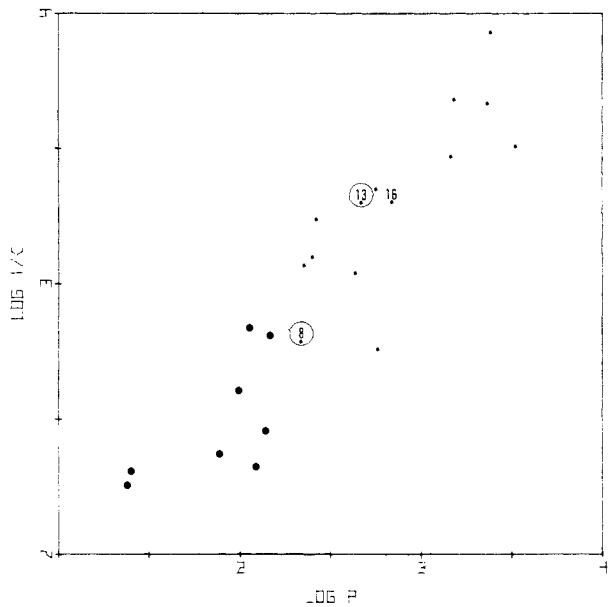

Figure 1. Plot of log $1/C$ vs. log P for data in Table IV of ref 2. Fibonacci progress is shown.

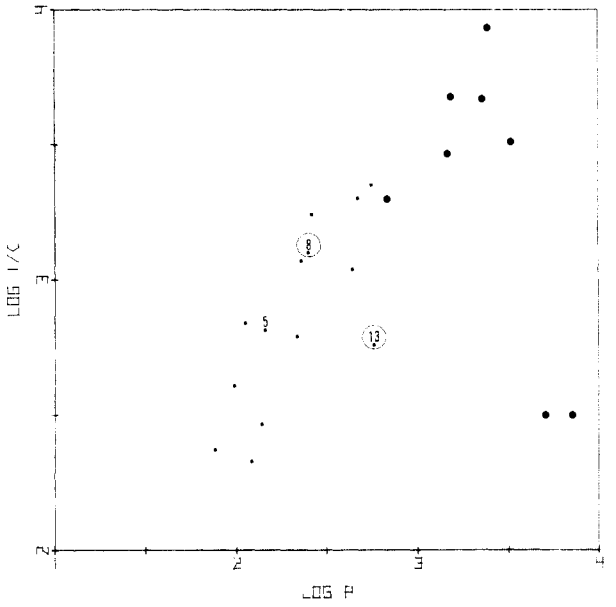

Figure 2. Plot of log $1/C$ vs. log P for data set of Figure 1 excluding first two data points. Fibonacci progress is shown.

points have been added at the right to give the desired total of 22 points. This situation is shown in Figure 2. The Fibonacci points 8 and 13 (circled) are evaluated. On the basis of these two results, the search proceeds to evaluate point 5 and in so doing *excludes from future search* points 14–21 (oversize dots). The consequences, in this case, are that the region containing the most active compounds will be overlooked entirely.

Efficient single-factor searches utilizing discrete levels of the factor and dealing with noise in the response surface are probably few if, in fact, any exist. More complete discussions of the general problem may be found in the literature.[5,6]

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Antimalarials. 9. Methylthio- and Methylsulfonyl-Substituted 9-Phenanthrenemethanols

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Ash Stevens Inc., Detroit, Michigan 48202. *Received November 24, 1975*

Nine di- and trisubstituted 9-phenanthrenemethanols bearing methylthio and methylsulfonyl substituents in the 2 and/or 6 positions of the phenanthrene nucleus were prepared and screened for antimalarial activity against *Plasmodium berghei* in mice. Six of the nine compounds were curative at or below 160 mg/kg. The most active structures contained a methylthio substituent in combination with two chlorine atoms.

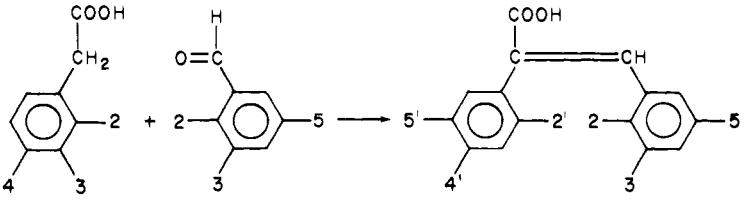
The efficacy of many simple 9-phenanthrenemethanols against *Plasmodium gallinaceum* in chicks was reported by Coatney et al.[1] in their monograph. The compound with the highest chemotherapeutic index was 6-bromo-α-(di-*n*-heptylaminomethyl)-9-phenanthrenemethanol prepared by May and Mosettig.[2] More recently, the search for drugs effective against drug-resistant *falciparum* malaria resulted in the reinvestigation of the 9-phenanthrenemethanols. Cheng et al.[3] investigated the effects of modifying the amino alcohol side chain upon antimalarial activity.[4] Also, Nodiff et al.[5] prepared a number of trifluoromethyl- and halo-substituted 9-phenanthrenemethanols which possessed superior activity against *P. berghei* in mice; one compound, 2,4-bis(trifluoromethyl)-6,7-dichloro-α-(di-*n*-propylaminomethyl)-9-phenanthrenemethanol, was curative at a dosage of 5 mg/kg.

The purpose of the present work was to investigate the effects of introducing sulfur-containing substituents onto the phenanthrene nucleus upon the antimalarial activity. No potential antimalarial amino alcohols bearing these substituents on the aromatic nucleus have been reported.

Chemistry. The requisite phenanthroic acids (Table II) were prepared by the standard Perkin–Pschorr phenanthrene synthesis.[6-8] Thus, the Perkin reaction between the appropriate phenylacetic acids and benzaldehydes afforded the intermediate nitrocinnamic acids shown in Table I. In two of the four cases, a mixture of *cis*- and *trans*-cinnamic acids was obtained. However, these mixtures were converted to the desired 9-phenanthroic acids without difficulty, albeit in relatively low yields.

In the cases where the methylthiophenylacetic acids were not purchasable, the properly substituted halo-

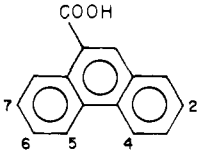
Table I. Nitro-α-phenylcinnamic Acids



No.	Phenylacetic acid	Benzaldehyde	Phenylcinnamic acid	Mp, °C (solvent)	Yield, %	Formula	Analyses[a]
Ia	4-SCH_3	2-NO_2, 5-Br	2-NO_2, 5-Br, 4′-SCH_3	156–159 (EtOH)	51	$C_{14}H_{12}BrNO_4S$	S
Ib	3,4-Cl_2	2-NO_2, 5-Cl	2-NO_2, 3′,4′,5-Cl_3	153–155 (C_6H_6-petr ether)	40	$C_{16}H_8Cl_3NO_4$	Cl, N
Ic			2-NO_2, 5-SCH_3, 3′,4′-Cl_2	180–182 (C_6H_6)	70[b]	$C_{16}H_{11}Cl_2NO_4S$	S; C[c]
Id	4-SCH_3	2-NO_2, 3,5-Cl_2	2-NO_2, 3,5-Cl_2, 4′-SCH_3	142–153[d] (C_6H_6-petr ether)	70	$C_{16}H_{11}Cl_2NO_4S$	Cl, S
Ie	4-SCH_3	2-NO_2, 5-Cl	2-NO_2, 5-Cl, 4′-SCH_3	134–145[d] (C_6H_6-petr ether)	53	$C_{16}H_{12}ClNO_4S$	
If			2-NO_2, 4′,5-$(SCH_3)_2$	135–152[d] (C_6H_6)	70[e]	$C_{17}H_{15}NO_4S_2$	N, S

[a] In addition to C, H. [b] From Ib. [c] C: calcd, 50.01; found, 49.44. [d] Compound is a mixture of *cis*- and *trans*-cinnamic acids, used without further purification. [e] From Ie.

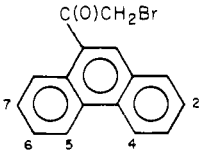
Table II. Phenanthrene-9-carboxylic Acids



No.	Substituents	Mp, °C (solvent)	Yield, %[a]	Formula	Analyses[b]
IIa	2-Br, 6-SCH_3	254–256 (EtOH-H_2O)	34	$C_{16}H_{11}BrO_2S$	S
IIb	2-Br, 6-SO_2CH_3	269–271 (EtOH-C_6H_6)	80[d]	$C_{16}H_{11}BrO_4S$	S
IIc[c]	2-SCH_3, 5,6-Cl_2	240–242 (EtOH-C_6H_6)	32	$C_{16}H_{10}Cl_2O_2S \cdot H_2O$	S
IId[c]	2-SO_2CH_3, 5,6-Cl_2	265–268 (EtOH-C_6H_6)	80[d]	$C_{16}H_{11}Cl_2O_4S$	
IIe[e]	2-SCH_3, 6,7-Cl_2	302–306 (dioxane)	41	$C_{16}H_{10}Cl_2O_2S$	
IIf[e]	2-SO_2CH_3, 6,7-Cl_2	315–317 (dioxane)	85[d]	$C_{16}H_{10}Cl_2O_4S$	S
IIg	2,6-$(SCH_3)_2$	224–226 (toluene)	35	$C_{17}H_{14}O_2S_2$	S
IIh	2,6-$(SO_2CH_3)_2$	320–324 (CH_2Cl_2)	80[d]	$C_{17}H_{14}O_6S$	S
IIi	2,4-Cl_2, 6-SCH_3	228–230 (HOAc)	21	$C_{16}H_{10}Cl_2O_2S$	Cl, S

[a] From the sodium salt of aminocinnamic acid. [b] In addition to C, H. [c] Or the 6,7-dichloro isomer. [d] From methylthiophenanthroic acid. [e] Or the 5,6-dichloro isomer.

Table III. Bromomethyl 9-Phenanthryl Ketones



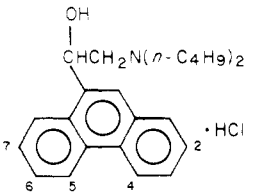
No.[a]	Mp, °C (solvent)	Yield, %[b]	Formula	Analyses
IIIa	165–170	57	$C_{17}H_{12}Br_2SO$	[c]
IIIb	203–205 (EtOH-C_6H_6)	72	$C_{17}H_{12}Br_2SO_3$	Br
IIIc	150–153	56	$C_{17}H_{11}BrCl_2OS$	[c]
IIId	175–179	51	$C_{17}H_{11}BrCl_2O_3S$	[c]
IIIe	156–159	44	$C_{17}H_{11}BrCl_2OS$	[c]
IIIf	184–187	57	$C_{17}H_{11}BrCl_2O_3S$	[c]
IIIg	152–154 ($CHCl_3$-petr ether)	83	$C_{18}H_{15}BrOS_2$	C, H, Br, S
IIIh	238–240 ($CHCl_3$-petr ether)	61	$C_{18}H_{15}BrO_5S_2$	C, H
IIIi	163–165 ($CHCl_3$-petr ether)	79	$C_{17}H_{11}BrCl_2OS$	C, H, S

[a] For nuclear substituents, see Table II. [b] From 9-phenanthroic acid. [c] Not purified.

nitrocinnamic acids were prepared, followed by displacement of the activated halogen atom with sodium thiomethylate to yield the desired sulfur-containing cinnamic acids. Reduction with ferrous sulfate and sodium hydroxide gave the corresponding aminocinnamic acids which were isolated as the sodium salts and used without further purification. Pschorr cyclization[7,8] gave the 9-phenanthroic acids (II) which were converted to the target amino alcohols **1–9** by the standard Lutz[9] side-chain procedure. The sequence, as applied to compounds **7** and **8**, is shown in Scheme I. The physical data are compiled in Tables I–IV.

It should be noted that the Pschorr ring closure of nitrocinnamic acid Ic can lead to the formation of two dichlorophenanthroic acid isomers. In this case, as in a previous example reported by May and Mosettig,[2] two isomers designated 6,x-dichloro and 6,y-dichloro were indeed formed and separated by fractional crystallization.

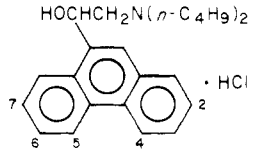
Table IV. α-Di(*n*-butylaminomethyl)-9-phenanthrenemethanols



No.	Substituents	Mp, °C (solvent)	Yield, %[a]	Formula	Analyses[b]
1	2-Br, 6-SCH_3	231-233 (*i*-PrOH)	29	$C_{25}H_{31}BrClNOS$	
2	2-Br, 6-SO_2CH_3	270-272 (CH_3CN-Et_2O)	27	$C_{25}H_{31}BrClNO_3S$	S
3	2-SCH_3, 5,6-Cl_2[c]	228-230 (EtOH-Et_2O)	25	$C_{25}H_{30}Cl_3NOS \cdot 0.5H_2O$	
4	2-SO_2CH_3, 5,6-Cl_2[c]	242-244 (*i*-PrOH)	24	$C_{25}H_{31}Cl_3NO_3S \cdot 0.5H_2O$	S
5	2-SCH_3, 6,7-Cl_2[d]	238-240 (CH_3CN)	31	$C_{25}H_{30}Cl_3NOS \cdot H_2O$	
6	2-SO_2CH_3, 6,7-Cl_2[d]	250-252 (*i*-PrOH)	20	$C_{25}H_{31}Cl_3NO_3S \cdot H_2O$	S
7	2,6-$(SCH_3)_2$	221-223 (*i*-PrOH)	33	$C_{26}H_{36}ClNOS_2$	Cl, S
8	2,6-$(SO_2CH_3)_2$	270-272 (EtOH-CH_3CN)	39	$C_{26}H_{36}ClNO_5S_2$	S
9	2,4-Cl_2, 6-SCH_3	216-218 (*i*-PrOH)	49	$C_{25}H_{32}Cl_3NOS$	Cl, S

[a] From bromomethyl ketone. [b] In addition to C, H, N. [c] Or the 6,7-dichloro isomer. [d] Or the 5,6-dichloro isomer.

Table V. Antimalarial Activity[a]



		ΔMST or C at dose, mg/kg				
No.	Substituents	20	40	80	160	320
1	2-Br, 6-SCH_3	2.8	8.6 (A)	9.5 (A)		
2	2-Br, 6-SO_2CH_3	0.6	1.2	10.8 (A)	2C	
3	2-SCH_3, 5,6-Cl_2	9.3 (A)	10.7 (A)	3C	3C	
4	2-SO_2CH_3, 5,6-Cl_2	4.7	7.7 (A)	14.9 (A)	3C	5C
5	2-SCH_3, 6,7-Cl_2	9.1 (A)	10.3 (A)	2C	5C	
6	2-SO_2CH_3, 6,7-Cl_2	4.9	8.5 (A)	2C	4C	5C
7	2,6-$(SCH_3)_2$	0.7	5.9	11.5 (A)	16.1 (A)	5C
8	2,6-$(SO_2CH_3)_2$		0.1	0.3	0.3	0.3
9	2,4-Cl_2, 6-SCH_3	10.5 (A)	2C	3C	5C	5C

[a] Test method described by T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). This test has been made as a highly standardized procedure in which the *P. berghei* causes death of control mice at an average of 6.2 days. An increase in survival of mice by more than 2.5 days beyond this time has been found to be statistically significant. Mice which live more than 60 days are regarded as cured (C). Drugs which double the survival time of mice compared to controls (ΔMST ≥ 6.2) are considered active (A). Groups of five mice have been used at each dose level of the drugs.

No attempt was made to determine their absolute structures since no appreciable difference in antimalarial activity was observed between the isomeric amino alcohols. Also, the amino alcohols, although moderately active against *P. berghei*, were clearly inferior to many of the compounds prepared by Nodiff and co-workers.[5]

Biological Activity. Antimalarial activity data against *P. berghei* in mice[4,10] are presented in Table V. Testing was performed at the Leo Rane Laboratory, University of Miami, Fla. Examination of the data indicates that optimum nuclear substitution is two chlorine atoms in addition to a methylthio group. Thus, the three most active compounds, **3**, **5**, and **9**, bear these substituents. Compound **9**, 2,4-dichloro-6-methylthio-9-phenanthrenemethanol, the most active compound of the nine reported herein, gives 5/5 cures at 160 and 320 mg/kg and a ΔMST value of 12.5 days at 20 mg/kg. In fact, **9** is approximately one dose level more active than the 2,4-dichloro-6-trifluoromethyl analogue prepared by Nodiff and co-workers;[5b] in this case at least, the methylthio group is superior to a trifluoromethyl group. On the other hand, the 2-bromo-6-methylthio analogue **1** is considerably less active than the corresponding 2-bromo-6-trifluoromethyl compound reported also by Nodiff.[5b] Comparing the relative efficacy of methylsulfonyl and methylthio groups, the latter group is clearly superior as evidenced by comparing **1** and **2**, **3** and **4**, **5** and **6**, and **7** and **8**.

Experimental Section

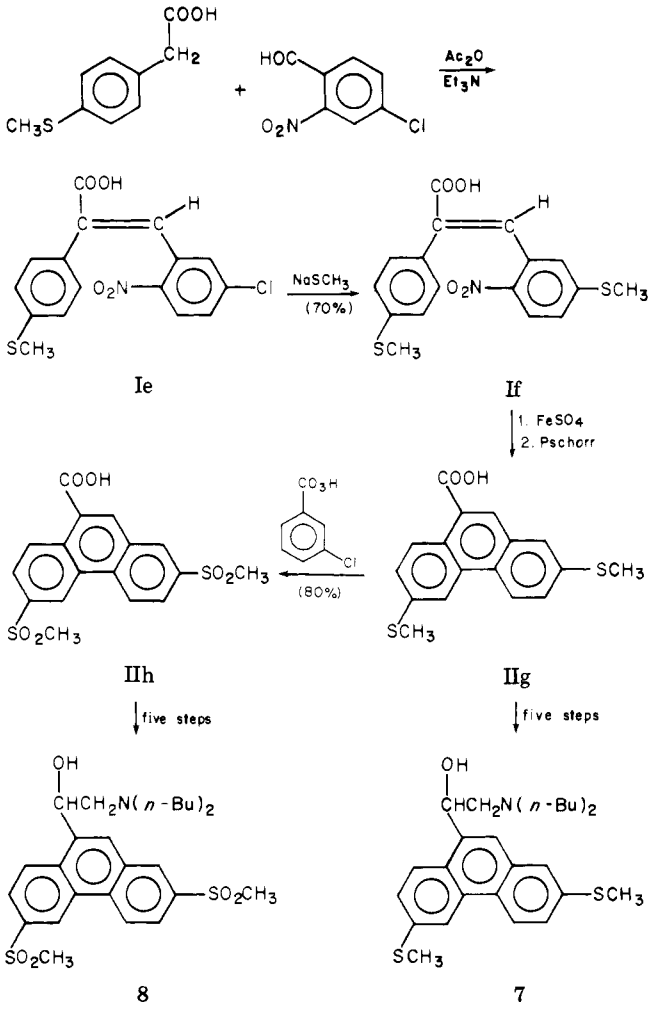
Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Analyses indicated by element symbols agree with calculated values within ±0.4%.

The following procedure, as applied to the preparation of compound **7**, is typical of that used to prepare the nine target amino alcohols.

α-(4-Methylthiophenyl)-2-nitro-5-chlorocinnamic Acid (Ie). A solution of 4-methylthiophenylacetic acid (38.3 g, 0.2 mol), 5-chloro-2-nitrobenzaldehyde (38.3 g, 0.2 mol), and triethylamine (30 ml) in acetic anhydride (450 ml) was heated at 80° (oil bath) for 18 h. Hot water (800 ml) was added and the mixture was allowed to cool to room temperature. The aqueous phase was decanted and the residual oil was dissolved in 10% aqueous potassium carbonate solution (800 ml). The basic solution was extracted with ether (2 × 500 ml) and acidified (HCl) to pH 2. The oil which separated crystallized on standing. The solid was filtered and recrystallized from benzene–petroleum ether to afford the desired product (36 g, 53%), mp 134–145°. This material is believed to be a mixture of *cis*- and *trans*-cinnamic acids.

α-(4-Methylthiophenyl)-2-nitro-5-methylthiocinnamic Acid (If). To a solution of the preceding acid (31 g, 0.09 mol)

Scheme I



in methanol (900 ml) was added slowly a solution of sodium thiomethylate (31 g) in methanol (450 ml). The solution was heated at reflux for 6 h. The cooled solution was acidified to pH 2 (HNO_3) and the solvent was removed under reduced pressure. The residual solid was dissolved in methylene chloride and washed with water (twice). The organic layer was dried (Na_2SO_4) and concentrated. The solid was crystallized from benzene (twice) to afford the title compound (22.5 g, 70%), mp 135–152°. This material is believed also to be a mixture of *cis*- and *trans*-cinnamic acids. Anal. ($C_{17}H_{15}NO_4S_2$) C, H, N, S.

Sodium Salt of α-(4-Methylthiophenyl)-2-amino-5-methylthiocinnamic Acid. A solution of the above acid (24.5 g, 0.068 mol), ferrous sulfate heptahydrate (175 g) in water (590 ml), and 10% sodium hydroxide (590 ml) was heated at reflux for 3 h. During this time, additional 10% sodium hydroxide (275 ml) was added portionwise. Charcoal was added and the solution was filtered through Celite. The filtrate was concentrated to one-half volume and cooled. The title sodium salt (23 g, 95%) was obtained upon filtration.

2,6-Bis(methylthio)-9-phenanthroic Acid (IIg). Isoamyl nitrite (8.2 ml) was added to a slurry of the aminocinnamic acid sodium salt (7.4 g, 0.021 mol) in ethanol (63 ml). The slurry was held at −10° and ethanol saturated with dry HCl (45 ml) was added over a 30-min period. The yellow slurry was stirred at about −10° for 2.5 h. The mixture was then carefully poured into a solution of sodium hypophosphite (25 g), copper bronze (0.13 g), and concentrated sulfuric acid (0.25 ml) in water (62 ml) at 50°. The resulting slurry was stirred at 40–50° for 3.5 h and filtered. The solid was washed with warm water and recrystallized from glacial acetic acid (150 ml) to afford the title acid (2.3 g, 35%), mp 224–226°. This material was dissolved in hot 2% sodium hydroxide (55 ml) and cooled. The sodium salt was filtered and slurried in dilute hydrochloric acid. The acid was filtered and crystallized from hot toluene (200 ml) to yield analytically pure colorless phenanthroic acid (1.4 g), mp 224–226°. Anal. ($C_{17}H_{14}O_2S_2$) C, H, S.

2,6-Bis(methylthio)-9-phenanthroic Acid Chloride. A slurry of 2,6-bis(methylthio)-9-phenanthroic acid (1.7 g, 5.4 mmol) in thionyl chloride (50 ml) was warmed until all the acid was dissolved. The solution was then stirred at room temperature for 30 min. The excess thionyl chloride was removed under reduced pressure and the last traces of reagent were removed by azeotroping with benzene (twice). The crude acid chloride was used in the next step without further purification.

Diazomethyl 2,6-Bis(methylthio)-9-phenanthryl Ketone. A slurry of the above acid chloride (1.7 g) in dichloromethane (100 ml) was added to a solution of diazomethane (ca. 5 g) in ether–dichloromethane (1:1, v/v, 200 ml). The solution was placed in the freezer for 17 h. The solvents were removed under reduced pressure to yield the crude diazo ketone, mp 123° dec. A sample was crystallized from chloroform–petroleum ether to afford an analytical sample, mp 128° dec. Anal. ($C_{18}H_{14}N_2OS_2$) N.

Bromomethyl 2,6-Bis(methylthio)-9-phenanthryl Ketone (IIIg). To a mixture of hydrobromic acid (48%, 7 ml) in acetic acid (70 ml) at 0–5° was added a solution of the above diazo ketone (1.5 g, 4.4 mmol) in chloroform (75 ml). The solution was stirred at room temperature for 30 min. Water (75 ml) and chloroform (75 ml) were added. The layers were separated. The organic layer was washed with water (twice) and 10% sodium carbonate (once), dried (Na_2SO_4), and concentrated under reduced pressure to yield the title compound. The material was crystallized from chloroform–petroleum ether to yield the pure title bromo ketone (1.43 g, 83%), mp 152–154° dec. Anal. ($C_{18}H_{15}BrOS_2$) C, H, Br, S.

α-Di-*n*-butylaminomethyl-2,6-bis(methylthio)-9-phenanthrenemethanol Hydrochloride (7). To a slurry of the above bromo ketone (1.5 g, 3.8 mmol) in ethoxyethanol (70 ml) at 0–5° was added a solution of sodium borohydride (300 mg) in water (3 ml). The solution was stirred at room temperature for 2 h. Water (100 ml) was added and the pH was adjusted to 5–6 with dilute hydrochloric acid. The slurry was extracted with chloroform. The organic layer was dried and concentrated to yield a mixture of epoxide and bromohydrin. This mixture, ethanol (70 ml), and dibutylamine (7 ml) were heated at reflux for 17 h. The solvent and excess dibutylamine were removed in vacuo. The residual oil was dissolved in ether and the solution was washed with water (three times). The organic layer was dried and ethereal hydrogen chloride was added to pH 2. The solid was filtered, washed with water, and crystallized from isopropyl alcohol to yield the title compound (0.6 g, 33%), mp 221–223°. Anal. ($C_{26}H_{36}ClNOS_2$) C, H, Cl, N, S.

2,6-Dimethylsulfonyl-9-phenanthroic Acid (IIh). 2,6-Dimethylthio-9-phenanthroic acid (2.2 g), *m*-chloroperbenzoic acid (8 g), and methylene chloride (200 ml) were refluxed for 3 h. After cooling, the title acid was filtered and washed with ether. The yield was 2.1 g (80%), mp 320–324° dec. Anal. ($C_{17}H_{14}O_6S_2$) C, H, S.

Preparation and Separation of Isomeric 2-Methylthio-6,x- and -6,y-dichlorophenanthroic Acids. Sodium Salt of α-(3,4-Dichlorophenyl)-2-amino-5-methylthiocinnamic Acid. To a solution of $FeSO_4 \cdot 7H_2O$ (110 g in 400 ml of water) was added 10% sodium hydroxide (400 ml). The suspension was heated to 90° and treated with the aqueous solution of Ic (19 g in 50 ml of water and 15 ml of 10% sodium hydroxide). The mixture was stirred and held at 95–100° for 3 h. The hot suspension was filtered and the filtrate was concentrated to one-third of the original volume. After cooling, the title sodium salt separated (18 g, 90%). It was dried and used for the next step without purification.

2-Methylthio-6,x- and -6,y-dichloro-9-phenanthroic Acids. Isoamyl nitrite (18 ml) was added to a slurry of the above salt (17.5 g, 0.05 ml) in ethanol (200 ml). The suspension was kept at −5° and ethanol saturated with HCl (100 ml) was added over a 30-min period. The yellow suspension was stirred at 0° for 4 h and then carefully poured into a mixture of sodium hypophosphite (80 g in 700 ml of water), copper bronze (2 g), and 4 drops of concentrated sulfuric acid. The reaction temperature during the addition was held at 50°. The suspension was stirred at 50° for another 3 h, then cooled to room temperature, and filtered. The mixture of the crude isomeric acids was suspended in hot 2% sodium hydroxide. The insoluble portion was filtered

and the filtrate was acidified. The isomeric acids were separated, washed with water, and dried (8.5 g, 51%), mp 215–230°.

Separation of 6,x-Dichloro Acid. The above crude mixture was refluxed with 100 ml of ethanol and refrigerated. Almost pure title acid separated. It was recrystallized (twice) from boiling dioxane to give 3.6 g (41%) of 6,x-acid, mp 302–306° dec. Anal. ($C_{16}H_{10}Cl_2O_2S$) C, H.

Separation of the 6,y-Dichloro Acid. The ethanolic mother liquor, after separation of the previous isomeric acid, was evaporated to dryness. The residue was recrystallized from a mixture of ethanol–benzene (three times) to give 2.6 g (32%) of the 6,y-acid, mp 240–242° dec. Anal. ($C_{16}H_{10}Cl_2O_2S \cdot H_2O$) C, H.

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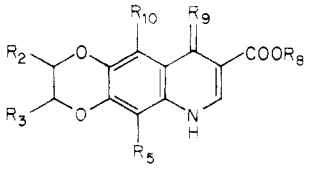
Communications to the Editor

A New Class of Diuretics with the 1,4-Dioxino[2,3-*g*]quinolone Structure

Sir:

We have synthesized a number of new 2,3,6,9-tetrahydro-9-oxo-1,4-dioxino[2,3-*g*]quinoline-8-carboxylic acid derivatives. Surprisingly, some of these compounds proved to possess an extremely high diuretic activity. The synthesis of the compounds started with 2-(hydroxymethyl)-7-nitrobenzo-1,4-dioxane,[1] which was successively alkylated with diethyl sulfate, reduced with hydrogen (Pd/C) to the amine, condensed with diethyl ethoxymethylenemalonate, and cyclized to the tricyclic ester **1**. The isomeric compound **11** and the 10-substituted derivatives **2**, **3**, and **4** were obtained similarly. Reaction of

Table I. Oral Diuretic Activity in Rats[a] and Physical Properties



R_2, R_5 = H; R_3 = $EtOCH_2$; R_8 = Et; R_9 = O[b]

No.	R_{10}	Deviations R_2–R_9	ED_{200},[c] mg/kg po	Formula	Analyses[d]	Mp,[e] °C
1	H		3.8	$C_{17}H_{19}NO_5$	C, H, N	266–268
2	Cl		0.08	$C_{17}H_{18}ClNO_5$	C, H, N, Cl	293–295
3	Br		~0.4	$C_{17}H_{18}BrNO_5$	C, H, N	258–263
4	CF_3		~0.5	$C_{18}H_{18}F_3NO_5$	H, N, F; C[f]	250–251
5	NO_2		~3	$C_{17}H_{18}N_2O_7$	H; C, N[g]	301–303
6	H	R_5 = Cl	na[h]	$C_{17}H_{18}ClNO_5$	H, Cl; C[i]	196.5–198
7	Cl	R_5 = Cl	na[h]	$C_{17}H_{17}Cl_2NO_5$	H, N; C[j]	212–214
8	Cl	R_8 = H	0.14	$C_{15}H_{14}ClNO_5$	C, H, N, Cl	266–267
9	H	R_9 = S	13	$C_{17}H_{19}NO_5S$	H, N, S; C[k]	199–202[l]
10	Cl	R_9 = NH	2	$C_{17}H_{19}ClN_2O_5$	C, H, N, Cl	174–176[m]
11	Cl	R_2 = $EtOCH_2$; R_3 = H	2.5	$C_{17}H_{18}ClNO_5$	H, N; C[n]	250–260
12	Furosemide[o]		28			
13	Chlorothiazide[p]		30			

[a] Male albino rats (strain Wistar-TNO; 160 ± 20 g). [b] Unless otherwise indicated (in the column "deviations R_2–R_9"). [c] The dose inducing a 100% increase of the urinary volume over the control value, measured over a 5-h period. [d] Unless otherwise indicated, the analyses were within ±0.4% of the theoretical values. The NMR spectra of all compounds were in agreement with the assigned structures. Most compounds were recrystallized from DMF. [e] Uncorrected; with decomposition. [f] C: calcd, 53.87; found, 53.31. [g] C: calcd, 53.96; found, 53.47. N: calcd, 7.41; found, 6.96. [h] Inactive at 50 mg/kg. [i] C: calcd, 55.51; found, 55.97. [j] C: calcd, 50.76; found, 49.93. [k] C: calcd, 58.43; found, 57.85. [l] From *i*-PrOH. [m] Hydrochloride salt (from Me_2CO-hexane). [n] C: calcd, 55.51; found, 53.42. [o] 4-Chloro-*N*-furfuryl-5-sulfamoylanthranilic acid. [p] 6-Chloro-2*H*-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide.