The Syntheses of Phenanthrene Amino Alcohols as Antimalarials[1]

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A series of phenanthrene amino alcohols has been prepared and evaluated for antimalarial effects. These compounds bear the amino alcohol on the 1 or 4 position, respectively. During the course of the syntheses, the halogenation and pyrolytic dehydrohalogenation of the methyl phenanthrene-1- and 4-carboxylates were studied. The epoxide cleavage of the various 1- and 4-phenanthrylethylene oxides with the amines employed often yielded both possible isomeric amino alcohols. Increasing the size of the amine side chain from C_3 to C_6 or C_7 and introducing ring halogen substituents increased the antimalarial activity.

New antimalarial agents are being sought to combat strains of malaria resistant to available drugs. During World War II, a large number of phenanthrene amino alcohols were prepared and many had a high level of antimalarial activity, with a therapeutic index as high as 53.4 reported.[2a] The majority of these phenanthrene derivatives had the dialkylamino alcohol moiety attached at either the 3 or 9 position;[2b] none was at the 4 position. The sole 1-phenanthryl amino alcohol, 2-(*n*-diamylamino-1-hydroxyethyl)-9-bromophenanthrene, had a therapeutic index of 13.2.[2c,d] We have prepared a series of 1-phenanthryl amino alcohols bearing H, Cl, or Br at the 9 position, and a series of 4-phenanthryl amino alcohols bearing H, Cl, or Br on the 10 position (see Scheme I). All of these compounds have exhibited antimalarial activity.

The two key intermediate phenanthrene-1- and phenanthrene-4-carboxylic acids were prepared by succinylation of naphthalene as described by Rutherford[3a] and Dixon,[3b] *et al.* The failure of 1,2-dihydrophenanthrene-4-carboxylic acid to undergo esterification in MeOH–HCl while 3,4-dihydrophenanthrene-1-carboxylic acid was esterified readily under these conditions permitted us to use 3-(α-naphthoyl)propanoic acid contaminated with as much as 25% 3-(β-naphthoyl)propanoic acid. We made the first purification of the α isomer from this reaction by recrystallization of the distilled Me ester from either MeOH or *i*-PrOH.

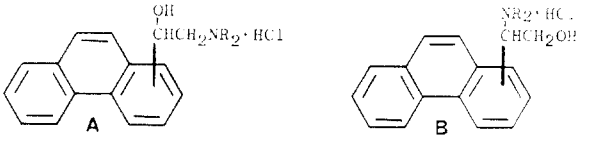
It is noteworthy that dehydrohalogenations of 9,10-dihalo-9,10-dihydrophenanthrenes gave good yields of 9-halophenanthrenes from 1-carboxylates, and 10-halophenanthrenes from 4-carboxylates.

Bromination of the corresponding Me esters furnished good yields of the expected methyl 9,10-di-bromo-9,10-dihydrophenanthrene-1- and 4-carboxylates. From the pyrolytic dehydrobromination of methyl 9,10-dibromo-9,10-dihydrophenanthrene-1-carboxylate, methyl 9-bromophenanthrene-1-carboxylate was isolated in approximately 30% yield. Its structure was assigned from its nmr spectrum. The volatile portion of the crude pyrolysis mixture was shown by glpc analysis to be 15% methyl phenanthrene-1-carboxylate, 15% methyl 10-bromophenanthrene-1-carboxylate, and 60% methyl 9-bromophenanthrene-1-carboxylate. The nonvolatile portion, amounting to only 10% of the reaction mixture, was about two-thirds 10-bromophenanthrene-1-carboxylic acid and one-third 9-bromophenanthrene-1-carboxylic acid.

The pyrolytic dehydrobromination of methyl 9,10-dibromo-9,10-dihydrophenanthrene-4-carboxylate gave an 80% yield of a single isomer. Glpc analysis of the crude reaction mixture showed about 5% methyl phenanthrene-4-carboxylate and <0.5% of another product, the remainder being methyl 10-bromophenanthrene-4-carboxylate, whose structure was assigned from its nmr spectrum.

The chlorination of methyl phenanthrene-4-carboxylate gave an oil which could not be purified. Dehydrochlorination experiments failed to furnish an isolable product. However, the pyrolysis of 9,10-dichloro-9,10-dihydrophenanthrene-4-carboxylic acid yielded 10-chlorophenanthrene-4-carboxylic acid which was identified from its nmr spectrum. Glpc analysis showed that the pyrolytic dehydrochlorination of methyl 9,10-dichloro-9,10-dihydrophenanthrene-1-carboxylate yielded essentially pure methyl 9-chlorophenanthrene-1-carboxylate, identified from its nmr spectrum.

All of the phenanthrylethylene oxides reacted with selected secondary amines to yield the target compounds. Some of these reactions at 160° or higher (possibly undesirable) gave two isomers. The isolated material was often a mixture of the desired 1- (or 4) (2-*n*-dialkylamino-1-hydroxyethyl)phenanthrene (A) and the unwanted 1- (or 4) (1-*n*-dialkylamino-2-hydroxyethyl)phenanthrene (B). The isomeric composition was determined by nmr.



Because some of the target compounds were mixtures of A and B, pure 1-(2-*n*-dibutylamino-1-hydroxyethyl)-phenanthrene was prepared also by reaction of α-bromo-1-acetylphenanthrene with *n*-Bu_2NH and subsequent reduction of the amino ketone with $NaBH_4$. The yield by this route was comparable to that from the epoxide, but the procedure was not reproducible.[4c]

The only 1-phenanthryl amino alcohol screened during World War II was prepared by Schultz, *et al.*, and identified by them as 1- (or 8)(2-*n*-diamylamino-1-hydroxyethyl)-9-bromophenanthrene.[2d] On the basis of nmr analysis, the structure of methyl 9-bromophenanthrene-1-carboxylate was assigned to the py-

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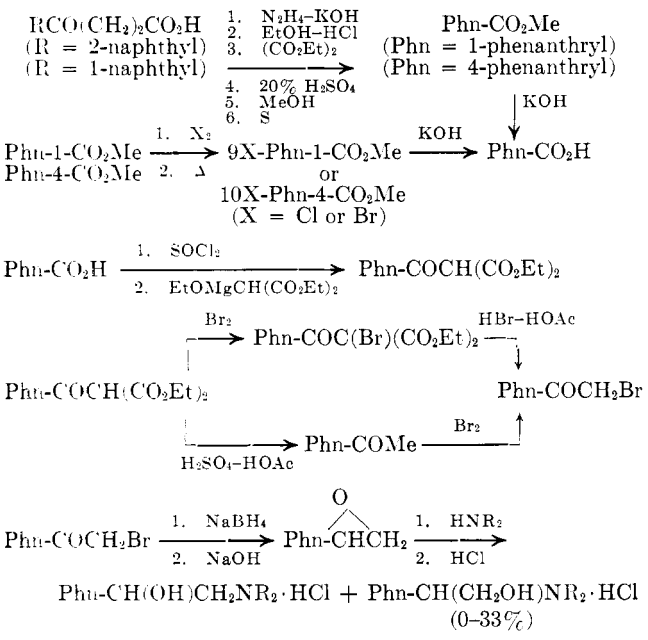
(2) G. R. Coatney, "Survey of Antimalarial Agents," Public Health Monograph No. 9, (a) p 22; (b) pp 5, 8; (c) p 5; (d) J. Schultz, M. A. Goldberg, E. P. Ordas, and G. Carsch, *J. Org. Chem.*, **11**, 329 (1946).

(3) (a) K. G. Rutherford and M. S. Newman, *J. Amer. Chem. Soc.*, **79**, 213 (1957); (b) J. A. Dixon and D. D. Neiswender, *J. Org. Chem.*, **25**, 499 (1960).

SCHEME I



rolysis product from methyl 9,10-dihydro-9,10-dibromophenanthrene-1-carboxylate, and methyl 9-chlorophenanthrene-1-carboxylate to that from pyrolysis of methyl 9,10-dihydro-9,10-dichlorophenanthrene-1-carboxylate. The physical constants of the intermediates from these two systems are in general agreement with those reported by Schultz, *et al.*[2d] Thus, the compound they prepared was 1-(2-*n*-diamylamino-1-hydroxyethyl)-9-bromophenanthrene.

Experimental Section[5-9]

3-(α- and β-Naphthoyl)propanoic Acids.—These acids were prepared by the method of Haworth.[10a] The isolation procedures were modified from those of Robinson and Slater[10c] and Wilds and Close.[10b]

A well-stirred mixture of 2 l. of $PhNO_2$ and 900 g of $AlCl_3$ was cooled to 20° in an ice bath. Starting at this temperature, 640 g (5 mol) of naphthalene and 320 g (3.2 mol) of succinic anhydride were added alternately over a period of about 5 min. The mixture was kept in an ice bath for 2 hr and then poured onto a mixture of 6 kg of ice and 500 ml of concentrated HCl. The mixture was heated to 80–90°, filtered, and allowed to cool to 30°. Crude 3-(β-naphthoyl)propanoic acid was collected by filtration. The $PhNO_2$ layer of the filtrate was extracted with 200 g of K_2CO_3 in 4 l. of H_2O. The alkaline extract was washed with $CHCl_3$, filtered, and acidified with HCl. The 3-(α-naphthoyl)propanoic acid was collected, air dried, and recrystallized from 3 l. of C_6H_6 to yield 290 g of α isomer, mp 120–127°, lit.[10a-d] 131–132°. The crude 3-(β-naphthoyl)propanoic acid was refluxed with the C_6H_6 filtrate from above and filtered hot to yield 182 g (25%) of β isomer, mp 165–171°, lit.[10a-d] 169–172°. The filtrate was concentrated to 1.5 l. and cooled to yield an additional 110 g [total 400 g (53%)], mp 120–126°.

These acids were sufficiently pure for the next steps.

Methyl 3-(α-Naphthoyl)propanoate.—A mixture of 95 g (0.42 mol) of crude 3-(α-naphthoyl)propanoic acid (mp 118–130°) and 500 ml of MeOH saturated with anhydrous HCl was refluxed for 4 hr. The MeOH was removed under reduced pressure. The remaining liquid was distilled to yield 71 g (70%) of methyl 3-(α-naphthoyl)propanoate, bp 158–175° (0.17 mm), lit.[10d] bp 196° (3 mm). It was crystallized from *i*-PrOH (10 ml/g) and dried to yield 47 g (66%), mp 36.5–37.5°. *Anal.* ($C_{15}H_{26}O_2$) C, H. No β isomer was detected by glpc in the product melting at 36.5–37.5°.

General Synthetic Methods. γ-(1- and 2-Naphthyl)butyric Acids and Ethyl Esters.—These compounds were prepared in 75–85% yield from the corresponding γ-naphthoylpropionic acids by the Huang-Minlon modification of the Wolff–Kishner reduction as described by Wilds and Werth,[11a] except that ethylene glycol was substituted for diethylene glycol. The corresponding Et esters were prepared[11b] in 85–90% yield by refluxing with EtOH saturated with HCl gas.

Dihydrophenanthrene-1- and -4-carboxylic Acids and Methyl Esters.—The synthetic procedure of Rutherford and Newman[3a] was modified by substitution of KO-*t*-Bu for KOEt in the diethyl oxalate condensation to give the carboxylic acids in 80–85% yield. Methyl 3,4-dihydrophenanthrene-1-carboxylate was prepared by refluxing the acid[12] in MeOH saturated with HCl gas. Methyl 1,2-dihydrophenanthrene-4-carboxylate was prepared by methanolysis of the acid chloride, prepared with $SOCl_2$.

Phenanthrenecarboxylic Acids (Table I). Method A.—Saponification of the corresponding methyl esters in refluxing aqueous 10% KOH gave these acids in 90–100% yield.

TABLE I

PHENANTHRENECARBOXYLIC ACIDS AND ESTERS

R	Method	Mp, °C	Recrystn from	% yield	Formula
4-CO_2H	A	170.5–172.5[a]	C_6H_{12}	100	$C_{15}H_{10}O_2$
1-CO_2H	A	232–234[b]	EtOH	90	$C_{15}H_{10}O_2$
4-CO_2Me	B	81–83[c]	MeOH	73	$C_{16}H_{12}O_2$
1-CO_2Me	B	54–55[d]	MeOH	81	$C_{16}H_{12}O_2$

[a] Lit.[3a] 173.5–174.5°. [b] Lit.[3b] 234.7–235.2°. [c] Bp 172–178° (1 mm), lit.[3a] mp 84–85°, lit. (L. F. Fieser, M. Fieser, and E. B. Hershberg, *J. Amer. Chem. Soc.*, **58**, 2322 (1936)) bp 173.5–174.5° (1 mm). [d] Bp 142–148° (0.075 mm), lit.[3b] mp 55–55.7°.

Method B.—Preparation following the procedure described by Rutherford and Newman.[3a]

9,10-Dihalo-9,10-dihydrophenanthrenecarboxylic Acids and Esters (Table II). Method A.—An equimolar amount of Br_2 was added slowly to a cooled solution or suspension of the acid or ester in 1:1 $CHCl_3$–Et_2O. The resulting solid was slurried or recrystallized from the indicated solvent.

Method B.—The acid or ester suspended in CH_2Cl_2 was treated with Cl_2 at room temperature with stirring. As the reaction proceeded, the suspended material dissolved. The solution was clarified by filtration, the solvent was removed, and the residue was triturated or recrystallized from a suitable solvent.

Halogenated Phenanthrenecarboxylic Acids and Esters (Table III). Method A.—These acids were prepared by hydrolysis of the corresponding methyl ester with refluxing 5% aqueous KOH containing 17% EtOH.

Method B.—The corresponding 9,10-dihalo-9,10-dihydrophenanthrene-1- or 4-carboxylic acid or ester was heated in an oil bath at the indicated temperature until acidic fumes were no longer evolved and poured into MeOH or C_6H_6, and the mixture was cooled. The crude product was collected an drecrystallized from the indicated solvent. In some cases, analytical samples were puri-

(4) (a) S. W. Chaikin and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 122 (1949). (b) E. T. McBee and T. M. Burton, *ibid.*, **74**, 3022 (1952). (c) A. Burger and E. Mosettig, *ibid.*, **56**, 1745 (1934).

(5) All melting points are uncorrected. The melting points of the intermediates were taken on a Thomas–Hoover apparatus and those of the phenanthrene amino alcohols on a Kofler hot-stage apparatus.

(6) The nmr spectrum were taken and interpreted by (a) W. Simon, Simon Research Laboratory, Elgin, Ill. (b) W. W. Simons, Sadtler Research Laboratories, Inc. (c) M. Jankowski, Varian Associates, Palo Alto, Calif. Those spectra taken on a Varian A-60-A, 60 MHz, spectrometer are designated by + and those taken on a Varian HA-100D, 100 MHz, spectrometer by ++. Me_4Si was used as an internal standard for all nmr spectra.

(7) Elemental analyses were performed by the analytical staff at International Minerals & Chemical Corp. and Microtech Laboratories, Skokie, Ill.

(8) Where analyses are indicated only by symbols of elements, analytical results were within ±0.4 of the theoretical values.

(9) The dta and tga analyses were performed by J. Currier and E. Bilinski of International Minerals & Chemical Corp.

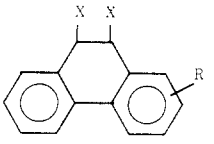
(10) (a) R. D. Haworth, *J. Chem. Soc.*, 1129 (1932). (b) A. L. Wilds and W. J. Close, *J. Amer. Chem. Soc.*, **68**, 83 (1946). (c) Sir R. Robinson and S. N. Slater, *J. Chem. Soc.*, 376 (1941). (d) M. Newman, R. Taylor, T. Hodgson, and A. Garrett, *J. Amer. Chem. Soc.*, **69**, 1784 (1947).

(11) (a) A. Wilds and R. Werth, *J. Org. Chem.*, **17**, 1154 (1952). (b) H. Adkins and E. Burgoyne, *J. Amer. Chem. Soc.*, **71**, 3528 (1949).

(12) W. E. Bachmann and N. C. Deno, *ibid.*, **71**, 3062 (1949).

TABLE II

9,10-DIHALO-9,10-DIHYDROPHENANTHRENECARBOXYLIC ACIDS AND ESTERS

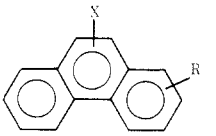


X	R	Method	Mp, °C (dec)	% yield	Formula[f]
Br	4-CO_2H	A[a]	175–180	70	$C_{15}H_{10}Br_2O_2$
Br	1-CO_2H	A[a]	170–220	83	$C_{15}H_{10}Br_2O_2$
Br	4-CO_2Me	A[b]	150–155	85	$C_{16}H_{12}Br_2O_2$
Br	1-CO_2Me	A[c]	120–128	80	$C_{16}H_{12}Br_2O_2$
Cl	4-CO_2H	B	215–220	46	$C_{15}H_{10}Cl_2O_2$
Cl	1-CO_2Me	B[d,e]	150–165	96	$C_{16}H_{12}Cl_2O_2$

[a] Triturated with $CHCl_3$. [b] Recrystallized from MeOH. [c] Triturated with EtOH. [d] Recrystallized from EtOH. [e] Loses HCl on standing at room temperature. [f] All analyzed for C and H.

TABLE III

HALOGENATED PHENANTHRENECARBOXYLIC ACIDS AND ESTERS



X	R	Method	Mp, °C	Recrystn from	% yield	Formula[h]
10-Br	4-CO_2H	A, B[a]	215–217	C_6H_6	94[i]	$C_{15}H_9BrO_2$
10-Cl	4-CO_2H	B[b]	179–181	MeOH	55	$C_{15}H_9ClO_2$
10-Br	4-CO_2Me	B[c]	114.5–116.5	MeOH	83	$C_{16}H_{11}BrO_2$[j]
10-Cl	4-CO_2Me	C	111–116[f]	MeOH	71	$C_{16}H_{11}ClO_2$[j]
9-Br	1-CO_2H	A	292–293[g]	EtOH	87	$C_{15}H_9BrO_2$
9-Cl	1-CO_2H	A	294[b]	EtOH		$C_{15}H_9ClO_2$
9-Br	1-CO_2Me	B[d]	128–131	EtOH[f]	32	$C_{16}H_{11}BrO_2$[j]
9-Cl	1-CO_2Me	B[e]	117–127	EtOH	38	$C_{16}H_{11}ClO_2$[j]

[a] Thermolysis $T \approx 175°$. [b] Thermolysis $T \approx 150°$. [c] Thermolysis $T \approx 155°$. [d] Thermolysis $T \approx 125°$. [e] Thermolysis $T \approx 220°$. [f] Bp 150–160° (0.1 mm). [g] Lit.[2d] 291–292°. [h] Lit.[2d] 293–294°. [i] Starting material, 25 g/100 ml of C_6H_6, filter and cool. [j] From method B. [k] All analyzed for C and H. [l] Structure verified by nmr.

fied by sublimation at reduced pressure. Dehydrobromination of the phenanthrene-1- and -4-carboxylic acids usually resulted in extensive decomposition. These pyrolytic dehydrohalogenation reactions were examined by dta and tga analyses. The temperatures employed for the dehydrohalogenations were in accordance with these findings. Dehydrobromination of the methyl 9,10-dibromo-9,10-dihydrophenanthrene-1- and 4-carboxylates with a tertiary amine yielded only the corresponding methyl phenanthrene-1- and 4-carboxylates.

Method C.—The corresponding acid chloride, prepared with $SOCl_2$, was refluxed with excess MeOH after removal of excess $SOCl_2$. The MeOH was removed and the residue was distilled and purified by recrystallization.

Phenanthroyl Chlorides (Table IV).—The phenanthrenecarboxylic acid was stirred under reflux with approximately a sixfold (w/v) excess of $SOCl_2$ for *ca.* 2 hr. Excess $SOCl_2$ was removed under reduced pressure and 4–5 ml/g of C_6H_6 was added to the residual oil and removed under reduced pressure. After repetition of this process, a fivefold excess of cyclohexane was added to the residue. Two-thirds of the cyclohexane was removed under reduced pressure and the resulting solid phenanthroyl chloride was collected.

Diethyl Phenanthroylmalonates (Table V). Method A.—These reactions were carried out with diethyl ethoxymagnesium malonate.[13] Increasing the diethyl ethoxymagnesium malonate from 1 to 2 mol per mol of acid chloride had little effect on the reaction.

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

TABLE IV

PHENANTHROYL CHLORIDES (R = COCl)

X	R	Mp, °C	% yield	Formula	*Anal.*
H	4	48.5–51		$C_{15}H_9ClO$	C, H
10-Br	4		*b*	$C_{15}H_8BrClO$	
10-Cl	4		*b*	$C_{15}H_8Cl_2O$	
H	1	119.5–121[a]	86	$C_{15}H_9ClO$	C, H
9-Br	1	155–162	86	$C_{15}H_8BrClO$	C, H
9-Cl	1	163–166[a]	94	$C_{15}H_8Cl_2O$	C, H

[a] Triturated with cyclohexane. [b] These compounds were used directly for the preparation of the corresponding diethyl malonates.

TABLE V

DIETHYL PHENANTHROYLMALONATES, R = $COCH(CO_2Et)_2$

X	R	Method	Mp, °C	Recrystn from	% yield	Formula	*Anal.*
H	4	A	82–84	*i*-PrOH	92	$C_{26}H_{28}O_5$	C, H
10-Br	4	B			*a*	$C_{26}H_{27}BrO_5$	
10-Cl	4	B			*a*	$C_{26}H_{27}ClO_5$	
H	1	A, B	91–92.5	EtOH	51[b], 80[c]	$C_{26}H_{28}O_5$	C, H
9-Br	1	A	117.5–120.5	EtOH	77	$C_{26}H_{27}BrO_5$	C, H
9-Cl	1	A	85–88	EtOH	84	$C_{26}H_{27}ClO_5$	C, H

[a] These materials were hydrolyzed and decarboxylated to the corresponding acetyl derivatives. [b] From method B. [c] From method A.

Method B.—This method employed the procedure described by Olsen[14] (see also ref 13, 15).

Acetylphenanthrenes (Table VI).—These compounds were prepared by hydrolysis and decarboxylation of the corresponding 1- and 4-phenanthroyl diethylmalonates according to the procedure of Walker and Hauser.[13]

TABLE VI

ACETYLPHENANTHRENES (R = $COCH_3$)

X	R	Mp, °C	Recrystn from	% yield	Formula	*Anal.*
H	4	87–88[a]	30–60 Petr ether	84	$C_{16}H_{12}O$	C, H
10-Br	4	97–100[b]	EtOH[c]	33	$C_{16}H_{11}BrO$	C, H
10-Cl	4	95–98[d]	EtOH	73	$C_{16}H_{11}ClO$	C, H
9-Br	1	182–186[e]	CH_2Cl_2–EtOH	86	$C_{16}H_{11}BrO$	
9-Cl	1	158.5–160[f]	*i*-PrOH	95	$C_{16}H_{11}ClO$	

[a] Lit. (Table I, footnote *c*) 89.3–90.3°. [b] Bp 175–185° (0.2 mm). [c] Crystallized from EtOH. [d] Bp 181–186° (0.3 mm). [e] Lit.[2d] 185.6°. [f] Lit.[2d] 159–160°.

α-Bromoacetylphenanthrenes (Table VII). Method A.—Br_2 was added to the diethyl 1-phenanthroylmalonate derivatives in refluxing $CHCl_3$ as described by Olsen.[14] After an additional 30-min reflux, the solution was washed (H_2O, 10% Na_2CO_3, H_2O), dried and concentrated. The residue was poured into EtOH from which the malonates shown in Table VIII were obtained by filtration.

The α-bromo-1-phenanthroylmalonates were hydrolyzed and decarboxylated according to the procedure of Olsen[14] by treatment with HOAc–HBr.

Method B.—This procedure, analogous to that described by May and Mosettig,[16] Schultz, *et al.*,[2d] as well as many other investigators, involved the $AlCl_3$-catalyzed addition of a $CHCl_3$ solution of 1 equiv of Br_2 to a solution of the acetylphenanthrene derivative in Et_2O at *ca.* 5°. The precipitated α-bromoacetyl derivative was filtered and purified as indicated.

Addition of 1 equiv of Br_2 to 1-acetyl-9-bromophenanthrene at reflux left a considerable amount of solid. Therefore Br_2 was added until the solution clarified and remained red. The mixture was filtered to remove a small amount of suspended material and the filtrate was cooled. The solid obtained was α,α,9-tribromo-1-acetylphenanthrene, mp 142–144°, yield 86%. *Anal.* ($C_{16}H_9Br_3O$) C, H.

(14) R. E. Olsen, Aerojet General Corp., Sacramento, Calif. Private communication, unpublished results.

(15) A. L. Wilds and L. W. Beck, *J. Amer. Chem. Soc.*, **66**, 1688 (1944).

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

TABLE VII

α-BROMOACETYLPHENANTHRENES (R = $COCH_2Br$)

X	R	Method	Mp, °C	Recrystn from	% yield	Formula	*Anal.*
H	4	B	91–95	EtOH	81	$C_{16}H_{11}BrO$	C, H
10-Br	4	B	146–148		90	$C_{16}H_{10}Br_2O$	C, H
10-Cl	4	B	137–138	*n*-C_7H_{16}	58	$C_{16}H_{10}BrClO$	C, H
H	1	A, B	103–105	*n*-C_7H_{16}	72,[a] 81[b]	$C_{16}H_{11}BrO$	C, H
9-Br	1	A	119–125[c]	*n*-C_7H_{16}	98	$C_{16}H_{10}Br_2O$	
9-Cl	1	B	125.5–127.5	EtOH	86	$C_6H_{10}BrClO$	C, H

[a] From method A. [b] From method B. [c] Lit.[2d] 126–127°.

TABLE VIII

DIETHYL α-BROMO-1-PHENANTHROYLMALONATES

X	Mp, °C	% yield	Formula	*Anal.*
H	118–120	73	$C_{22}H_{19}BrO_5$	C, H
9-Br	109–111	56	$C_{22}H_{18}Br_2O_5$	C, H
9-Cl	75–78	46	$C_{22}H_{18}BrClO_5$	C, H

Phenanthrylethylene Oxides (Table IX).—These compounds were prepared by reduction of the corresponding α-bromoacetyl derivatives with $NaBH_4$, followed by treatment with NaOH, as described generally by Chaikin and Brown[4a] and McBee and Burton.[4b] In cases for which diglyme wa sused as solvent the reduction was carried out at room temperature and the diglyme was removed at reduced pressure after treatment with aqueous

TABLE IX

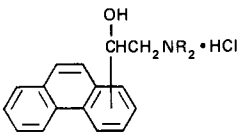
PHENANTHRYLETHYLENE OXIDES (R =)

X	R	Mp, °C	Recrystn from	% yield	Formula	*Anal.*
H	4	82–84		82	$C_{16}H_{12}O$	C, H
10-Br	4	105–106	MeOH[a]	63	$C_{16}H_{11}BrO$	C, H
10-Cl	4	113–114	*n*-C_7H_{16}[a]	35	$C_{16}H_{11}ClO$	C, H
H	1	135–137 (133)		95	$C_{16}H_{12}O$	C, H[b]
9-Br	1	101–103		53	$C_{16}H_{11}BrO$	C, H
9-Cl	1	103–105		84	$C_{16}H_{11}ClO$	C, H

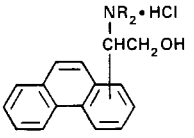
[a] Diglyme used as solvent rather than MeOH. [b] Calcd: C, 87.24; H, 5.49. Found: C, 86.81; H, 5.34.

TABLE X

ANTIMALARIAL ACTIVITY OF PHENANTHRENE 1- AND 4-AMINO ALCOHOLS



A



B

Substituents: Halogen	Substituents: Amino Alcohol	R[a]	Mp, °C	R_f[b]	Yield, %[c]	Formula[d]	Nmr analyses: % A	Nmr analyses: % B	Act IMST[e,f]
	4	C_4	131–134	0.38	21	$C_{24}H_{32}ClNO$	88	12	4.1
	1	C_4	109–112	0.50	57	$C_{24}H_{32}ClNO$	86	14	3.3
	1	C_6	98–115	0.50	33	$C_{28}H_{40}ClNO$	100		3.5
	1	C_7	92–112	0.79	35	$C_{30}H_{44}ClNO$	100		13.9
	4	C_6	131–134	0.62	35	$C_{28}H_{40}ClNO$	67	33	5.7
	4	C_7	132–142	0.68	51	$C_{30}H_{44}ClNO$	90	10	8.4
9-Br	1	C_4	179–181	0.37	69	$C_{24}H_{31}BrClNO$	100		4.9
9-Br	1	C_6	129–132	0.60	42	$C_{28}H_{39}BrClNO$	100		17.9[g]
10-Br	4	C_4	172–174	0.38	40	$C_{24}H_{31}BrClNO$	81	19	9.6
10-Br	4	C_6	132–135	0.76	47[h]	$C_{28}H_{39}BrClNO$	100		8.6
10-Br	4	C_7	149–155	0.82	20	$C_{30}H_{43}BrClNO$	100		9.8
9-Cl	1	C_3	200–203	0.43	54	$C_{22}H_{27}Cl_2NO$	100		3.7
9-Cl	1	C_4	175–178	0.38	77	$C_{24}H_{31}Cl_2NO$	100		6.1
9-Cl	1	C_5	175–177	0.68	66	$C_{26}H_{35}Cl_2NO$	100		8.1
9-Cl	1	C_6	125–127	0.45	64	$C_{28}H_{39}Cl_2NO$	100		14.7
9-Cl	1	C_7	128–130	0.65	25	$C_{30}H_{43}Cl_2NO$	100		14.0
10-Cl	4	C_4	179–181	0.59	42	$C_{24}H_{31}Cl_2NO$	100		10.1

[a] All *n*-alkyl groups. [b] Tlc on silica gel, developed with 1% MeOH in C_6H_6. Visualization with short-wave uv. [c] From the epoxide. [d] The C, H, and N analyses for all compounds agreed with the indicated formulas ±0.30%. [e] For details of test procedure see T. S. Osdene, P. B. Russell, and Leo Rane, *J. Med. Chem.*, **10,** 431 (1967). Test data supplied by Walter Reed Army Institute of Research. [f] Increase in mean survival time at dose = 640 mg/kg. At 320 mg/kg, all IMST <7.1, unless otherwise noted. [g] IMST = 16.9 at 320 mg/kg; one cure. Two cures at 640 mg/kg. [h] Yield of free base.

NaOH at 5°. Other unsuccessful attempts at reduction employed $NaBH_4$ in EtOH, *i*-PrOH, and methyl Cellosolve, and LAH in *i*-PrOH.[17] All resulted in high recoveries of starting material. LAH in THF gave an unidentified product from α,10-dibromo-4-acetylphenanthrene.

Phenanthrene Amino Alcohols (Table X).—All the phenanthrene amino alcohols were prepared by reaction of the epoxide with the appropriate amine as first reported by Horne and Shriner[18a] and Headler, *et al.*,[18b] and subsequently utilized by many investigators. The procedure employed is basically that of Rice.[18c] Possibly a reaction temperature lower than that presently used (160°) would give better results.

With the higher boiling amines it was frequently necessary to steam distil the crude product to remove the remaining traces of amine prior to molecular distillation. Preparation of the hydro-

(17) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **77,** 6209 (1955).

(18) (a) W. H. Horne and R. L. Shriner, *ibid.*, **54,** 2925 (1932). (b) A. J. W. Headler, A. R. Collett, and C. L. Lazzell, *ibid.*, **55,** 1066 (1933). (c) Capt. K. Rice, U. S. Army, WRAIR Symposium, Nov 27, 1967.

chlorides in Et_2O was usually followed by recrystallization from cyclohexane and/or C_6H_6. The tlc's were done on silica gel. They were developed in 99% C_6H_6–1% MeOH or *i*-PrOH and visualized with uv light. The R_f values were essentially the same with either of these two developing media.

4-(2-*n*-Dibutylamino-1-hydroxyethyl)phenanthrene Hydrochloride.—A solution of 5.0 g (0.227 mol) of 4-phenanthrylethylene oxide in 35 ml of *n*-Bu_2NH was refluxed at 160° for 16 hr. The excess amine was removed at reduced pressure. The residue was distilled at 199–212° (0.05 mm) with a molecular still to yield 1.8 g (23%) of 4-(2-*n*-dibutylamino-1-hydroxyethyl)-phenanthrene. This was dissolved in 250 ml of C_6H_6 and saturated with HCl. The solution was refluxed for 2 hr with a Dean–Stark trap. The C_6H_6 was removed under reduced pressure and 250 ml of Et_2O was added to the oily residue. The solution was refluxed overnight and the solid collected by filtration to yield 1.8 g (90%) of product, mp 131–134° (softens 125°). *Anal.* ($C_{24}H_{32}ClNO$) C, H, N.

The nmr spectrum[3] of the product was as expected and typical of these compounds, *e.g.*, δ ($CDCl_3$) 0.80 (CH_3), 1.24 (CH_2), 1.62 (NCH_2CH_2), 3.06 (NCH_2), 6.56 (CHOH), 7.35–8.07 (phenanthryl protons), and 8.60–8.70 (phenanthryl 4 and 5 protons) ppm. Formation of the free base by washing the $CDCl_3$ solution with aqueous $NaHCO_3$ resulted in a shift in CH_2 peaks centered at δ 3.50–2.70 ppm (peak at δ 3.06 ppm) to 3.50–2.50 ppm as well as a concentration-dependent shift in the CH proton peaks to a doublet of doublets at δ 6.26 ppm ($CH(OH)CH_2NR_2$) and to a triplet at 4.62 ppm ($CH(CH_2OH)NR_2$). The integration ratios of these two groups permitted an analysis of the isomer content of the sample when the undesirable isomer was present. This nmr analysis showed the product to be 88% isomer A and 12% of the undesired isomer B (see Table X).

All of the amino alcohols showed some antimalarial activity in mice. Only 1-(2-*n*-dihexylamino-1-hydroxyethyl)-9-bromophenanthrene gave cures (2 out of 5) at 640 mg/kg. This series is being extended to include additional halogenated phenanthrenes.

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Nitrones. II.[1] α-(5-Nitro-2-furyl)-*N*-cycloalkyl- and -*N*-alkylnitrones

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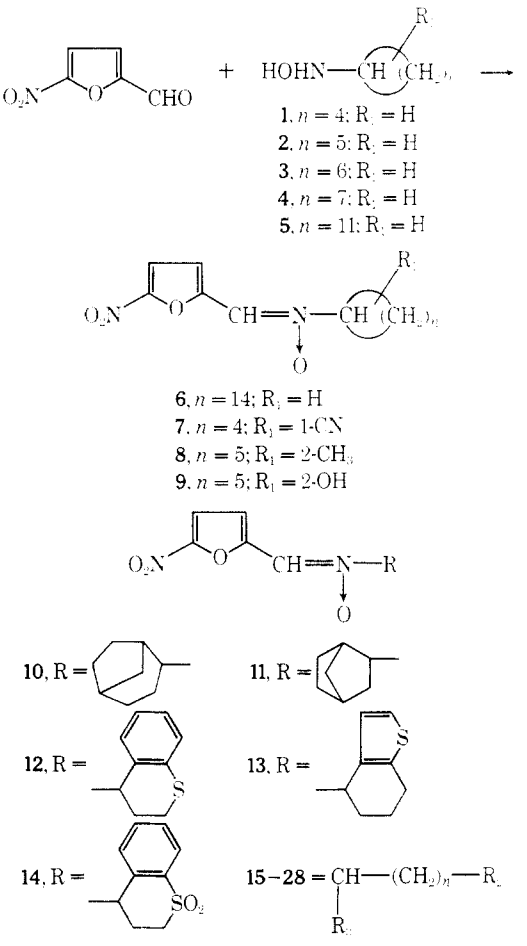
A series of α-(5-nitro-2-furyl)-*N*-cycloalkylnitrones, *N*-bicycloalkyl and *N*-heterocycloalkylnitrones, and *N*-alkylnitrones were synthesized and evaluated as antibacterial, antifungal, and anticoccidial agents. Saturation of the phenyl ring of α-(5-nitro-2-furyl)-*N*-phenylnitrone[1] enhanced its antibacterial activity. Replacement of the cyclohexyl moiety by Me (**15**) further enhanced the antibacterial activity. Structure–activity relationships are discussed.

In a previous paper,[1] the preparation and biological activities of some α-(5-nitro-2-furyl)-*N*-arylnitrones were reported. This paper describes an extension of this series to include analogs in which the *N*-aryl group was replaced by cycloalkyl, bicycloalkyl, heterocycloalkyl, and alkyl groups. Compounds **1–28** were obtained in 6–93% yield by the reaction of 5-nitrofurfural and the corresponding *N*-substituted hydroxylamines either directly or by liberating them *in situ* from their HCl salts as illustrated in eq 1. Physical and analytical data for the nitrones are listed in Tables I and II. Compounds **15–17** and **22** were reported[3] subsequent to our work.

Direct interaction of free lower *N*-alkylhydroxylamines, *e.g.*, *N*-propylhydroxylamine, with 5-nitrofurfural caused rapid decomposition of the aldehyde, whereas treatment with cycloalkyl-, heterocycloalkyl-, *e.g.*, **30–32**, and higher alkylhydroxylamines, *e.g.*, **33–39**, resulted in the formation of the desired nitrones without difficulty. In the case of **28**, the reaction was carried out in an aqueous medium containing base to give the product as its Na salt.

The *N*-substituted hydroxylamines (Table III) were prepared by diborane reduction of the corresponding oximes according to Feuer, *et al.*,[4] or by the cyanide–



(1) For paper I, see H. K. Kim and R. E. Bambury, *J. Med. Chem.*, **12**, 719 (1969).

(2) Deceased May 21, 1968.

(3) Dainippon Pharmaceutical Co., Ltd., British Patent 1,105,007; *Chem. Abstr.*, **69**, 86809 (1968).

(4) H. Feuer, B. F. Vincent, Jr., and R. S. Bartlett, *J. Org. Chem.*, **30**, 2877 (1965).