Werth, *J. Org. Chem.*, **17**, 1154 (1952).
(14) M. S. Newman and S. Seshadri, *ibid.*, **27**, 76 (1962).
(15) V. Braun, *Justus Liebigs Ann. Chem.*, **451**, 44 (1940).
(16) W. E. Bachmann and N. L. Wendler, *J. Amer. Chem. Soc.*, **68**, 2582 (1946).
(17) A. S. Dreiding and R. J. Pratt, *ibid.*, **75**, 3717 (1953).
(18) K. G. Rutherford and M. S. Newman, *ibid.*, **79**, 213 (1957).
(19) W. E. Bachmann and N. C. Deno, *ibid.*, **71**, 3062 (1949).
(20) J. A. Dixon and D. D. Neiswender, *J. Org. Chem.*, **25**, 499 (1960).

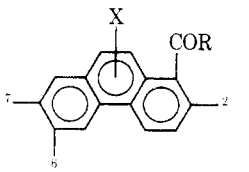
TABLE II
METHYL HALODIHYDRO-1-PHENANTHRYLATES



1	2	3	4	6	7	9	10	Method	Mp, °C	% yield	Formula[a]
	Br	H_2	H_2	H	H	H	H	A[b]	100–102	27	$C_{16}H_{13}BrO_2$
	H	H_2	H_2	Cl	H	H	H	B	81.5–82.5[c]	50	$C_{16}H_{13}ClO_2$
	H	H_2	H_2	Cl	Cl	H	H	B	137–138	60	$C_{16}H_{12}Cl_2O_2$
Br	H, Br	H_2	H_2	H	H	H	H	C	130–134[d]	86	$C_{16}H_{14}Br_2O_2$
	H	H	H	Cl	H	H, Cl	H, Cl	D	170[d]	83	$C_{16}H_{11}Cl_3O_2$
	H	H	H	Cl	Cl	H, Cl	H, Cl	D	165–193[d]	65	$C_{16}H_{10}Cl_4O_2$

[a] Correct C and H analyses were obtained for all compounds. [b] Thermolysis ≈ 150°. [c] Bp 170–175° (5 mm). [d] Decomp at mp.

TABLE III
HALOGENATED 1-PHENANTHROIC ACIDS AND ESTERS



R	2	6	7	X	Method	Recrystn solvent	Mp, °C	% yield	Formula[a]
OMe	Br	H	H	H	A	EtOH	123–125	73	$C_{16}H_{11}BrO_2$[b]
OMe	H	H	H	10-Br	B	EtOH–C_6H_6	142.5–143.5		$C_{16}H_{11}BrO_2$[b]
OMe	H	Cl	H	H	C	[c]	115–118	85	$C_{16}H_{11}ClO_2$
OMe	H	Cl	Cl	H	C	EtOH	196–201	70	$C_{16}H_{10}Cl_2O_2$[b]
OMe	H	Cl	H	9-Cl	B	EtOH	180–182	76	$C_{16}H_{10}Cl_2O_2$[b]
OMe	H	Cl	Cl	9-Cl	B	THF[d]	195–196	85	$C_{16}H_9Cl_3O_2$[b]
OH	Br	H	H	H	D	MeCN	220–222	84	$C_{15}H_9BrO_2$[e]
OH	H	H	H	10-Br	D	THF[d]	319–323	100	$C_{15}H_9BrO_2$
OH	H	Cl	H	H	D	[f]	285–287	82	$C_{15}H_9ClO_2$[g]
OH	H	Cl	Cl	H	D	THF[d]	314–317	81	$C_{15}H_8Cl_2O_2$
OH	H	Cl	H	9-Cl	D	[f]	251–253	82	$C_{15}H_8Cl_2O_2$
OH	H	Cl	Cl	9-Cl	D	EtOH	319–320.5		$C_{15}H_7Cl_3O_2$

[a] Correct C and H analyses were obtd for the formulas shown unless otherwise indicated. [b] Structure verified by nmr. [c] Purified by distn, bp 175–180° (0.25 mm). [d] A second crop was obtained by addn of EtOH to the filtrate. [e] Calcd: C, 59.82; H, 3.01. Found: C, 60.12; H, 3.48. [f] Sufficiently pure product pptd on addn of the reaction soln to cold dil HCl. [g] Calcd: C, 70.18; H, 3.54. Found: C, 69.25; H, 3.65.

yields of the methyl halo-3,4-dihydro-1-phenanthrylates, which were purified finally by recrystn from EtOH.

Method C.—Br_2 (32 g, 0.20 mole) was added to a refluxing soln of 48 g (0.20 mole) of methyl 3,4-dihydro-1-phenanthrylate[4,19] in 400 ml of Et_2O and 400 ml of CH_2Cl_2. The mixture was stirred under reflux for 1 hr and cooled. The ppt was collected and washed with EtOH.

Method D.—The ester, suspended in CH_2Cl_2, was treated with Cl_2 at room temp until a soln formed. The product pptd upon cooling in an ice bath.

Halogenated 1-Phenanthroic Acids and Esters (Table III). Method A.—An equimolar mixture of methyl halo-3,4-dihydro-1-phenanthrylate and NBS in CCl_4 was stirred under reflux for 1.5 hr. The mixture was cooled to room temp, filtered, and concd under reduced pressure. The residue recrystd from the solvents indicated.

Method B.—The substituted methyl 9,10-dihalo-9,10-dihydro-1-phenanthrylate was heated neat at 200–220° until no further acidic fumes were evolved (*ca.* 1.5 hr). The residue was then purified as indicated.

Method C.—Equimolar amounts of methyl halo-3,4-dihydro-1-phenanthrylate and S were heated at 200–250° until evoln of H_2S was complete. A small amount of powdered Zn was added to the hot mixture and the resulting material was purified as indicated.

Method D.—The substituted methyl 1-phenanthrylate was refluxed in aq alcoholic 5–10% KOH until hydrolysis was complete (4–10 hr) and acidified with aq HCl. The solid product was collected and purified as indicated.

TABLE IV
HALOGENATED 1-PHENANTHROYL CHLORIDES
(R = Cl)

2	6	7	Mp, °C	% yield	Formula	Anal.
H	Cl	Cl	191–193[a]	100	$C_{15}H_7Cl_3O$	C, H
Br	H	H	134–137		$C_{15}H_8BrClO$	C, H

[a] Triturated with cyclohexane.

Halogenated 1-Phenanthroyl Chlorides (Table IV).—The halogenated 1-phenanthroic acid (*ca.* 0.02 mole) was heated under reflux with *ca.* 150 ml of $SOCl_2$ for 2–8 hr and the excess $SOCl_2$ was removed under reduced pressure. About 200 ml of C_6H_6 was added and removed under reduced pressure to give the crude halogenated 1-phenanthroyl chloride, which, in most cases, was used immediately for the prepn of the diethyl malonate derivative.

Halogenated Diethyl 1-Phenanthroylmalonates (Table V).—These compounds were prepd by reaction of the acid chloride with diethylethoxymagnesium malonate in THF according to the method of Walker and Hauser.[21] Considerable difficulty was encountered in the prepn of analytically pure samples of these materials, presumably because of the presence of small amounts of ester or unconverted acid in the crude acid chlorides employed.

(21) H. G. Walker and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 1386 (1946).

TABLE V
HALOGENATED DIETHYL 1-PHENANTHROYLMALONATES
R = $CH(CO_2Et)_2$

2	6	7	X	Recrystn from	Mp, °C	% yield	Formula	Anal.
Br	H	H	H	EtOH	130–131.5	91	$C_{22}H_{19}BrO_5$	H; C[a]
H	H	H	10-Br	EtOH	93–95	73	$C_{22}H_{19}BrO_5$	H; C[b]
H	Cl	H	H	EtOH	93–96	50	$C_{22}H_{19}ClO_5$	H; C[c]
H	Cl	Cl	H	CH_3CN	124–128	70	$C_{22}H_{18}Cl_2O_5$	C, H
H	Cl	H	9-Cl	*d*	110–115		$C_{22}H_{18}Cl_2O_5$	
H	Cl	Cl	9-Cl	EtOH	135–136.5	82	$C_{22}H_{17}Cl_3O_5$	C, H

[a] C: Calcd, 59.60. Found, 59.06. [b] C: Calcd, 59.60. Found, 59.17. [c] C: Calcd, 66.26. Found, 65.83. [d] The crude product was converted immediately into the corresponding Ac derivative.

TABLE VI
HALOGENATED 1-ACETYLPHENANTHRENE
R = CH_3

2	6	7	X	Recrystn from	Mp, °C	% yield	Formula	Anal.
Br	H	H	H	EtOH	116–118	81	$C_{16}H_{11}BrO$	C, H
H	H	H	10-Br	C_6H_6	123–125	78	$C_{16}H_{11}BrO$	C, H
H	Cl	H	H	EtOH	129–130	74	$C_{16}H_{11}ClO$	C, H
H	Cl	Cl	H	*a*	186–187.5	92	$C_{16}H_{10}Cl_2O$	C, H
H	Cl	H	9-Cl	EtOH	147–151	60	$C_{16}H_{10}Cl_2O$	*b*
H	Cl	Cl	9-Cl	C_6H_6	228–229	83	$C_{16}H_9Cl_3O$	C, H

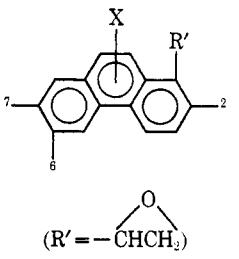
[a] Triturated with *i*-PrOH and sublimed at 160–170° (0.1 mm). [b] Calcd ($C_{16}H_{10}Cl_2O \cdot 0.5H_2O$): C, 64.46; H, 3.72. Found: C, 64.19; H, 3.29.

TABLE VII
HALOGENATED 1-BROMOACETYLPHENANTHRENES
R = CH_2Br

2	6	7	X	Method	Recrystn from	Mp, °C	% yield	Formula[a]
Br	H	H	H	A	EtOH	120–124	75	$C_{16}H_{10}Br_2O$
H	H	H	10-Br	B	EtOH	161–163	74	$C_{16}H_{10}Br_2O$
H	Cl	H	H	A	*b*	138–140	26	$C_{16}H_{10}BrClO$
H	Cl	Cl	H	B	C_6H_6	178–180	75	$C_{16}H_9BrCl_2O$
H	Cl	H	9-Cl	A	*b*	210–213	75	$C_{16}H_9BrCl_2O$
H	Cl	Cl	9-Cl	A	EtOH	228–230	85	$C_{16}H_8BrCl_3O$

[a] All analyzed correctly for C and H. [b] Sufficiently pure product pptd from chilled reaction soln.

TABLE VIII
1-PHENANTHRYLETHYLENE OXIDES



2	6	7	X	Reaction solvent	Recrystn from	Mp, °C	% yield	Formula[a]
Br	H	H	H	Diglyme	EtOH	125–128	63	$C_{16}H_{11}BrO$
H	H	H	10-Br	Diglyme	EtOH	168–169.5	97	$C_{16}H_{11}BrO$
H	Cl	H	H	MeOH	*b*	119–121	96	$C_{16}H_{11}ClO$
H	Cl	Cl	H	MeOH		160–163	71	$C_{16}H_{10}Cl_2O$
H	Cl	H	9-Cl	Diglyme	EtOH	138–141	89	$C_{16}H_{10}Cl_2O$[c]
H	Cl	Cl	9-Cl	Diglyme		202–206	83	$C_{16}H_9Cl_3O$

[a] Correct C and H analysis were obtd unless otherwise noted. [b] Sufficiently pure product pptd from the reaction mixture. [c] Calcd ($C_{16}H_{10}Cl_2O \cdot 0.5H_2O$): C, 64.46; H, 3.72. Found: C, 64.36; H, 3.35.

Halogenated 1-Acetylphenanthrenes (Table VI).—These compounds were prepared by hydrolysis and decarboxylation of the corresponding 1-phenanthroylmalonates as described previously.[21]

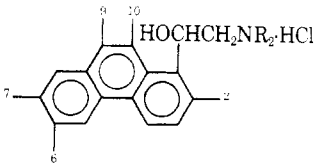
Halogenated 1-Bromoacetylphenanthrenes (Table VII). Method A.—This procedure utilized the $AlCl_3$-catalyzed reaction of Br_2 in $CHCl_3$ with the substituted 1-acetylphenanthrene in Et_2O–CH_2Cl_2.[3,22]

(22) E. May and E. Mosettig, *J. Org. Chem.*, **11**, 10 (1946).

Method B.—A soln of 0.04 mole of Br_2 in *ca.* 10 ml of CH_2Cl_2 was added slowly to a suspension of 0.04 mole of halogenated 1-acetylphenanthrene in 150 ml of Et_2O and 65 ml of CH_2Cl_2 at room temp. This mixture was stirred an additional hour and cooled. The resulting product was collected and purified as indicated.

1-Phenanthrylethylene Oxides (Table VIII).—These compounds were prepd as previously described.[4] In cases in which

TABLE IX
PROPERTIES AND ANTIMALARIAL ACTIVITY OF PHENANTHRENE-1-AMINO ALCOHOLS



									Antimalarial activity[d] IMST[e] at indicated dosage (mg/kg)					Cures	
2	6	7	9	10	R[a]	Mp, °C	% yield[b]	Formula[c]	40	80	160	320	640	320	640
Br	H	H	H	H	C_7	155–157	86	$C_{30}H_{43}BrClNO$	1.4	4.0	5.8	12.2	14.2	Active	Active
H	H	H	H	Br	C_7	126–129	66	$C_{30}H_{43}BrClNO$	0.3	3.7	4.3	7.9	9.5	Active	Active
H	Cl	H	H	H	C_7	109–112	28	$C_{30}H_{43}Cl_2NO$	0.6	2.4	4.2	5.2			
H	Cl	Cl	H	H	C_4	74–75[f]	52	$C_{24}H_{29}Cl_2NO$	3.0	6.6	10.4	15.1	14.8	1	3
H	Cl	Cl	H	H	C_7	150–155	22	$C_{30}H_{42}Cl_3NO$	0.2	0.4	4.2	4.8			
H	Cl	H	Cl	H	C_7	197–198.5	22	$C_{30}H_{42}Cl_3NO$	1.0	6.6	7.8	15.3		3	5
H	Cl	Cl	Cl	H	C_7	193–196	38	$C_{30}H_{41}Cl_4NO$	0.3	3.3	5.9	7.1	10.4	Active	1

[a] All *n*-alkyl groups. [b] From the epoxide. [c] Correct analyses for C, H, and N were obtained for all compds. [d] For details of test procedure, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). Test data supplied by Walter Reed Army Institute of Research. [e] Increase in mean survival time. Mean survival time for mice infected with *P. berghei*, 6.5 ± 0.5 days. [f] Isolated and submitted as the free base.

Diglyme was used as solvent, the reduction and treatment with NaOH were carried out at a slightly above room temp, and the reaction mixture was worked up by addn to ice–water. The pptd product was collected by filtration.

Phenanthrene-1-amino Alcohols (Table IX).—All of the phenanthrene amino alcohols were prepd by reaction of the corresponding epoxide with an excess of the appropriate amine.[23] In accordance with earlier recommendations,[4] the reaction was carried out at 125° for 16 hr. Under these conditions, ir, nmr, and mass spectra of the products were as expected for the structure indicated, with no evidence for the presence of the isomer resulting from attack by the secondary amine at the secondary epoxide carbon, *i.e.*, the undesired $ArCH(CH_2OH)NR_2$. The reaction products were purified by removal of excess amine by vacuum and/or steam distillation and usually were isolated as the hydrochlorides from Et_2O, followed by recrystn from C_6H_6 and/or cyclohexane.

The antimalarial activity of the halogen-substituted phenanthrene-1-amino alcohols was comparable with the activity of related compds that we described earlier.[4] Some showed moderate curative activity against *P. berghei* in mice. None of the intermediates had any antimalarial activity, and no toxic deaths resulted from treatment with either target or intermediate compds.

Acknowledgment.—We express our appreciation to Drs. E. Sweeney, R. Strube, D. P. Jacobus of WRAIR, and Professor R. Mariella of Loyola University for helpful advice.

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Chemotherapeutic Nitroheterocycles. 6.[1] Substituted 5-Aminomethyl-3-(5-nitro-2-imidazolylmethyleneamino)-2-oxazolidinones[2]

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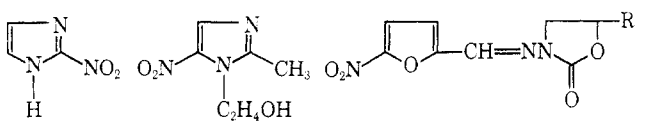
A series of nitroimidazole derivatives was synthesized by condensation of 1-substituted 5-nitroimidazole-2-carboxaldehydes with 3-amino-5-methyl-2-oxazolidinones substituted at the 5-methyl group by secondary amines. The compounds displayed high activity against *Trichomonas vaginalis in vitro* and most of them *in vivo*.

The antibiotic azomycin[3] (**1**) was the first nitroimidazole which was reported to be active against *Trichomonas vaginalis*. Later 5-nitroimidazoles were shown to have better therapeutic qualities and of this series metronidazole[4] (**2**) became the drug of choice against trichomoniasis. In contrast to the 5-nitromidazoles biologically active nitrofurans such as furazolidone[5] (**3**, R = H) and furaltadone[6] (**3**, R = morpholinomethyl) are in general derived from a carboxaldehyde or carboxyl group in position 2 of this heterocycle.



1 2 3

In some patents[7,8] corresponding 5-nitroimidazoles

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(1) Part V: R. Albrecht, H.-J. Kessler, and E. Schröder, *Chim. Ther.*, in press.

(2) A preliminary report of part of this work has been presented at the VIth International Congress of Chemotherapy, Tokyo, August 1969.

(3) S. Nakamura and H. Umezawa, *J. Antibiot., Ser. A*, **9**, 66 (1955).

(4) C. Cosar, *Arzneim-Forsch.*, **16**, 23 (1966).

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(6) D. F. Kefauver, I. Paberzs, and T. F. McNamara, *Antibiot. Annu.*, **1958–1959**, 81 (1959).

(7) Merck and Co., Inc., Netherlands Application 6,413,814 (1965); *Chem. Abstr.*, **63**, 18097 (1965).

(8) Merck and Co., Inc., Belgium Application 661,262 (1965); *Chem. Abstr.*, **64**, 2093 (1966).