It has been reported[4] that many effective antitumor alkaloids possess two oxygens and one nitrogen, which three functions define a triangle of certain optimum interatomic distances for optimum activity. The O-O bond distances in all the compounds listed here fall within the accepted range for one leg of the triangle. The N-O bond distances in all the compounds are, however, shorter than the minimum value listed[4] for effective structures. However, the closest match does come with **3**, **4**, and **9** where the distances from the ring B nitrogen to the ring A oxygens are 6.2 and 6.3 Å# as compared to the lowest optimum values of about 6.5 and 8.0 Å.

A second more likely possibility is that the important active site of the molecule is the $-C=N^+$ region of ring B in **3** and **9** since the carbon of the iminium function represents an effective alkylation site. This functionality has previously been invoked[5] to account for other biological activities of **2** which disappear upon conversion to the dihydro derivative **5f**. Presence of the peri group of ring A in the sanguinarine and chelerythrine derivatives could sterically block attack at the ring iminium carbon, while this position is open in nitidine and fagaronine. We are actively pursuing structural modifications in these series in order to more closely define structure-activity relationships.

Experimental Section

Synthesis. Commercial "sanguinarine nitrate" (Aldrich Chemical Co. and K and K Laboratories), which is mainly a mixture of sanguinarine, chelerythrine, and protopine nitrates, was used as a source of **2** and **8**. The mixture was converted to a mixture of the free bases and 1 and 6 could be separated and isolated pure by column chromatography on Florisil. Treatment of each with HCl yielded **2** and **8**. The alkoxy derivatives were prepared by recrystallization of 1 and 6 several times from the appropriate solvent (*e.g.*, methanol for **5a** and **7a**, ethanol for **5b** and **7b**, etc.). The acetonyl derivatives **5e** and **7e** were prepared by the literature[6] method for **7e**.

Previously known compounds were **1**, **2**, **5a**, **5f**, **6**, **7a**, **7b**, **7e**, and **7f**. New compounds prepared in this study were **5b** (13,14-dihydro-14-ethoxysanguinarine), mp 200–202° ($C_{22}H_{20}NO_5$); **5c** (13,14-dihydro-14-propoxysanguinarine), mp 191–192° ($C_{23}H_{22}NO_5$); **5d** (13,14-dihydro-14-butoxysanguinarine), mp 172–174° ($C_{24}H_{24}NO_5$); **5e** (13,14-dihydro-14-acetonylsanguinarine), mp 183–184° ($C_{23}H_{20}NO_5$); **7c** (12,13-dihydro-13-propoxychelerythrine), mp 202–203° ($C_{24}H_{25}NO_5$); and **7d** (12,13-dihydro-13-butoxychelerythrine), mp 192–195° ($C_{25}H_{27}NO_5$). The nmr, mass spectral fragmentations on electron impact, and elemental analyses were consistent with the assigned structures.

Pharmacological Testing. Cytotoxicity was measured *in vitro* against "KB" tumor cells and *in vivo* activity was measured in the P388 and L1210 leukemias in mice.[7] We are indebted to Dr. Jim England and Mr. Noland Dunnan for assistance with these tests. *In vivo* activity of **5a–d**, **5f**, **6**, **7a**, and **7f** was also measured in the P388 and L1210 systems by National Cancer Institute contractors through the cooperation of Dr. Harry B. Wood, Drug Development Branch, National Cancer Institute, U. S. Public Health Service.

Acknowledgment. This work was supported in part by the Vipont Chemical Co. and in part by the National Institutes of Health Research Grant CA 13648 from the National Cancer Institute.

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Preparation and Antimalarial Activity of Some Derivatives of 6-Bromo-α-(di-*n*-heptylaminomethyl)-9-phenanthrenemethanol

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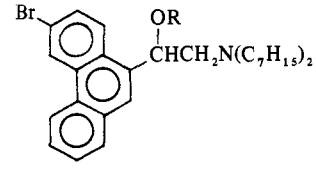
The appearance of drug resistant *falciparum* malaria has stimulated the search for new antimalarials. In their monograph Coatney, *et al.*,[1] discussed the efficacy of many simple 9-phenanthrenemethanols against *Plasmodium gallinaceum* in chicks. The most active compounds in this group were those which contained a Cl or Br atom in positions 3 and 6 and in which R was an unbranched alkyl 4–7 C long. The problem of water insolubility experienced in dialkylaminophenanthrenemethanols can be approached by converting them into ester or salt derivatives with polar ends. This should also improve the transport and absorption of these antimalarials in physiological media. In this paper the preparation and antimalarial activity of several derivatives of 6-bromo-α-(di-*n*-heptylaminomethyl)-9-phenanthrenemethanol (**1a**, R = H) are reported. The synthesis of **1a**† was reported in 1946 by May and Mosettig.[2]

First it was decided to prepare the sulfate and phosphate esters. The crystalline sulfate ester **1b** was prepared in 86% yield by treating a pyridine solution of **1a**·HCl with a pyridine solution of freshly prepared sulfur trioxide-pyridine complex.[3] Several different approaches for the preparation of the dihydrogenphosphate ester **1d** were tried, none of which were successful. As part of the first approach the intermediate diphenyl phosphate ester **1c** was prepared in 91% yield by treating **1a**·HCl with diphenylphosphorochloridate in pyridine.[4] Attempted conversion of diphenyl phosphate ester **1c** to **1d** by catalytic hydrogenation afforded a product whose elemental analysis indicated the absence of phosphorus. Perhaps this product resulted from the cleavage of the O-P bond. Alkaline hydrolysis of **1c** was also unsuccessful.



1a, R = H
b, R = SO_3H
c, R = $PO(OC_6H_5)_2$
d, R = $PO(OH)_2$
e, R = $PO(OC_6H_4NO_2)_2$
f, R = $C(=O)(CH_2)_3CO_2H$

The second approach involved the use of 2-cyanoethyl phosphate in conjunction with dicyclohexyl carbodiimide (DCC).[5-7] Treatment of the amino alcohol **1a** with freshly

#These measurements were performed on Cenco-Petersen molecular models.

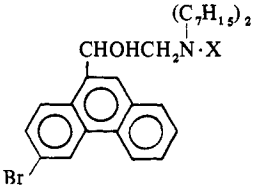
†A generous sample of the hydrochloride of 1a was supplied by Walter Reed Army Medical Center, Washington, D. C. 20012.

Table I. Dicarboxylic Acid Salts of Compound 1a

Salt	Yield, %	Mp, °C	Ir (Nujol), cm^{-1}	Formula	Analyses
Malonate **2a**	79	90–95 dec	3280 (m, –OH) 1740 (s, –C(=O)OH) 1610 (s, –C(=O)O⁻)	$C_{33}H_{46}BrNO_5$	C, H, N
Glutarate **2b**	88	90–93	3150 (b, –OH) 1700 (s, –C(=O)OH) 1565 (s, –C(=O)O⁻)	$C_{35}H_{50}BrNO_5$	C, H, N
Adipate **2c**	93	80–83	3380 (b, w, –OH) 1690 (s, –C(=O)OH) 1570 (s, –C(=O)O⁻)	$C_{36}H_{52}BrNO_5$	C, H, N
Pimelate **2d**	87	101–103	3120 (w, –OH) 1720 (s, –C(=O)OH) 1575 (s, –C(=O)O⁻)	$C_{37}H_{54}BrNO_5$	C, H, N
Azelate **2e**	87	95–97	3150 (w, –OH) 1720 (s, –C(=O)OH) 1570 (s, –C(=O)O⁻)	$C_{39}H_{58}BrNO_5$	C, H, N
Citrate **2f**	98	80–83 dec	3440 (m, –OH) 1725 (s, –C(=O)OH) 1570 (s, –C(=O)O⁻)	$C_{36}H_{50}BrNO_8$	C, H, N
Tartrate **2g**	84	136–138	3400 (m, –OH) 1600 (s, –C(=O)O⁻)	$C_{64}H_{90}Br_2N_2O_8$	C, H, N
Malate **2h**	72	100–102	3400 (w, –OH) 1570 (s, –C(=O)O⁻)	$C_{64}H_{90}Br_2N_2O_7$	C, H, N

prepared 2-cyanoethyl phosphate in the presence of DCC did not lead to any isolable product. Finally, the di-*O*-*p*-nitrophenyl phosphate **1e** was prepared by treating the amino alcohol **1a** · HCl with di(*p*-nitrophenyl) phosphorochloridate in the presence of pyridine.[8] However, alkaline hydrolysis of **1e** resulted in the isolation of potassium di(*p*-nitrophenyl) phosphate only. In view of these unsatisfactory results, the preparation of the phosphate ester **1d** was abandoned.

It was thought that the dicarboxylic acid salts of the phenanthrene amino alcohol **1a** would be more water soluble than the parent compound. Using the general procedure given in the Experimental Section, eight dicarboxylic acid salts **2a–h** were prepared. The salts **2a–f** consisted of the amino alcohol **1a** and the appropriate dicarboxylic acid in equimolar amounts, whereas the formation of salts **2g** and **2h** involved 2 mol of **1a** and 1 mol of the corresponding dicarboxylic acid.



2a, X = $CH_2(CO_2H)_2$
b, X = $HCO_2(CH_2)_3CO_2H$
c, X = $HCO_2(CH_2)_4CO_2H$
d, X = $HCO_2(CH_2)_5CO_2H$
e, X = $HCO_2(CH_2)_7CO_2H$
f, X = $HCO_2C(OH)(CH_2CO_2H)_2$
g, X = $0.5HO_2CCH(OH)CH(OH)CO_2H$
h, X = $0.5HO_2CCH(OH)CH_2CO_2H$

The *O*-glutaroyl half ester **1f** was prepared by refluxing compound **1a** · HCl and glutaric anhydride in dry pyridine for 12 hr. The yields, melting points, ir data, and analyses of these compounds are given in Table I.

Determination of Water Solubility. Distribution coefficients of the parent compound **1a** · HCl as well as its derivatives were determined using 1-octanol and water as solvents. The concentrations of each compound in octanol before and after extraction with water were determined using uv spectroscopy[9] as discussed in the Experimental Section. The distribution coefficients given in Table II indicate that the parent compound **1a** · HCl was much more soluble in water than any of its dicarboxylic acid salts and esters prepared with the idea of enhancing the water solubility of **1a**.

Table II. Distribution Coefficients (*K*)

Compd	Concn, mol/l. × 10^8		$K = \frac{C_{H_2O}}{C_{n\text{-}C_8H_{17}OH}} \times 10^4$
	C_{H_2O}	$C_{n\text{-}C_8H_{17}OH}$	
1a · HCl	13.8	6810	20.3
1c	2.96	5340	5.54
1f	1.71	6100	2.80
2a	0	6880	0
2b	1.49	6880	2.17
2c	1.72	5800	2.97
2d	0.889	5960	1.49
2e	0.607	6480	0.938
2f	1.89	6440	2.93
3a	0	3610	0
3b	0	3550	0

Table III. Antimalarial Activity,[a,b] ΔMST or C[c]

Compd	Single sc dose, mg/kg					
	20	40	80	160	320	640
1a · HCl	4.5	6.7	1C	3C	4C	4C
1c	10.17	11.9	2C	3C	5C	5C
1e	0.5	0.7	1.1	4.1	7.7	15.1
1f	0.5	0.5	1.9	3.9	9.4	9.4
2a	1.1	6.1	8.1	9.1	5C	5C
2b	5.9	7.9	12.1	5C	5C	5C
2c	4.9	11.7	3C	5C	5C	5C
2d	0.5	2.7	5.1	10.5	5C	5C
2e	0.7	2.5	6.5	14.1	5C	5C
2f	0.3	1.5	3.3	11.1	12.1	13.9
3a	2.5	6.9	12.3	3C	5C	5C
3b	3.1	7.1	12.1	3C	5C	5C

[a] Tests were carried out in five mice infected with a lethal dose of *P. berghei*. For details of test procedure, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967). Test data were supplied by Drs. T. R. Sweeney and R. E. Strube of Walter Reed Army Institute of Research. [b] No toxic deaths were reported. [c] ΔMST, mean survival time over controls (6.2 ± 0.49 days); C, number of cures (mice surviving at 61 days postinfection).

Antimalarial Activity. Table III includes comparison data (*Plasmodium berghei*[10]) for the standard, 6-bromo-α-(di-*n*-heptylaminomethyl)-9-phenanthrenemethanol hydrochloride, and its derivatives. These data show that adipic acid salt **2c** is more active than the other salts, while among the esters, the phosphate ester **1c** is the best one. The com-

pounds were nontoxic to mice. Apparently there was no correlation between the water solubility and antimalarial activity of these derivatives.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. The uv spectra were obtained on a Cary-14 spectrophotometer. The nmr spectra were run on a Varian A-60 spectrometer using Me_4Si as internal standard. The elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Preparation of the Sulfate Ester 1b. A suspension of SO_3-pyridine complex was prepared by stirring dry pyridine (30 ml) and $ClSO_3H$ (3.5 g, 0.03 mol) in a 300-ml round-bottom flask cooled in an ice bath. A solution of 1a·HCl obtained by warming 5.4 g (0.01 mol) of this compound in dry pyridine (70 ml) was added to the above suspension dropwise with stirring. The resulting mixture was refluxed for 30 min with stirring and kept at room temperature overnight. The pyridine was removed by evaporation under reduced pressure and the residual white cake extracted several times with $CHCl_3$ (300 ml). The $CHCl_3$ extract was washed with H_2O (5 × 100 ml), dried (Na_2SO_4), and evaporated under reduced pressure to dryness. The resulting white solid was crystallized from $CHCl_3$ to give 5.1 g (86%) of 1b, mp 225–227° dec. *Anal.* ($C_{30}H_{42}BrNO_4S$) C, H, N, S. The ir spectrum ($CHCl_3$) showed strong absorption around 1140–1320 cm^{-1} (OSO_3H) and no absorption in the OH region. The uv spectra of compound 1a·HCl and 1b were very similar: 1a·HCl (1.27×10^{-5} mol, $CHCl_3$) λ_{max} 343 nm (ϵ 2600), 327 (3070), 294 (35,400), 282 (30,700); 1b (1.33×10^{-5} mol, $CHCl_3$) λ_{max} 343 nm (ϵ 2630), 327 (3080), 294 (35,380), 282 (30,800).

Preparation of Di(*O*-phenylphosphoro)-6-bromo-α-(di-*n*-heptylaminomethyl)-9-phenanthrenemethanol (1c). Diphenyl phosphorochloridate (3.2 g, 0.01 mol) was added to a solution of 1a·HCl (4.9 g, 0.009 mol) in dry pyridine (75 ml) at 0°. After keeping the solution at 0° for 18 hr the pyridine was removed by evaporation under reduced pressure. The residue was dissolved in $CHCl_3$ (200 ml); the $CHCl_3$ layer was washed with H_2O (5 × 100 ml), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Upon crystallization from $CHCl_3$–pentane, the residue yielded 6.06 g (91%) of compound 1c, mp 100–103°. *Anal.* ($C_{42}H_{51}BrNO_4P$) C, H, N, P. Its ir spectrum had no absorption around 3320 cm^{-1} (OH) and strong absorptions at 1208, 1228, 1090, and 910 cm^{-1} ($OPOC_6H_5$); nmr ($CDCl_3$) δ 7.2–8.8 (m, 18, Ar H), 3.1 [m, 6, $-CH_2N(CH_2)_2$], 1.2 [m, 21, $C(CH_2)_5C)_2$, OCH–], 0.9 [(m 6, $(CCH_3)_2$].

Preparation of Di(*p*-nitrophenyl) Phosphorochloridate. Diphenyl phosphorochloridate (16.5 g, 0.06 mol) was dissolved in dry CCl_4 (50 ml) in a three-necked round-bottom flask equipped with a stirrer, thermometer, dropping funnel, and drying tube. A mixture (14.6 ml) of 30% HNO_3 and 70% H_2SO_4 was added to it dropwise so as to keep the reaction mixture at 5–15°. After stirring at 5–15° for 4 hr the reaction mixture was extracted with dry CH_2Cl_2 (300 ml). The CH_2Cl_2 solution was neutralized with anhydrous $CaCO_3$. The solid was removed by filtration and the solvent removed *in vacuo*. The residue was dissolved in a small amount of $CHCl_3$, followed by addition of petroleum ether (bp 30–60°) into the flask until an oily layer separated out. On keeping the flask in the refrigerator overnight, the title compound crystallized out as white prisms: yield 12.1 g (62%); mp 90–92° (lit.[8] mp 97–97.5°).

Preparation of Di(*O*-*p*-nitrophenylphosphoro)-6-bromo-α-(di-*n*-heptylaminomethyl)-9-phenanthrenemethanol (1e). To a solution of compound 1a·HCl (1.1 g, 0.002 mol) in dry pyridine (30 ml) was added a solution of di(*p*-nitrophenyl) phosphorochloridate (0.75 g, 0.002 mol) in dry pyridine (10 ml). The resulting mixture was kept at room temperature overnight. The pyridine was removed *in vacuo* and the resulting yellow solid dissolved in $CHCl_3$ (100 ml) and washed with H_2O (3 × 30 ml). The $CHCl_3$ solution was dried (Na_2CO_3) and evaporated under reduced pressure. The residue on crystallization from $CHCl_3$–pentane gave compound 1e as pale yellow needles: 1.2 g (72%); mp 87–90°; ir (Nujol) 1083 (s), 1103 (w), 1170 (m), 1229 (s), 1260 cm^{-1} (s, *O*-*p*-nitrophenyl), 1349 (s, CNO_2), 1520 and 1600 (s, CN=O); nmr ($CDCl_3$) δ 0.8–3.4 (m, 33, aliphatic), 7.2–8.8 (m, 16, Ar H). *Anal.* ($C_{42}H_{39}BrN_3O_8P$) H, N, P; C: calcd, 60.43; found, 58.91.

Alkaline Hydrolysis of 1e. A solution of 1e in 95% EtOH (10 ml) was treated with alcoholic KOH (1 g dissolved in 15 ml of 95% EtOH) at room temperature for 2 hr. Work-up afforded the isolation of only potassium di(*p*-nitrophenyl) phosphate, which was identified by comparison with an authentic sample (identical ir spectrum).

General Procedure for the Preparation of the Dicarboxylic Acid Salts of Compound 1a. A solution of 1a·HCl (11.0 g, 0.03 mol) in 250 ml of CH_2Cl_2 was vigorously stirred with an aqueous NaOH solution (1 *N*, 100 ml) for 30 min. The CH_2Cl_2 layer was separated and washed with 50 ml of H_2O, dried (Na_2CO_3), and evaporated under reduced pressure at room temperature. The residue containing the free base 1a was then treated with a solution of the dicarboxylic acid (0.02 mol) in 70 ml of absolute EtOH and 1 ml of H_2O. The reaction mixture was heated over steam bath for 5 min, cooled, and kept at room temperature for 4 hr. After removal of EtOH *in vacuo*, absolute ether (50 ml) was added and the flask kept in the refrigerator overnight. White crystals of the salt which separated out were collected by filtration. The salts were recrystallized from absolute EtOH–ether. The yields, ir spectra, and analyses of the salts are listed in Table I.

Preparation of 1f. Glutaric anhydride (4.0 g, 0.0035 mol) was added to a solution of 1a HCl (16.5 g, 0.03 mol) in dry pyridine (250 ml). The mixture was refluxed for 12 hr. The pyridine was removed *in vacuo* and the resulting yellow residue dissolved in 250 ml of $CHCl_3$ and washed with H_2O (5 × 100 ml). The $CHCl_3$ solution was dried (Na_2CO_3) and evaporated to dryness under reduced pressure The residue on crystallization from ether–pentane gave compound 1f as a white solid (15.0 g, 80%), mp 79–81°. *Anal.* ($C_{35}H_{48}BrNO_4$) C, H, N.

General Procedure for the Determination of Distribution Coefficients of the Dicarboxylic Acid Salts and Esters of Compound 1a. Stock solutions were prepared by dissolving 10 mg of each sample in 250 ml of 1-octanol at room temperature. The optical density of the solution at 291 nm was measured using a Cary-14 uv spectrophotometer. In each case 10 ml of the stock solution was shaken with 500 ml of distilled water for 3 min. After letting it stand for 30 min at room temperature to ensure that the equilibrium had been reached, the organic layer was separated, dried (Na_2SO_4), and filtered, and the optical density of the solution was measured again. From the differences in the optical density of each solution before and after shaking with H_2O, the equilibrium concentrations of the compound in 1-octanol and water were calculated. The distribution coefficients given in Table II were calculated for these concentrations. Recently, Higuchi and Pitman[9] had also reported the use of absorbance values for calculating the equilibrium concentrations of dissolved caffeine.

Acknowledgments. This work was supported by the U. S. Army Medical Research and Development Command, Contract No. DADA-17-71-C1054. This is Contribution No. 1020 to the Army Research Program on Malaria.

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Mechanism of Narcosis. Entropy of Hydration of Gaseous General Anesthetics

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Received January 24, 1973

One of the most widely studied, yet poorly understood phenomena in the realm of neurochemistry may well be that of general anesthesia. The chemical agents responsible for this type of narcosis span a wide spectrum of chemical