TLC of both materials showed radioactivity hR_f 0–3 (system 2), hR_f 11–19 (system 5).

(2) Metabolites in Urine. Urine was lyophilized and the residue taken up in aqueous H_3PO_4 and exhaustively extracted with Et_2O. After evaporation the extract was dissolved in aqueous NaOH, washed with Et_2O, acidified with HCl, reextracted into Et_2O, and evaporated under reduced pressure to yield ca. 8 g of dark oil containing 85% of the radioactivity in the urine. Preparative TLC using system 5 revealed four major bands—I, hR_f 0–14 (4% of the radioactivity); II, hR_f 14–30 (19%); III, hR_f 30–46 (53%); IV, hR_f 46–63 (24%)—which were extracted with acetone. Band III was further fractionated by preparative TLC with 5-, 6-, 7-, 8-, 2'-, 3'-, and 4'-hydroxyphenprocoumon as markers using successively system 2, 3, 2 (each plate developed ×3), and 3 to yield fractions U_1, U_2, U_3, and U_4 chromatographically equivalent to 4'-, 6-, 7-, and 8-hydroxyphenprocoumon, respectively: EIMS of U_3 and U_4 *m/e* 296 ($C_{18}H_{16}O_4$), 267 ($C_{16}H_{11}O_4$), 137 ($C_7H_5O_3$), and 119 (C_9H_{11}). Samples of band I were incubated at pH 5.2 both with and without glusulase as described for band A above. The Et_2O extracts were examined by TLC (system 2 developed ×2).

Samples of crude urine and feces extracts were cochromatographed with a mixture containing 5 μg each of phenprocoumon and 5-, 6-, 7-, 8-, 2'-, and 4'-hydroxyphenprocoumon using systems 2 and 3. Bands were located with uv light, cut out, and placed in liquid scintillation vials with 1 ml of EtOH, and 10 ml of Aquasol was added for liquid scintillation counting.

(3) Metabolites in the Bile. Samples of bile were acidified to pH 2 with H_3PO_4 and extracted with Et_2O. Further samples were incubated at 37°, 72 hr, with glusulase in acetate buffer, pH 5.2, acidified, and extracted with Et_2O. Controls were run without the enzyme. These extracts were examined by TLC in systems 2 and 4 and compared with standards.

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Notes

Potential Antimalarials. 9. Resolution of α-Diheptylaminomethyl-6-bromo-9-phenanthrenemethanol by an Unusual Method[1]

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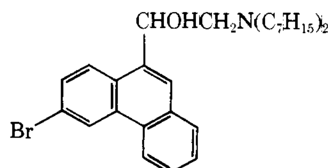
The titled base was resolved by crystallization of its *d*-tartrate salt from a solution of about 40% *d*-tartaric acid in aqueous methanol, a solvent system which might be called a chiral solution.

The resolution of the title compound, known as the May compound, proved to be a difficult task because of the soft, waxy, almost noncrystalline nature of its organic acid salts.



All standard methods failed. The resolution finally was accomplished by employing a very large excess of the resolving agent, in this case, *d*-tartaric acid, in a partially aqueous methanol solution. One might consider this separation a resolution from a chiral solution, a technique which apparently has not been employed previously.[3] However, Buchanan and Graham[4] have resolved optically unstable antipodes by crystallization from the optically active solvent, (+)-ethyl tartrate. This difference in solubility of the antipodes in (+)-ethyl tartrate has been explained theoreti-

Table I. Comparison of Activities of *d*-, *l*-, and *dl*-α-Di-*n*-heptylaminomethyl-6-bromo-9-phenanthrenemethanol against *P. berghei*

	ΔMST[a-c]			
	160 mg/kg	80 mg/kg	40 mg/kg	20 mg/kg
d	23.2, 25.5[d]	12.3, 12.1	9.1, 9.5	5.9, 6.1
l	4.7, 4.5	3.5	1.9, 1.7	0.7
dl	9.9, 9.9	9.5, 8.4	7.9, 8.1	5.9, 6.1

[a] ΔMST is the mean survival time (days) above that for controls for an average of five mice at the concentration (mg/kg) given. When two sets of figures are given, such as 23.2, 25.5, the tests were repeated at a different time. [b] All compounds were tested as free bases. We have established that the free base and its hydrochloride essentially have the same activity. [c] All *P. berghei* tests were conducted by the Walter Reed Army Institute of Research. [d] Three cures for five mice.

cally by Amaya.[5] The resolution from a chiral solvent as shown in this paper may be more practical and applicable to other bulky racemates or diastereoisomeric salts which tend to dissociate easily. The most interesting feature of the resolution is that the optically active salt did not crystallize in a 1:1 stoichiometry of amine to acid but rather one amine to several molecules of acid. This fact made the resolution feasible.

The *Plasmodium berghei* test in mice[6] gave the results shown in Table I. Interpretation must be qualified because all forms are active, and differences are small. The *d* form appears more active than *dl* which in turn appears slightly more active than *l*. This sequence suggests that, if the intercalation theory of activity applies,[7,8] the side-chain fixation wrought by amine–phosphate binding together with adjacent hydroxyl group hydrogen bonding to the 2-carbonyl group of a thymine residue does not wholly control the manner or protrusion of the aromatic group into the loop of the helical DNA structure, at least as far as optical antipodes are concerned.

Experimental Section

Stock Solution. The stock solution for resolution was a mixture of 200 g of *d*-tartaric acid, 200 ml of MeOH, and 90 ml of H_2O, the total volume being 396 ml. The solution did not deposit crystals at room temperature but did become cloudy occasionally with the organic base. In this case a few milliliters of a second stock solution (30 g of *d*-tartaric acid in 80 ml of MeOH) was used to clear the cloudiness.

Recovery of Free Base from Salt. Since the rotation values of the base–tartaric acid salt were variable, the salt was reconverted to the free base in the following manner whenever rotations were desired. The tartrate salt was dissolved in hot MeOH. The solution was partially cooled and strongly rotated while concentrated NH_4OH was added dropwise until strongly basic. Excess H_2O was added and the heterogeneous mixture was heated on the steam bath to remove MeOH. The free base was extracted from the cooled aqueous mixture with C_6H_6. This solution was washed with H_2O, dried, and evaporated to give the crystalline free base.

Resolution of α-Diheptylaminomethyl-6-bromo-9-phenanthrenemethanol. The *dl* base (27 g) was dissolved in 225 ml of the stock solution and held at room temperature until crystallization occurred, a time interval of several days to weeks. The crop was redissolved in more stock solution (in the proportion above) and recrystallized, and this process repeated to give ever-diminishing amounts of crop 1. Crops from the mother liquor were taken also. Rotations (αD) of crops varied from +38.2 to +10.2°. The fifth crop, 3.82 g, was recrystallized from the stock solution and monitored as the free base, the weights and αD of which are shown.

Fraction 1	0.65	+43.57°
Fraction 2	0.95	+43.8°
Fraction 3	0.45	+43.6°
Fraction 4	1.5	+38.8°

Fractions 1, 2, and 3 were combined and recrystallized from MeOH with just enough *i*-C_3H_7OH added to dissolve the base at the boiling point to give transparent plates: mp 51.5–56°; αD +43.6°; NMR spectrum identical with the *dl* base. The resolution perhaps could have been accomplished by the systematic triangular crystallization technique.[9]

The crude *l* base from the mother liquors of the above recrystallization was resolved in a manner similar to that of the *d* base except that *l*-tartaric acid was used as the resolving agent. The presumably pure *l* base was obtained as a white powder: mp 55–58°; NMR identical with that of the *dl* base; αD 41° (1 g in 10 ml of *i*-C_3H_7OH). The *dl* base was a white powder of mp 59–62°.

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Substituted 1-[(5-Nitrofurfurylidene)amino]-4-imidazolin-2-ones

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A series of 1-[(5-nitrofurfurylidene)amino]-4-imidazolin-2-ones has been prepared. A new synthesis of 4-alkyl-1-[(5-nitrofurfurylidene)amino]-4-imidazolin-2-ones involving the oxidative ring closure of 5-nitro-2-furaldehyde 2-(2-hydroxyethylalkyl)semicarbazones is described. The in vitro testing of the compounds against a variety of bacteria is reported.

The discovery that 1-[(5-nitrofurfurylidene)amino]-4-imidazolin-2-one (1)[1] is a degradative product of nifuradene[2] and that it possesses antibacterial properties prompted the synthesis of a series of substituted derivatives of 1.

Chemistry. The *N*-hydroxymethyl compound **2** was pre-