Optical Isomers of Aryl-2-piperidylmethanol Antimalarial Agents. Preparation, Optical Purity, and Absolute Stereochemistry

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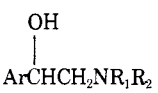
α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol hydrochloride (3·HCl) and α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol hydrochloride (4·HCl) are highly active antimalarial agents which are mixtures of optical isomers. All four optical isomers of both α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol hydrochloride and α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol hydrochloride were prepared. Methods were developed for establishing the optical purity, relative stereochemistry, and absolute configuration of these compounds. All four optical isomers of 3 and 4 have been tested for antimalarial activity against *Plasmodium berghei* in mice. In the case of 3, the (+)- and (−)-threo isomers were slightly more active than the (+)- and (−)-erythro isomers. None of the optically active forms of 4 showed any significant differences.

During World War II, a large number of arylcarbinolamines were prepared, and some showed significant therapeutic effect against blood-induced *Plasmodium gallinaceum* malaria.[1,2] The appearance of drug-resistant *P. falciparum* malaria necessitated a search for new antimalarial agents in this class. In this current Army research program on malaria, a large number of phenanthrene-, quinoline-, and pyridinearylcarbinolamines of type 1 and 2 were prepared for antimalarial screening. As a part of



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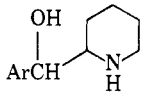

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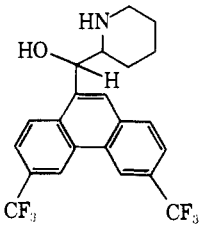
this program, Nodiff and coworkers[3] prepared one racemate (**3a**) of α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (**3**) and Olsen[4] isolated the other racemate (**3b**).† Both of the compounds were found to be very active against resistant strains of both *P. berghei* in rodents and *P. falciparum* in Aotus monkeys.‡ In addition, both the major and minor racemates of α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (**4**) have been prepared by Lutz and coworkers[5] and Olsen,‡ respectively, and shown to be highly active against *P. berghei* in mice and *P. falciparum* in Aotus monkeys.‡



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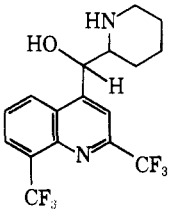

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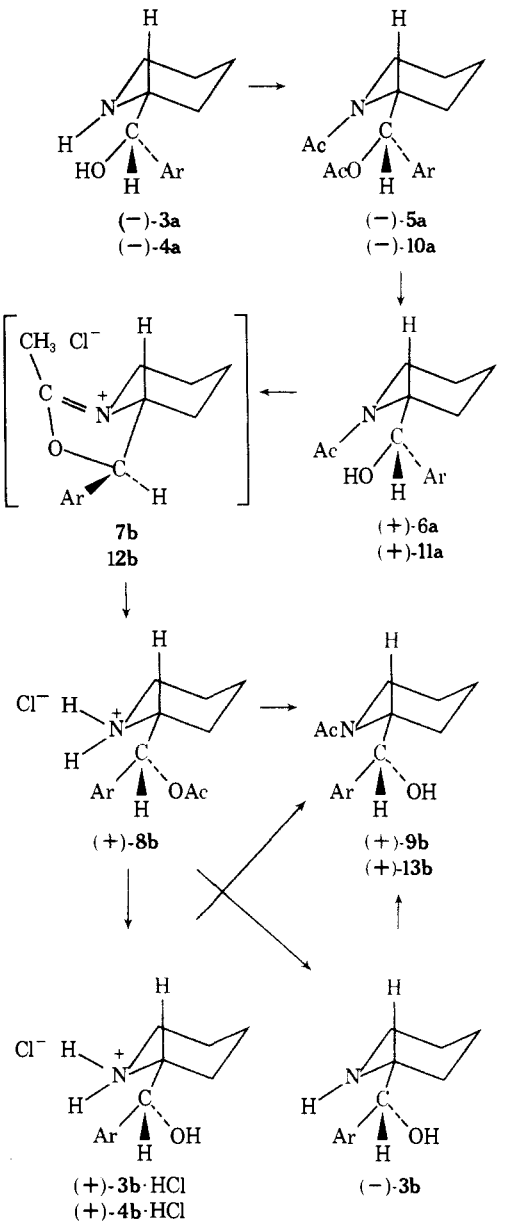
In this paper we report the preparation of all four optical isomers of both **3** and **4**, describe methods for establishing their optical purity, and discuss procedures for establishing both the relative and absolute configuration of these compounds.

Resolution and Synthesis. We found that (−)- and (+)-*O,O*-di-*p*-toluoyltartaric acid effected a high yield optical resolution of **3a**,[6] whereas **4a** was best resolved *via* its hydrochloride salt with (+)- and (−)-3-bromo-8-camphorsulfonic acid ammonium salts.

Isomer (−)-**3a** was converted to (−)-**3b** by a method similar to that used by Stevens and coworkers[7] for converting *trans*-α-aminocyclohexanols into *cis*-α-aminocyclohexanols. The reaction sequence is shown in Scheme I. Treatment of (−)-**3a** with acetic anhydride in pyridine gave the diacetyl derivative (−)-**5a**. Selective hydrolysis of (−)-**5a** with lithium hydroxide in methanol afforded the *N*-acetyl derivative (+)-**6a**. Thionyl chloride treatment of (+)-**6a** inverted it to the *O*-acetyl hydrochloride (+)-**8b**,† presumably *via* the oxazoline **7b**.§ Hydrolysis of (+)-**8b**

Scheme I



for **3**, **5–9**, Ar = 3,6-bis(trifluoromethyl)-9-phenanthryl
for **4**, **10–13**, Ar = 2,8-bis(trifluoromethyl)-4-quinolinyl

†One racemate of the mixture will be referred to as **a** the other as **b**.
‡Drs. Bing T. Poon and Richard E. Strube, personal communication.

Table I. Melting Points and Optical Rotations of the α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol Hydrochloride Isomers and the α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol Hydrochloride Isomers

Compd	Mp,[a] °C	[α]D[b]	Compd	Mp,[a] °C	[α]D[b]
(±)-**3a**	324–327[c]	0	(±)-**4a**	259–260[f]	0
(+)-**3a**	279–279.5	+33.20	(+)-**4a**	275–276.5	−33.00
(−)-**3a**	279–281	−33.60	(−)-**4a**	276–277	+33.90
(±)-**3b**	284–285[d]	0	(±)-**4b**	258–260	0
(+)-**3b**	251–254[e] 278–281	+30.98	(+)-**4b**	148–150.5[g]	+55.27
(−)-**3b**	249.5–250[e] 277–280	−33.92	(−)-**4b**	151–155[g]	−53.57

[a]The melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. All these compounds melt with decomposition. [b]The [α]D's were determined with a Perkin-Elmer Model 141 polarimeter (1-dm cell). [c]E. A. Nodiff, *et al.*, *J. Med. Chem.*, **14**, 921 (1971). [d]R. E. Olsen, *ibid.*, **15**, 207 (1972). [e]These compounds melt at the lower temperature recorded, resolidify, and then decompose at the higher temperature. [f]C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **14**, 926 (1971). [g]A sample of (±)-**4b** obtained by mixing equal amounts of (+)- and (−)-**4b** followed by recrystallization from an ethyl acetate and hexane mixture had mp 256–258° dec. A mixture of this compound and (±)-**4b** (from WRAIR) had mp 258–260° dec.

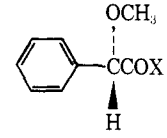
with refluxing 6 *N* hydrochloric acid gave (+)-**3b**·HCl. Neutralization of (+)-8b with aqueous ammonium hydroxide at 25° followed by extraction into ether effected an O → N acyl migration and gave (+)-*N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(+)-9b]. Hydrolysis of (+)-8b with refluxing aqueous ethanolic sodium hydroxide solution gave (−)-3b.‡ In an analogous manner (+)-**3a** was converted to (−)-8b, (−)-9b, (+)-3b, and (−)-3b·HCl. The *N*-acetyl derivatives (+)- and (−)-9b could also be prepared by diacetylation of (−)- and (+)-3b followed by selective hydrolysis of the *O*-acetyl group.

Compound (−)-**4a**† was converted to (+)-**4b**·HCl by a reaction sequence similar to that used for the conversion of (−)-**3a** to (+)-3b·HCl (Scheme I). Treatment of (−)-**4a** with acetic anhydride in pyridine gave the diacetyl derivative (−)-**10a**. Selective hydrolysis of (−)-10a with lithium hydroxide in methanol afforded the *N*-acetyl derivative (+)-**11a**. Thionyl chloride treatment of (+)-**11a** followed by hydrolysis with refluxing 6 *N* hydrochloric acid gave (+)-4b·HCl presumably *via* the oxazoline **12b**.** In an analogous manner (+)-**4a** was converted to (−)-4b·HCl. Treatment of (±)-, (+), and (−)-4b·HCl with pyridine and acetic anhydride followed by selective *O*-acetyl hydrolysis gave the *N*-acetyl-4b derivatives (±)-, (+)-, and (−)-**13b**, respectively.

The physical constants of all four optical isomers of both **3**·HCl and **4**·HCl along with those of the two racemic pairs in each case are recorded in Table I. Although the magnitude of the rotation at the sodium D line of the two (+) isomers of **3** and the two (−) isomers of **3** is almost identical, the CD curves (see later section) of the two **3a**·HCl isomers are quite different from the **3b**·HCl isomers. In addition, the tlc, melting points, and the ir and nmr spectra of the two **3a**·HCl isomers were different from the two **3b**·HCl isomers. In addition to the rotation differences the tlc, melting points, and the ir and nmr spectra of the two **4a** isomers were different from the two **4b** isomers.

Optical Purity. In order to compare the biological activity and the metabolism as well as other properties of the optical isomers of **3** and **4** to the racemic compounds, it was necessary to determine the optical purity of our optical isomers. The use of nmr spectroscopy seemed best suited for the determination. Several related methods which make use of this technique have been reported. In each case advantage is taken of the magnetic nonequivalence of diastereotopic nuclei obtained when enantiomeric compounds are either suitably derivatized with optically active reagents[8,9] or mixed with a chiral lanthanide shift reagent[10-13] or chiral solvent.[14] We have developed methods whereby the optical purity of arylcarbinolamines can be determined using either an optically active derivatizing reagent or chiral lanthanide shift reagents.

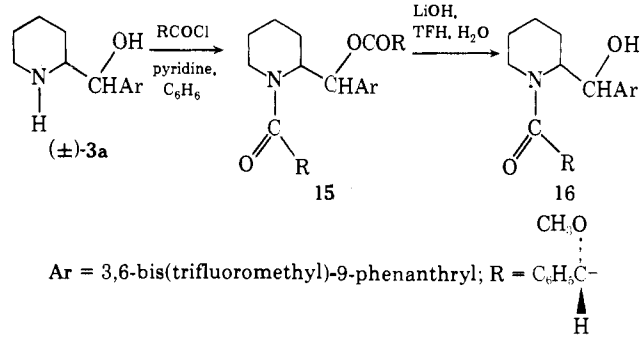
A. *O*-Methylmandelamide or *N*-Acyl-*O*-methylmandelate Derivatives. (*R*)-*O*-Methylmandelic acid (**14a**) is a general reagent that has been used for the nmr determination of the optical purity of amines and alcohols.[8,9] However, its use has not been applied to carbinolamines.



14a, X = OH
b, X = Cl
c, X = NR, R′

1. Determination of the Optical Purity of (+)- and (−)-3a. We have investigated two nmr methods whereby the optical purity of the optical isomers of **3a** might be determined by the use of **14**. In method I, shown in Scheme II, (±)-**3a** is diacylated with optically pure (*R*)-

Scheme II



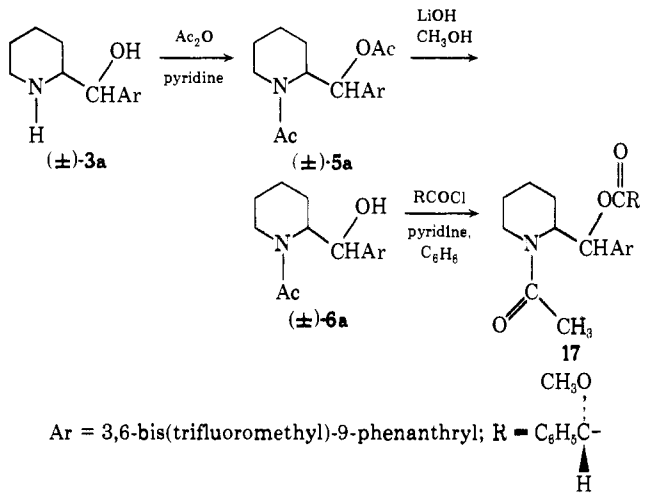
O-methylmandelic acid chloride (**14b**). The diacyl derivative **15** is then treated with lithium hydroxide in aqueous tetrahydrofuran to effect specific *O*-acyl hydrolysis and give the *O*-methylmandelamide derivative **16**. The nmr spectrum of **16** shows two *O*-methyl resonances of unequal intensity indicating that racemization might have taken

§If the reaction was stopped after 10 min, the infrared spectrum of the product obtained showed the absence of hydroxyl absorption and showed strong absorption at 1665 cm^{-1} (>C=N< of 7).

‡(−) isomer **3b** could also be obtained *via* resolution using its L-2-pyrrolidone-5-carboxylate salt.

No attempt was made to isolate and identify the intermediate products in this case. The reaction probably proceeds through the oxazoline **12b in a manner analogous to that described for the *N*-acetyl derivatives of **3a**.

Scheme III

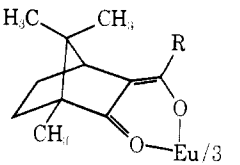


place during the preparation of **15** or **16**. Application of method I to (+)- and (−)-**3a** gave an (*R*)-*O*-methylmandelamide derivative whose nmr spectrum showed two *O*-methyl resonances in a ratio of 90:10. These results indicated that either racemization was taking place during the preparation of the (*R*)-*O*-methylmandelamide or that the (+)- and (−)-**3a** samples were not optically pure. Since (±)-**3a** gave an *O*-methylmandelamide derivative whose nmr spectrum showed *O*-methyl resonances of unequal intensity, the former suggestion seems most likely. This is supported by the fact that application of method I to an optically pure sample of (−)-ephedrine gives an (*R*)-*O*-methylmandelamide derivative whose nmr spectrum showed two *O*-methyl resonances in a ratio of 95:5.

In method 2, shown in Scheme III, (±)-**3a** is treated with acetic anhydride and pyridine to give the diacyl derivative (±)-**5a**. Treatment of (±)-**5a** with lithium hydroxide in methanol gives the *N*-acetyl derivative (±)-**6a**. Acylation of (±)-**6a** with (*R*)-*O*-methylmandelic acid chloride gives the (*R*)-*O*-methylmandelate derivative **17**. The nmr spectrum shows only one *O*-methyl resonance but shows two resonances of approximately equal intensity for the methyl of the *N*-acetyl group. Since the nmr spectrum of **17** gives two *N*-acylmethyl groups of near equal intensity, this method could be used to determine the optical purity of the (+) and (−) isomers of **3a**. The nmr spectrum of the (*R*)-*O*-methylmandelate ester **17** of the *N*-acetyl derivatives of (+)-**3a** (method 2) shows only one *N*-acetyl methyl group resonance indicating that (+)-**3a** is optically pure. See the following sections for additional evidence indicating that (+)- and (−)-**3a** are indeed optically pure.

2. Determination of the Optical Purity of (+)- and (−)-3b. In contrast to the results with **3a** we found that the optical purity of **3b** could be determined by method 1.†† The nmr spectrum of the (*R*)-*O*-methylmandelamide of (−)-**3b**, $[\alpha]_{365}$ −38.5, prepared by resolution with (−)-2-pyrrolidone-5-carboxylic acid showed only one methoxy resonance indicating that the compound was optically pure. The fact that this sample of (−)-**3b** has approximately the same rotation as (−)-**3b** prepared from (−)-**3a** would indicate that (−)-**3a** is also optically pure.

B. Using Chiral Lanthanide Shift Reagents. Since lanthanide shift reagents complex strongly with a variety of functional groups and induce remarkable changes in chemical shifts,[10] an optically active lanthanide shift reagent would be expected to effect different chemical shift changes for enantiomeric substrates. During the time we were studying methods to establish the optical purity of **3** and **4**, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) (**18**)[11] and tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (**19**)[12,13] were shown to induce pseudocontact shifts of different magnitude in corresponding protons of enantiomeric alcohols and amines. This finding was of importance since it provided a potentially simpler method of determining the optical purity of our amino alcohols.



18, R = CF_3
19, R = C_3F_7

In order to establish whether the nmr shift reagent method was applicable to amino alcohols similar to our resolved 2-piperidylmethanols, we studied the use of **18** for determining the optical purity of *erythro*-ephedrine (**20**) and threo-ψ-ephedrine (**21**). The nmr spectrum of racemic ephedrine or ψ-ephedrine containing varying amount of **18** showed no shift differences useful for establishing the optical purity of these compounds. In contrast, the nmr spectrum (CCl_4) of (±)-*N*-acetylephedrine [(±)-**22**] (Figure 1A) or (±)-*N*-acetyl-ψ-ephedrine [(±)-**23**] (Figure 2A) containing **18** showed two singlet *N*-acetylmethyl peaks, whereas the nmr spectrum of optically pure (+)-*N*-acetylephedrine [(+)-**22**] (Figure 1B) and (−)-*N*-acetyl-ψ-ephedrine [(−)-**23**] (Figure 2B) obtained under these conditions showed only one methyl resonance.

The fact that racemic *N*-acetylephedrine [(±)-**22**] and *N*-acetyl-ψ-ephedrine [(±)-**23**] show two *N*-acetylmethyl resonances whereas the optically pure isomers show only one *N*-acetylmethyl resonance indicates that the optical

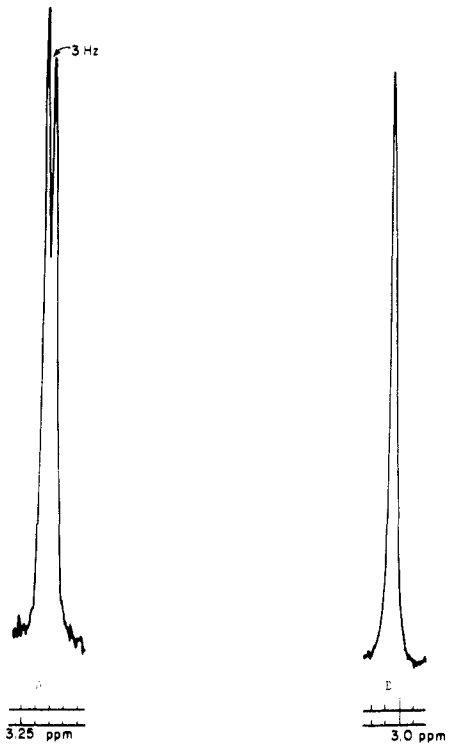


Figure 1. Nmr spectra of (A) 20 mg of (±)-*N*-acetylephedrine [(±)-**22**] and (B) 20 mg of (+)-*N*-acetylephedrine [(+)-**22**], respectively, in 0.3 ml of CCl_4 containing 16 mg of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III).

††The nmr spectrum of the (*R*)-*O*-methylmandelamide of (±)-**3b** showed two CH_3O resonances of equal intensity.

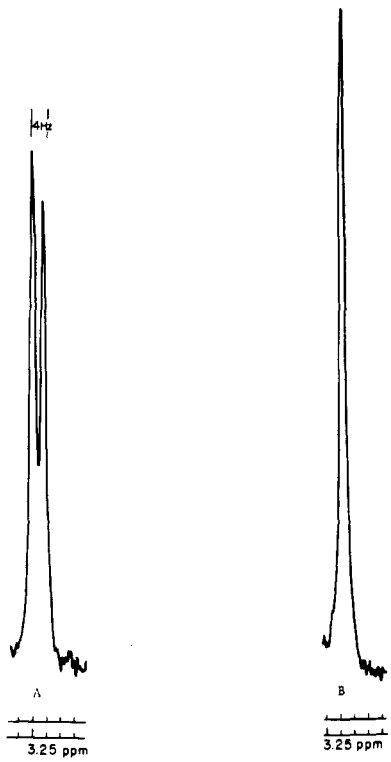
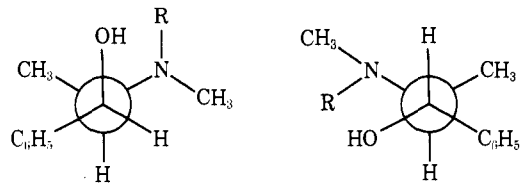


Figure 2. Nmr spectra of (A) 20 mg of (±)-*N*-acetyl-ψ-ephedrine [(±)-**23**] and (B) 20 mg of (−)-*N*-acetyl-ψ-ephedrine [(−)-**23**], respectively, in 0.3 ml of CCl_4 containing 16 mg of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III).



20, R = H
22, R = CH_3CO

21, R = H
23, R = CH_3CO

purity of amino alcohols can be determined by first conversion to their *N*-acetyl derivative followed by nmr analysis of the *N*-acetyl derivatives in the presence of **18**.

1. Determination of the Optical Purity of (+)- and (−)-3a. We have examined the use of **18** for the determination of the optical purity of the *N*-acetyl derivatives of **3a**. The nmr spectrum (Figure 3A) of a solution of 20 mg of the partially resolved *N*-acetyl derivative of **3a** in 0.3 ml of carbon tetrachloride containing 14 mg of **18** showed two singlet *N*-acetylmethyl peaks separated by 14 Hz. The nmr spectrum of the (−)-*N*-acetyl derivative of **3a** determined in a similar fashion showed only one *N*-acetyl methyl resonance (Figure 3B) indicating that this compound and thus (+)- and (−)-**3a** are indeed optically pure. Since considerable line broadening was observed in this case, the use of **19** was investigated. The results obtained are shown in Figure 4. It is apparent that **19** is a much superior reagent for the determination of the optical purity of **3a** samples. In this case a greater separation of the *N*-acetylmethyl resonances of the two optically active *N*-acetyl derivatives was observed, and, in addition, much less line broadening was observed.

2. Determination of the Optical Purity of (+)- and (−)-4a. We have also examined the use of **18** for the determination of the optical purity of the *N*-acetyl derivatives (+)- and (−)-**4a**. The nmr spectrum of a solution of 20 mg of racemic and (+)- and (−)-*N*-acetyl **4a** in 0.3 ml of carbon tetrachloride containing 10 mg of **18** is shown in

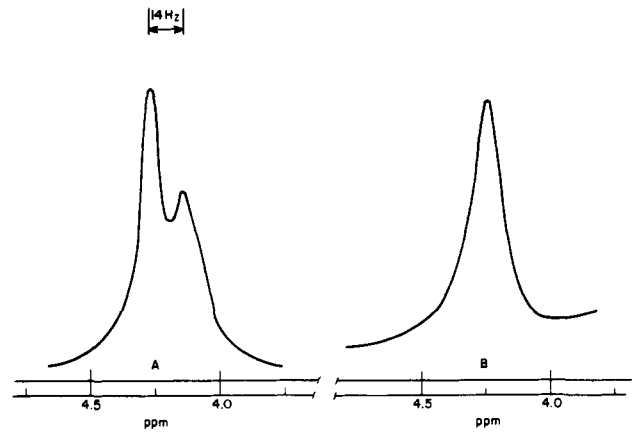


Figure 3. Nmr spectra of (A) 20 mg of partially resolved *N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (**6a**) and (B) 20 mg of (−)-*N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(−)-**6a**], respectively, in 0.3 ml of CCl_4 containing 14 mg of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III).

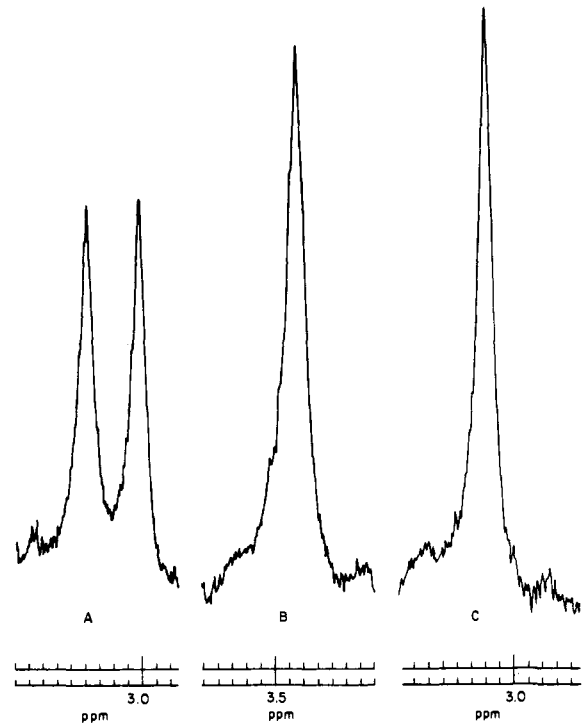


Figure 4. Nmr spectra of (A) 20 mg of (±)-*N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(±)-**6a**], (B) 20 mg of (−)-*N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(−)-**6a**], and (C) 20 mg of (+)-*N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(+)-**6a**], respectively, in 0.3 ml of CCl_4 containing 10 mg of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) in case A and 14 mg in case B and C.

Figure 5. The fact that racemic *N*-acetyl **4a** shows two *N*-acetylmethyl resonances separated by 13 Hz (Figure 5A) whereas (+)- and (−)-*N*-acetyl **4a** (Figure 5B and 5C, respectively) shows only one *N*-acetylmethyl resonance indicates that the latter compounds are optically pure. Since the (+)- and (−)-*N*-acetyl derivatives of **4a** were derived from (−)- and (+)-**4a**, respectively, it follows that the latter compounds are also optically pure.

3. Determination of the Optical Purity of (+)- and (−)-4b. The optical purity of (+)- and (−)-**4b** was determined in exactly the same manner as described for (+)- and (−)-**4a** using **18** and the (+)- and (−)-*N*-acetyl derivatives of **4b**. The results obtained are shown in Figure 6.

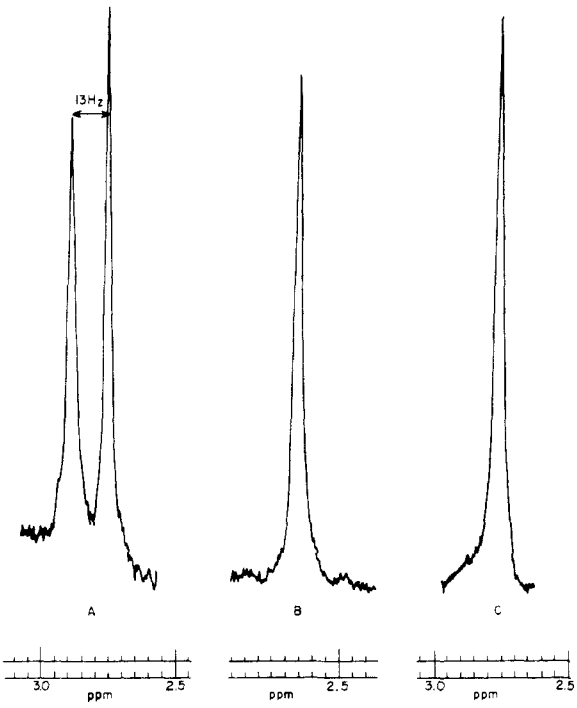


Figure 5. Nmr spectra of (A) 20 mg of (±)-*N*-acetyl-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol [(±)-**11a**], (B) 20 mg of (+)-*N*-acetyl-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol [(+)-**11a**], and (C) 20 mg of (−)-*N*-acetyl-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol [(−)-**11a**], respectively, in 0.3 ml of CCl_4 containing 10 mg of tris[3-trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III).

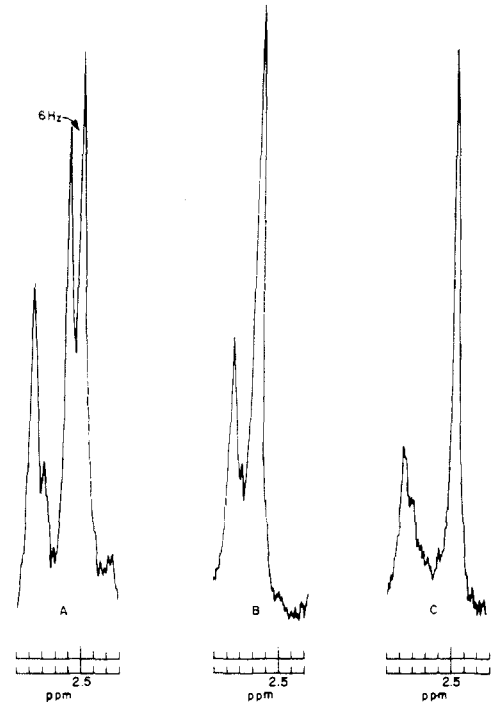
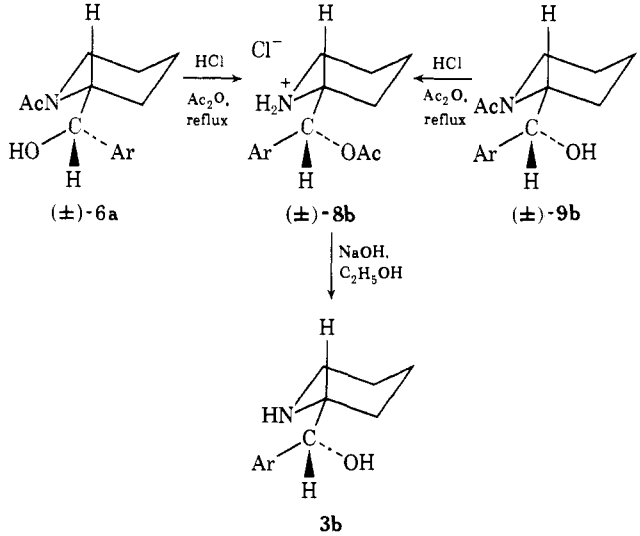


Figure 6. Nmr spectra of (A) 20 mg of (±)-*N*-acetyl-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol [(±)-**13b**], (B) 20 mg of (+)-*N*-acetyl-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol [(+)-**13b**], and (C) 20 mg of (−)-*N*-acetyl-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol [(−)-**13b**], respectively, in 0.3 ml of CCl_4 containing 5 mg of tris[3-trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III).

Relative Configuration. From a detailed analysis of the nmr spectra of **3a** and **3b**, their hydrochloride salts, and their corresponding oxazolidine derivatives, Olsen[4] suggested that **3a** and **3b** had the erythro and threo structures, respectively. In a similar study we arrived at the same assignments.

The relative configuration of the racemates of **3a** and **3b** was confirmed by acyl migration studies of their *N*-acetyl derivatives (±)-**6a** and (±)-**9b**, respectively (Scheme IV).[15]

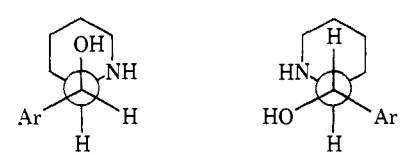
Scheme IV



Ar = 3,6-bis(trifluoromethyl)-9-phenanthryl
(only one epimer in each structure is shown)

Treatment of the *N*-acetyl derivative of **3a** and **3b** with refluxing acetic anhydride containing hydrogen chloride yields the *O*-acetyl derivative [(±)-**8b**] of **3b**. In the first case the N → O migration occurs with inversion at the carbinol carbon, whereas the latter migration proceeds with retention of configuration. Alkaline hydrolysis of the *O*-acetyl derivative gives **3b**. Since it is well established that *erythro*-*N*-acetylcarbinolamines undergo N → O acyl migration with inversion whereas *threo*-*N*-acetylcarbinolamines proceed with retention of configuration,[15] these results give added evidence for the erythro and threo assignments arrived at *via* nmr studies.

A comparison of the nmr spectra of **4a** and **4b** to those of **3a** and **3b** indicates that these compounds have the structures shown. The nmr data for the free bases of **4a** and **4b** as well as those of **3a** and **3b** are listed in Table II. The vicinal coupling constants $J_{1,2}$ (at room temperature) of the free bases of **3b** and **4b** are larger than corresponding diastereoisomers **3a** and **4a**, respectively. If it is assumed that all these compounds exist predominantly in a hydrogen bonded conformation, it would be expected that $J_{1,2}$ in the threo isomers (H_1H_2 *trans*) would be larger than that in the erythro isomers (H_1H_2 gauche).[16] The observed relative values of $J_{1,2}$ show that **3a** and **4a** have the erythro configuration and **3b** and **4b** have the threo configuration.



4a (erythro) **4b** (threo)

Ar = 2,8-bis(trifluoromethyl)-4-quinolyl group

Absolute Stereochemistry. The circular dichroism (CD) spectra of the four optical isomers of **3** are shown in Figure 7. Comparison of the sign of the ^1L_b π-π^* transition in the CD of these compounds with the sign of the same transition in the CD spectra of the stereoisomers of

Table II. Nmr Data for Some Aryl-α-(2-piperidyl)carbinols

Compd[a]	Nmr, δ (solvent), C_1–H[b]	Coupling constant, Hz ($J_{1,2}$[b])	Assignment: Erythro–threo system	Assignment: *R* and *S* system[c]
3a	5.32 (polysol-*d*)	4.0	Erythro	1*RS*, 2*SR*
3b	5.17 (polysol-*d*)	7.0	Threo	1*RS*, 2*RS*
4a	5.50 ($CDCl_3$)	3.0	Erythro	1*RS*, 2*SR*
4b	5.13 ($CDCl_3$)	6.0	Threo	1*RS*, 2*RS*

[a]The nmr spectra were obtained on the free bases. [b]Carbon-1 is the carbinol carbon and carbon-2 is the amino carbon. [c]See R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).

Table III. Circular Dichroism Data for Cinchona Alkaloid and α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol Stereoisomers

Compd	^1L_b π–π^* transition, λ (mm), $[\theta]$[a]	Rel stereochemistry	Configuration: C-1[b]	Configuration: C-2[b]
(+)-Quinidine·HCl	351, +9,240	Erythro	*S*	*R*
(−)-Quinine·HCl	351, −11,300	Erythro	*R*	*S*
(+)-Epiquinine·HCl	311, −1,190	Threo	*R*	*R*
(−)-Epiquinidine·HCl	311, +1,530	Threo	*S*	*S*
(−)-**4a**·HCl	321, +293	Erythro	*S*	*R*
(+)-**4a**·HCl	321, −292	Erythro	*R*	*S*
(+)-**4b**·HCl	319, −897	Threo	*R*	*R*
(−)-**4b**·HCl	319, +929	Threo	*S*	*S*

[a]See Experimental Section for complete CD data on (+)- and (−)-**4a**·HCl and (+)- and (−)-**4b**·HCl. [b]C-1 is the carbinol carbon and C-2 is the amino carbon. This is C-9 and C-8, respectively, in the case of the cinchona alkaloids.

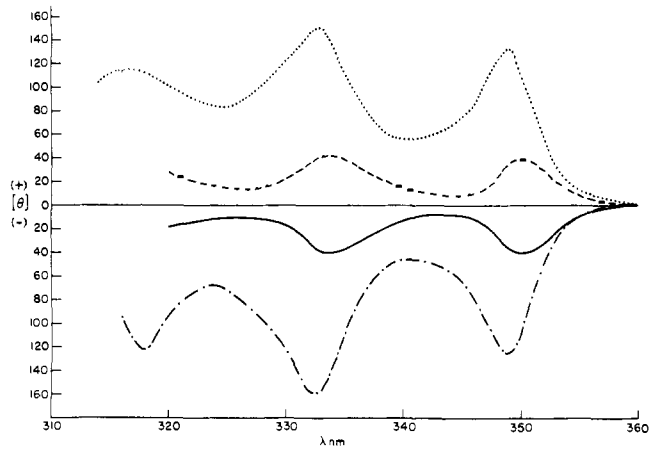


Figure 7. Circular dichroism curves of (+)-3a·HCl (····), (−)-3a·HCl (-·-·-), (+)-3b·HCl (----), and (−)-3b·HCl (—) in methanol.

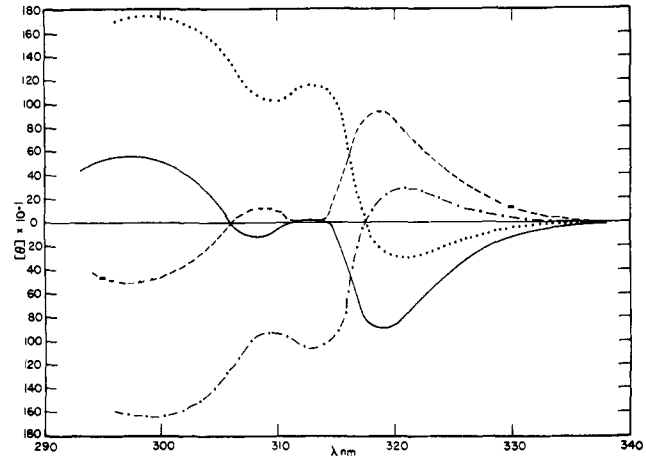


Figure 8. Circular dichroism curves of (+)-4a·HCl (····), (−)-4a·HCl (-·-·-), (+)-4b·HCl (----), and (−)-4b·HCl (——) in methanol.

ephedrine allowed us to tentatively assign the 1*S*,2*R*, 1*R*,2*S*, 1*R*,2*R*, and 1*S*,2*S*‡‡ configuration to (−)- and (+)-3a and (+)- and (−)-3b, respectively.[6]

A similar comparison of the CD spectra of the optical isomers of 4a and 4b to those of the cinchona alkaloids (Table III, Figure 8) suggests that (−)-4a and (+)-4b have the 1*S*,2*R*‡‡ and 1*R*,2*R*‡‡ configurations, respectively, and thus the 1*R*,2*S*‡‡ and 1*S*,2*S*‡‡ configurations belong to (+)-4a and (−)-4b.

In the case of various chloramphenicol derivatives of constant absolute configuration and identical conformation, Mitscher and coworkers[17] found that the sign of the ^1L_b transition observed in the CD spectra was changed by alteration of the aryl group. Therefore, additional work will be necessary before the absolute configuration of the isomers of 3 and 4 can be considered rigorously established.

Biological Data. Table IV lists the biological data that have thus far been obtained on the optical isomers of 3 and 4 along with the results from the racemic compounds. Test results were obtained by Dr. Leo Rane and coworkers, Malaria Screening Laboratory, University of Miami, Miami, Fla.§§ In the primary test against *P. berghei* five mice were infected with a lethal dose of *P. berghei* 3 days prior to administration of the chemical. Routinely, the chemical was administered subcutaneously in sesame or peanut oil. The mean survival time (MST) of infected control mice is 6.2 ± 0.5 days. Extension in survival time (ΔMST) of the chemically treated mice is interpreted as evidence of antimalarial activity. Compounds are arbitrarily considered to be "active" when the mean survival time of the treatment group is more than twice the mean survival time of the control group. Mice surviving 60 days are considered cured.

The test results obtained are listed in Table IV. It appears that (+)- and (−)-3b are both slightly more active than (+)- and (−)-3a. However, none of the optically active forms of 4 showed any significant differences in antimalarial activity against *P. berghei* in rodents.

Summary. Through a combination of optical resolution and chemical conversions, all four optical isomers of α-

‡‡Carbon-1 is the carbinol carbon and carbon-2 is the amino carbon.

§§For a description of the test procedure, see ref 18. The test results were supplied through the courtesy of Drs. T. R. Sweeney, B. T. Poon, and R. E. Strube of the Walter Reed Army Institute of Research, Washington, D.C.

Table IV. Antimalarial Test Results[a]

Compd	ΔMST or C,[b] dose (mg/kg)								
	2.5	5	10	20	40	80	160	320	640
(+)-**3a**	0.7	1.3	13.2 (1C)	21.9 (4C)	5C	5C	5C	5C	5C
(−)-**3a**	0.5	1.7	13.7 (1C)	28.9 (3C)	5C	5C	5C	5C	5C
(±)-**3a**[c]			9.1	18.9	2C	5C	5C	5C	5C
(+)-**3b**	0.5	5.9	13.9 (1C)	28.4 (3C)	5C	5C	5C	5C	5C
(−)-**3b**	0.7	5.9	13.9 (2C)	5C	5C	5C	5C	5C	5C
(±)-**3b**[d]			10.1	2C	5C	5C	5C	5C	5C
(+)-**4a**	0.5	0.9	9.9	20.4 (1C)	26.6 (2C)	28.9 (3C)	5C	5C	5C
(−)-**4a**	0.3	0.5	9.7	18.2 (2C)	24.4 (3C)	30.9 (4C)	5C	5C	5C
(±)-**4a**[d]				9.4	1C	1C	4C	4C	5C
		0.7	12.5	4C	5C				
(+)-**4b**	0.3	2.9	9.5	19.9 (1C)	19.2 (2C)	24.4 (3C)	5C	5C	5C
(−)-**4b**	0.7	1.9	10.1	20.4 (1C)	29.2 (2C)	31.6 (2C)	5C	5C	5C
(±)-**4b**[d]			9.1	2C	3C	5C	5C	5C	

[a] See ref 17. [b] ΔMST, mean survival time over controls (6.2 ± 0.5 days); C, number of cures (mice surviving to 60 days). [c] Taken from E. A. Nodiff, K. Tanabe, C. Seyfried, S. Matsuura, Y. Kondo, E. H. Chen, and M. P. Tyagi, *J. Med. Chem.*, **14**, 921 (1971). [d] Data supplied through courtesy of Dr. R. E. Strube.

(2-piperidyl)-3,6-bis(trifluoromethyl-9-phenanthrenemethanol (**3**) and α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (**4**) have been prepared. Nmr methods were developed whereby the optical purity of the optical isomers of **3** and **4** could be determined through the use of (a) the chiral lanthanide shift reagents **18** or **19** and/or (b) their *R*-(*O*)-methylmandelic acid derivative. These studies represent the first application of either method to optically active amino alcohols. The methods should be applicable to other optically active amino alcohols. Through a combination of chemical conversions and nmr and CD analyses, the relative stereochemistry and tentatively absolute configuration of the isomers of **3** and **4** were determined.

The optical isomers of **3** and **4** were tested as antimalarial agents and found to show only slight differences in activity. However, the availability of these compounds of known optical purity and stereochemistry should prove extremely useful for metabolism and other biological studies.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. Ir spectra were measured with a Perkin-Elmer 221 spectrophotometer. Nmr spectra were recorded on a Varian Model HA-100 spectrometer with tetramethylsilane as an internal standard. CD measurements were made with a Jasco Model 20 spectropolarimeter at 25°. All observed rotations at the sodium D line were determined with a Perkin-Elmer Model 141 polarimeter (1-dm cell). Mass spectra were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill. Where analyses were indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of theoretical values.

Resolution of α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (3a). To a solution-suspension of 174.8 g (0.38 mol) of **3a** [mp 223.5–224°. *Anal.* ($C_{22}H_{19}F_6NO$) C, H, N]‡‡ in 4000 ml of refluxing MeOH was added 158.2 g (0.41 mol) of (−)-*O,O*-di-*p*-toluoyl-*d*-tartaric acid. The solid which separated on standing overnight at 25° was isolated by filtration, and the filtrate was retained for further examination. The salt, 101.9 g, had $[\alpha]^{25}D$ −51.5° (*c* 0.204, CH_3OH). *Anal.* ($C_{42}H_{37}F_6NO_9$) C, H, N.

To a solution-suspension of the salt in 200 ml of MeOH was added 1000 ml of 1 *N* NaOH, and the mixture was stirred at 26° for 21 hr. The solid was separated by filtration, washed with H_2O, recrystallized from a MeOH and H_2O mixture, and dried under vacuum to give 49.8 g of (+)-**3a**: mp 196.5–197.5°; $[\alpha]^{25}D$ +11.67° (*c* 0.677, CH_3OH). *Anal.* ($C_{22}H_{19}F_6NO$) C, H, N.

A sample of (+)-**3a** was converted to its hydrochloride salt with ethanolic HCl. The analytical sample prepared by two recrystallizations from 95% EtOH had mp 279–279.5°, $[\alpha]^{26}D$ +33.20° (*c* 0.428, CH_3OH). *Anal.* ($C_{22}H_{20}ClF_6NO$) C, H, Cl, F, N.

The (+)-*N,O*-diacetyl derivative (+)-**5a** was prepared in 94% yield with C_5H_5N-Ac_2O (3:1). The analytical sample prepared by recrystallization from a MeOH and H_2O mixture had mp 193.5–195°; ν_{max} (CH_2Cl_2) 1745 (ester C=O) and 1630 cm^{-1} (amide C=O); nmr spectrum ($CDCl_3$) showed resonances at δ 2.03 (CH_3CO_2) and 2.27 ppm ($CH_3CON<$); $[\alpha]^{26}D$ +3.02° (*c* 0.397, CH_3OH). *Anal.* ($C_{26}H_{23}F_6NO_3$) C, H, N.

The racemic *N,O*-diacetyl derivative (±)-**5a** prepared from (±)-**3a** in the same manner had mp 200–201.5°. *Anal.* ($C_{26}H_{23}F_6NO_3$) C, H, N.

The filtrate retained from the preparation of (+)-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (−)-*O,O*-di-*p*-toluoyl-*d*-tartrate was evaporated *in vacuo* and the free base regenerated. The solid obtained was suspended in 2350 ml of MeOH, and 93.6 g (0.24 mol) of (+)-*O,O*-di-*p*-toluoyl-*l*-tartaric acid was added. The solid which separated on standing overnight at 25° was isolated by filtration. The solid, 165.8 g, $[\alpha]^{24}D$ +47.46° (*c* 0.182, CH_3OH), was recrystallized one time from MeOH to give 106.9 g of (−)-**3a** (+)-*O,O*-di-*p*-toluoyl-*l*-tartrate: mp 200–201°; $[\alpha]^{25}D$ +49.26° (*c* 0.217, CH_3OH). *Anal.* ($C_{42}H_{37}F_6NO_9$) C, H, N.

By the same procedure described for the preparation of (+)-**3a**, 106.9 g of (−)-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (+)-*O,O*-di-*p*-toluoyl-*l*-tartrate gave 54.4 g of (−)-**3a**: mp 197–198°; $[\alpha]^{26}D$ −11.99° (*c* 0.542, CH_3OH). *Anal.* ($C_{22}H_{19}F_6NO$) C, H, N.

The hydrochloride salt (−)-**3a**·HCl was prepared in the same manner as described for (+)-**3a**. The analytical sample prepared by two recrystallizations from 95% EtOH had mp 279–281°, $[\alpha]^{26}D$ −33.6° (*c* 0.370, CH_3OH). *Anal.* ($C_{22}H_{20}ClF_6NO$) C, H, Cl, F, N.

The (−)-*N,O*-diacetyl derivative (−)-**5a** was prepared as described for (+)-**5a** in 98% yield. The analytical sample prepared by recrystallization from a MeOH and H_2O mixture had mp 194–195.5°, $[\alpha]^{27}D$ −2.94° (*c* 0.374, CH_3OH). The ir and nmr spectra were identical with those of (+)-**5a**. *Anal.* ($C_{26}H_{23}F_6NO_3$) C, H, N.

(−)-*N*-Acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(−)-6a] from (+)-5a. To a suspension of 39 g (0.076 mol) of (+)-**5a** in 1000 ml of MeOH was added 1.83 g of LiOH. The reaction mixture was stirred at 25° for 1.5 hr, concentrated on a rotary evaporator, diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4), concentrated on a rotary evaporator, and dried under vacuum. The remaining residue was recrystallized from a MeOH and H_2O mixture to give 31.3 g (94%) of (−)-**6a**, mp 225–228°. The analytical sample prepared by recrystallization from the same solvent system had mp 226–228°; ν_{max} (CH_2Cl_2) 3605 (OH) and 1635 cm^{-1} (amide C=O); the nmr spectrum ($CDCl_3$) showed a singlet at δ 2.17 ppm ($CH_3CON<$); $[\alpha]^{24}D$ −17.46° (*c* 0.773, CH_3OH). *Anal.* ($C_{24}H_{21}F_6NO_2$) C, H, N. The racemic *N*-acetyl derivative (±)-**6a** prepared in the same manner had mp 220–221°. *Anal.* ($C_{24}H_{21}F_6NO_2$) C, H, N.

(−)-α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol Hydrochloride [(−)-3b·HCl] from (−)-6a. To 60 ml of freshly distilled $SOCl_2$, cooled to 0°, was added 5.0 g (0.011 mol) of the (−)-**6a**. The cooling bath was removed, and the reac-

‡‡ Samples of the hydrochloride salts were supplied by Drs. B. T. Poon and R. E. Strube.

tion mixture was stirred at 25° overnight. The $SOCl_2$ was removed *in vacuo* on a rotary evaporator. The remaining residue was dissolved in a mixture of 125 ml of 6 *N* HCl and 125 ml of EtOH and refluxed for 3 hr, concentrated *in vacuo*, dried, and recrystallized from a CH_2Cl_2 and CH_3CN mixture to give 4.88 g (98%) of (−)-**3b**·HCl, mp 252–255.5° and 265–273° dec. Tlc on aluminum oxide HF-254 using hexane–chloroform–piperidine (4:4:1) solvent showed one spot which had an R_f identical with (±)-**3b**·HCl.## The analytical sample prepared by recrystallization from the same solvent mixture had mp 249.5–250° and 277–280° dec, $[\alpha]^{27}D$ −33.92° (*c* 0.277, CH_3OH). *Anal.* ($C_{22}H_{20}ClF_6NO$) C, H, Cl, F, N.

(+)-*N*-Acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(+)-6a]. In a manner completely analogous to that described for the preparation of the (−)-*N*-acetyl derivative, (−)-**5a** (46.2 g, 0.09 mol) was converted to 41.0 g (97%) of (+)-**6a**, mp 225–227°. The analytical sample prepared by recrystallization from the same solvent system had mp 224.5–226.5°; ν_{max} (KBr) 3600 (OH) and 1640 cm^{-1} (amide carbonyl); the nmr spectrum ($CDCl_3$) showed a singlet at δ 2.17 ppm ($CH_3CON<$); $[\alpha]^{25}D$ +16.12° (*c* 1.17, CH_3OH). *Anal.* ($C_{24}H_{21}F_6NO_2$) C, H, N.

(+)-α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol Hydrochloride [(+)-3b·HCl] from (+)-6a. In a manner completely analogous to that described for the preparation of (−)-**3b**·HCl, (+)-**6a**, 15 g (0.032 mol), was inverted to 13.3 g (96%) of (+)-**3b**·HCl, mp 256–258° and 262–267° dec. Tlc on aluminum oxide HF-254 using hexane–chloroform–piperidine (4:4:1) solvent showed one spot which had an R_f identical with (±)-**3b**·HCl.## The analytical sample prepared by recrystallization from a CH_2Cl_2 and MeCN mixture followed by drying at 150° had mp 251–254° and 278–281° dec; $[\alpha]^{28}D$ +30.98°; $[\alpha]^{28}_{365}$ +104.55° (*c* 0.427, CH_3OH). *Anal.* ($C_{22}H_{20}ClF_6NO$) C, H, Cl, F, N.

(−)-α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(−)-3b] from (+)-8b. A 198-mg (0.41 mmol) sample of (+)-**8b** was dissolved in 7 ml of EtOH, and the solution was heated to reflux. Three milliliters of 20% NaOH solution was added dropwise, and the mixture was refluxed for 6 hr. The solution turned bright yellow on the addition of the base but gradually became colorless again as the hydrolysis progressed. The reaction mixture was cooled and diluted with H_2O, and the resulting solid was separated by filtration and dried. Recrystallization from MeOH and H_2O gave 0.149 g (85%) of (−)-**3b**: mp 175–176°; $[\alpha]^{25}D$ −1.92°; $[\alpha]^{25}_{365}$ −39.54° (*c* 0.364, CH_3OH). The ir and nmr spectra were identical with those of (±)-**3b**. *Anal.* ($C_{22}H_{19}F_6NO$) C, H, N.

(+)-α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(+)-3b] from (−)-8b. In a manner analogous to that described for the preparation of (−)-**3b** from (+)-**8b**, (−)-**8b** (198 mg, 0.41 mmol) was hydrolyzed to 0.16 g (91%) of (+)-**3b**: mp 176–177°; $[\alpha]^{25}D$ +1.90°, $[\alpha]_{365}$ +39.0° (*c* 0.350, CH_3OH). The ir and nmr spectra were identical with those of (−)- and (±)-**3b**. *Anal.* ($C_{22}H_{19}F_6NO$) C, H, N.

(−)-α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(−)-3b] from Resolution. To a solution of 20 g (0.046 mol) of **3b** and 6.0 g (0.046 mol) of (+)-2-pyrrolidone-5-carboxylic acid in 25 ml of MeOH was added 4000 ml of Et_2O. The crystals which separated on standing overnight at 25° were isolated by filtration. The 20.9 g of crystals obtained were recrystallized eight times from a MeOH and Et_2O mixture to give 1.6 g of (−)-**3b** (+)-2-pyrrolidone-5-carboxylate: mp 219–221°, then resolidifies and melts with decomposition at 230–275°; $[\alpha]^{25}D$ +22.89°; $[\alpha]^{27}_{365}$ +90.38° (*c* 0.498, CH_3OH). *Anal.* ($C_{27}H_{26}F_6N_2O_4$) C, H, N.

To a solution of 1.4 g (0.0025 mol) of the above salt in 10 ml of MeOH was added 50 ml of 1 *N* NaOH, and the mixture was stirred at 26° overnight. The solid was separated by filtration, washed with H_2O, and dried. Recrystallization from a MeOH and H_2O mixture gave 0.81 g of (−)-**3b**, mp 173–174°. The analytical sample prepared by two recrystallizations from the same solvent system had mp 176–177°, $[\alpha]^{25}_{365}$ −38.54° (*c* 0.229, CH_3OH). The ir and nmr spectra of this sample were identical with (−)-**3b** prepared from (+)-**8b**. *Anal.* ($C_{22}H_{19}F_6NO$) C, H, N.

The hydrochloride salt was prepared with ethanolic HCl. The analytical sample prepared by recrystallization from 2-propanol and drying at 150° had mp 140–150° (crystal change) followed by mp 264–267°; $[\alpha]^{26}D$ +30.18°; $[\alpha]^{26}_{365}$ +100.00° (*c* 0.434, CH_3OH). *Anal.* ($C_{22}H_{20}ClF_6NO$) C, H, Cl, F, N.

(+)-*O*-Acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol Hydrochloride [(+)-8b] from (+)-6a. To 12 ml of freshly distilled $SOCl_2$, cooled to 0°, was added 1.0 g (0.002 mol) of the *N*-acetyl derivative (+)-**6a**. The cooling bath was removed, and the reaction mixture was stirred at 25° overnight. The $SOCl_2$ was removed *in vacuo* on a rotary evaporator. The remaining residue was recrystallized from 2-propanol to give 0.74 g (69%) of (+)-**8b**, mp 215–218.5°. The analytical sample prepared by recrystallization from a CH_2Cl_2 and 2-propanol mixture had mp 219–220.5° (dried at 150°); ν_{max} (KBr) 1748 cm^{-1} (ester carbonyl absorption); $[\alpha]^{25}D$ +20.45°; $[\alpha]^{25}_{365}$ +99.53° (*c* 0.406, CH_3OH). *Anal.* ($C_{24}H_{22}ClF_6NO_2$) C, H, N.

If the reaction was stopped after 10 min at 25° and worked up as above, 2-methyl-9-[3,6-bis(trifluoromethyl)-9′-phenanthryl]oxazolino[3,4-*a*]piperidinium chloride (**7b**) was obtained; ν_{max} (CH_2Cl_2) showed the absence of hydroxyl absorption and showed strong absorption at 1665 cm^{-1} (>C=N⁺<).

If the reaction was stopped after 1 hr, the infrared spectrum of the product obtained showed absorption at 1748 and 1665 cm^{-1} indicating that the product was a mixture of **8b** and **7b**.

(−)-*O*-Acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol Hydrochloride [(−)-8b] from (−)-6a. In a manner analogous to that described for the preparation of (+)-**8b**, (−)-**6a** (250 mg, 0.53 mmol) was converted to 0.20 g (81%) of (−)-**8b**: mp 219–221°; ν_{max} (KBr) 1748 cm^{-1} (ester C=O); $[\alpha]^{27}D$ −21.17°; $[\alpha]^{27}_{365}$ −96.48° (*c* 0.364, CH_3OH). *Anal.* ($C_{24}H_{22}ClF_6NO_2$) C, H, N.

(−)-*N*-Acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(−)-9b] from (−)-8b. *O*-Acetyl hydrochloride [(−)-**8b**] (230 mg, 0.50 mmol) was suspended in a mixture of 20 ml of Et_2O and 20 ml of concentrated NH_4OH and stirred for 5 hr. The organic layer was separated, washed with H_2O, dried (Na_2SO_4), and concentrated on a rotary evaporator. The remaining residue was recrystallized twice from a MeOH and H_2O mixture to give 0.2 g (94%) of (−)-**9b**: mp 232–233°; ν_{max} (CH_2Cl_2) 3600 (OH) and 1625 cm^{-1} (amide C=O); the nmr spectrum ($CDCl_3$) showed a singlet at δ 2.24 ppm ($CH_3CON<$); $[\alpha]^{27}D$ −81.4° (*c* 0.204, CH_3OH). *Anal.* ($C_{24}H_{21}F_6NO_2$) C, H, N.

This sample of (−)-**9b** was identical with a sample of (−)-**9b** obtained from (−)-**3b**·HCl by diacetylation with C_5H_5N–Ac_2O (3:1) followed by selective hydrolysis with CH_3OH–LiOH. (+)-**9b** obtained in the same manner from (±)-**3b** had mp 211–212°. *Anal.* ($C_{24}H_{21}F_6NO_2$) C, H, N.

(+)-*N*-Acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(+)-9b] from (+)-8b. In a manner analogous to that described for the preparation of (−)-**9b**, (+)-**8b** (230 mg, 0.50 mmol) was converted to 0.19 g (90%) of (+)-**9b**: mp 232.5–233°; the ir spectrum (CH_2Cl_2) and nmr spectrum were identical with (−)-**9b**; $[\alpha]^{27}D$ +85.9° (*c* 0.156, CH_3OH). *Anal.* ($C_{24}H_{21}F_6NO_2$) C, H, N.

This sample of (+)-**9b** was identical with a sample of (+)-**9b** obtained from (+)-**3b**·HCl as described for (−)-**9b** above.

Resolution of (±)-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol [(±)-4a]. A mixture of 85.4 g (0.26 mol) of (+)-3-bromo-8-camphorsulfonic acid ammonium salt and 107.8 g (0.26 mol) of (±)-**4a**·HCl was dissolved in 1900 ml of MeOH and 2470 ml of H_2O was added. The crystals that separated were filtered and washed with cold H_2O to give 119 g of salt. Two recrystallizations from aqueous MeOH gave 71.8 g of pure (−)-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (+)-3-bromo-8-camphorsulfonate, $[\alpha]^{24}D$ +22.27° (*c* 0.400, CH_3OH). *Anal.* ($C_{27}H_{31}BrF_6N_2O_5S$) C, H, N.

The free base obtained on neutralization of 68.8 g of salt was recrystallized from a MeOH and H_2O mixture and dried to give 35.8 g of (−)-**4a**, mp 172–172.5°. The analytical sample prepared by recrystallization from the same solvent system had mp 171–171.5°; $[\alpha]^{25}D$ −34.00° (*c* 0.447, CH_3OH). *Anal.* ($C_{17}H_{16}F_6NO$) C, H, N. The ir and nmr spectra were identical with ±-4a [mp 178–178.5°. *Anal.* ($C_{17}H_{16}F_6N_2O$) C, H, N].##

A sample of (−)-**4a** was converted to the hydrochloride salt (−)-**4a**·HCl with methanolic HCl. The analytical sample prepared by recrystallization from a CH_2Cl_2 and MeCN mixture followed by drying at 110° had mp 275–276.5° dec; $[\alpha]^{25}D$ −33.0° (*c* 0.306, CH_3OH). The ir and nmr spectra were identical with that of (±)-**4a**·HCl.## *Anal.* ($C_{17}H_{17}ClF_6N_2O$) C, H, Cl, F, N.

(−)-**4a** was converted to (+)-*N*-acetyl-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol [(+)-**11a**] (99% yield) in the same manner that **3a** was converted to **5a**. The analytical sample prepared by recrystallization from the same solvent system had mp 208–208.5°; ν_{max} ($CHCl_3$) 3615 and 3550–3150 (OH) and 1612 cm^{-1} (amide C=O); $[\alpha]^{25}D$ +20.3° (*c* 0.528, CH_3OH). *Anal.* ($C_{19}H_{18}F_6N_2O_2$) C, H, N.

The racemic *N*-acetyl derivative (±)-**11a** prepared in the same manner had mp 202.5–203°. The ir and nmr spectra were identi-

cal with those of (+)-**11a**. *Anal.* ($C_{19}H_{18}F_6N_2O_2$) C, H, N.

The filtrate from the first crystallization of the (+)-sulfonate salt above was cooled to +15°. The crystals that separated were collected to give 21.6 g of (+)-4a (+)-3-bromo-8-camphorsulfonate, $[\alpha]^{24}D$ +61.5° (*c* 0.646, CH_3OH). Neutralization of this salt gave 11.0 g of (+)-4a, mp 171–172°. The analytical sample prepared by recrystallization from a MeOH and H_2O mixture had mp 171–172°, $[\alpha]^{26}D$ +34.14° (*c* 0.354, CH_3OH). The ir and nmr spectra were identical with (±)- and (−)-**4b**. *Anal.* ($C_{17}H_{16}F_6N_2O$) C, H, N.

The filtrate from the salt above was concentrated by freeze-drying, and the residue was neutralized as described in the previous experiment to give the free base. The free base was dissolved in 200 ml of MeOH, and 4 ml of concentrated HCl was added to give 15.25 g (36.8 mmol) of (+)- and (±)-**4a**·HCl. This hydrochloride and 12.05 g (36.8 mmol) of (−)-3-bromo-8-camphorsulfonic acid ammonium salt were dissolved in MeOH–H_2O (270–350 ml). The crystals that separated were collected and recrystallized once from the same solvent system to give 17.8 g of pure (+)-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (−)-3-bromo-8-camphorsulfonate, $[\alpha]^{24}D$ −23.49° (*c* 0.468, CH_3OH). *Anal.* ($C_{27}H_{31}BrF_6N_2O_5S$) C, H, N.

The free base obtained on neutralization of the above salt was separated by filtration, washed with H_2O, recrystallized from a MeOH and H_2O mixture, and dried to give 9.8 g more of (+)-**4a**: mp 171–172°: $[\alpha]^{25}D$ +33.3° (*c* 0.397, CH_3OH).

A sample of (+)-**4a** was converted to its hydrochloride salt (+)-**4a**·HCl in the same manner as described for (−)-**4a**. The analytical sample prepared by two recrystallizations from a CH_2Cl_2 and MeCN mixture followed by drying at 100° had mp 276–277° dec, $[\alpha]^{22}D$ +33.90° (*c* 0.280, CH_3OH). The ir and nmr spectra were identical with those of (±)- and (−)-4a·HCl. *Anal.* ($C_{17}H_{17}ClF_6N_2O$) C, H, Cl, F, N.

In a manner completely analogous to that described for the preparation of the (+)-*N*-acetyl derivative, (+)-**4a** (11.8 g, 0.003 mol) was converted to 10.2 g (78%) of (−)-**11a**, mp 197–202°. The analytical sample prepared by recrystallization from a MeOH and H_2O system had mp 206–207°; the ir spectrum was identical with that of (+)-**11a**, $[\alpha]^{27}D$ −21.3° (*c* 0.272, CH_3OH). *Anal.* ($C_{19}H_{18}F_6N_2O_2$) C, H, N.

(+)-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinoline-methanol Hydrochloride [(+)-4b·HCl] from (+)-11a. A 16-g (0.038 mol) sample of (+)-**11a** was converted to 14.9 g (96%) of (+)-**4b**·HCl in the same manner that (+)-**6a** was converted to (+)-**3b**·HCl. Tlc on aluminum oxide HF-254 using hexane–chloroform–piperidine (4:4:1) solvent showed one spot which had an R_f identical with (±)-4b·HCl. The analytical sample prepared by recrystallization from a CH_2Cl_2 and C_6H_{14} mixture (dried at 100°) had mp 148–150.5°, $[\alpha]^{24}D$ +55.27° (*c* 0.431, CH_3OH). *Anal.* ($C_{17}H_{17}ClF_6N_2O$) C, H, Cl, F, N.

In a manner analogous to that described for the preparation of (+)-**5a**, (+)-4b·HCl (200 mg, 0.48 mmol) was converted to 0.19 g (94%) of the (+)-*N*-acetyl derivative (+)-**13b**: mp 187–187.5°; $[\alpha]^{25}D$ +84.9° (*c* 0.312, CH_3OH); ν_{max} (CH_2Cl_2) 3595 and 3500–3120 (OH), 1622 (amide C=O), and 1588 cm^{-1} (aromatic); the nmr spectrum ($CDCl_3$) showed a singlet at δ 2.19 ppm ($CH_3CON<$). *Anal.* ($C_{19}H_{18}F_6N_2O_2$) C, H, N.

The racemic *N*-acetyl derivative (±)-**13b** prepared similarly had mp 162.5–163.5°. The ir and nmr spectra were identical with that of (+)-13b.

(−)-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinoline-methanol Hydrochloride [(−)-4b·HCl]. In a manner completely analogous to that described for the preparation of (+)-**4b**·HCl, (−)-**11a**, 10.2 g (0.024 mol), was inverted to 9.9 g (99%) of (−)-**4b**·HCl, mp 148–151°. Tlc on aluminum oxide HF-254 using hexane–chloroform–piperidine (4:4:1) solvent showed one spot which had an R_f identical with (±)-**4b**·HCl. The analytical sample prepared by recrystallization from an EtOAc and C_6H_{14} mixture followed by drying at 100° had mp 151–155°, $[\alpha]^{25}D$ −53.37° (*c* 0.308, CH_3OH). *Anal.* ($C_{17}H_{17}ClF_6N_2O$) C, H, Cl, F, N.

In a manner analogous to that described for the preparation of (+)-**13b**, (−)-**4b**·HCl (0.10 g, 0.24 mmol) was converted to 0.90 g (90%) of (−)-**13b**: mp 184–185°; $[\alpha]^{27}D$ −79.7° (*c* 0.192, CH_3OH). The ir and nmr spectra were identical with those of (±)- and (+)-**13b**. *Anal.* ($C_{19}H_{18}F_6N_2O_2$) C, H, N.

α-(2-Piperidyl-3,6-bis(trifluoromethyl)-9-phenanthrene-methanol (*R*)-*O*-Methylmandelamide (16) from (±)-, (−)-, and (+)-3a. To a solution of (*R*)-*O*-methylmandelyl chloride [prepared from 117 mg (0.7 mmol) of (*R*)-*O*-methylmandelic acid][8,9] in 4 ml of dry C_6H_6 containing 1 ml of C_5H_5N (dried over barium oxide) was added 0.053 g (0.215 mmol) of (±)-, (+)-, or (−)-**3a**, and the mixture was stirred at 25° for 5 hr. The tan solid obtained after standard work-up was dissolved in $CHCl_3$ and eluted through a short alumina column. Concentration of the eluent gave the corresponding diacyl derivative **15**. This solid was dissolved in 4 ml of a THF–H_2O mixture (3:1) and 0.006 g of LiOH was added. After 1 hr the usual work-up gave 0.035–0.040 g of (±)-, (+)-, or (−)-3a (*R*)-*O*-methylmandelamide (**16**). The 100-MHz nmr spectrum ($CDCl_3$) of the mixture of diastereomers obtained from (±)-**3a** exhibited resonances at δ 3.36 and 3.44 ppm of unequal intensity for the two CH_3O groups. The 100-MHz nmr spectrum ($CDCl_3$) of **16** from (−)-**3a** was essentially identical with that derived from racemic **3a** except that the CH_3O signal at δ 3.44 was more intense than that at 3.36 ppm. Integration of these signals gave a ratio of 88:12 indicating that racemization was probably occurring during the preparation. This is based on optical purity determination by other methods. The 100-MHz nmr spectrum ($CDCl_3$) of **16** from (+)-**3a** was essentially identical with that derived from (−)-**3a** except that the CH_3O signal at δ 3.36 was more intense that that at 3.44 ppm. Integration of these signals gave a ratio of 90:10.

***N*-Acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (*R*)-*O*-Methylmandelate (17) from (±)-, (+)-, and (−)-3a.** To a solution of (*R*)-*O*-methylmandelyl chloride [prepared from 117 mg (0.7 mmol) of (*R*)-*O*-methylmandelic acid][8,9] in 4 ml of dry C_6H_6 containing 1 ml of C_5H_5N (dried over barium oxide) was added 50 mg (0.107 mmol) of (±)-, (+)-, or (−)-**6a**, and the mixture was stirred at 25° for 1 hr. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator, and the remaining residue was dried under vacuum. The oil obtained was dissolved in $CHCl_3$ and eluted through a short alumina column. Concentration of the eluent gave a foam which was subjected to tlc on silica gel HF using CCl_4–Me_2CO (4:1) solvent. The product band was detected by uv quenching. The band was separated and extracted with Me_2CO. Concentration of the extracts gave 0.060–0.062 g of the *N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol (*R*)-*O*-methylmandelate obtained from (±)-, (+)-, or (−)-**3a**. The 100-MHz nmr spectrum ($CDCl_3$) of the mixture of diastereomers obtained from (±)-3a exhibited resonances at δ 2.03 and 2.11 ppm for the two $CH_3CON<$ groups. Both CH_3O peaks appeared at 3.48 ppm. The 100-MHz nmr spectrum ($CDCl_3$) of **17** obtained from (+)-3a showed one CH_3O- and one $CH_3CON<$ resonance at δ 3.41 and 2.03 ppm, respectively, indicating that this compound is optically pure.

α-(2-Piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrene-methanol (*R*)-*O*-Methylmandelamide from (±)- and (−)-3b. The (*R*)-*O*-methylmandelamides of (±)- and (−)-**3b** were prepared in a manner analogous to that described for the (*R*)-*O*-methylmandelamides of **3a**. The 100-MHz nmr spectrum ($CDCl_3$) of the mixture of diastereomers from (±)-**3b** exhibited resonances at δ 3.54 and 3.57 ppm for the two CH_3O groups. The 100-MHz nmr spectrum ($CDCl_3$) of the product from (−)-**3b** showed only one CH_3O resonance at δ 3.58 ppm indicating that the compound is optically pure.

(±)- and (+)-*N*-Acetylephedrine [(±)- and (+)-22]. The title compounds were prepared according to the procedure reported by Welsh:[19] (±)-**22** had mp 77–79° (lit.[19] 77–78.5°); (+)-22 had mp 85–87.5° (lit.[19] mp 85.5–86.5°).

(±)- and (−)-*N*-Acetyl-ψ-ephedrine [(±)- and (−)-23]. In a manner completely analogous to that described for the preparation of (−)-*N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(−)-**6a**], (±)- and (−)-ψ-ephedrine was converted to (±)- and (−)-23; (±)-23 had mp 83–86° (lit.[19] mp 76–77.5°); (−)-**23** had mp 106–107° (lit.[19] mp 103.5–104°).

(±)-*O*-Acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthrenemethanol [(±)-8b] from (±)-6a or (±)-9b (N → O Acyl Migration Studies). A solution of 100 mg (0.213 mmol) of (±)-*N*-acetyl-α-(2-piperidyl)-3,6-bis(trifluoromethyl-9-phenanthrenemethanol (±)-**6a** or (±)-**9b** in 4 ml of acetic anhydride was refluxed for 2 hr while a slow stream of HCl was passed through the solution. The reaction mixture was concentrated under vacuum, dried, and triturated with Et_2O. The resulting solid was filtered and dried to give 0.070 g (65%) and 0.088 g (82%) of (±)-**8b** from (±)-**6a** and (±)-**9b**, respectively. The mp 212–215° and ir spectra of the two samples were identical. The analytical sample prepared by recrystallization from an EtOH and Et_2O mixture had mp 219–222°; ν_{max} (KBr) 2800–2500 ($>NH_2^+$) and 1755 cm^{-1} (ester carbonyl). *Anal.* ($C_{24}H_{22}ClF_6NO_2$) C, H, N.

A 0.05-g sample of (±)-**8b** from the above experiment was dissolved in 0.5 ml of EtOH containing 5 drops of 10% NaOH solu-

tion, and the mixture was refluxed 4 hr. The usual work-up gave 0.04 g of **3b**.

Circular Dichroism Measurements. (−)-**3a**·HCl. The CD measurements were obtained at a concentration of 9.21×10^{-3} *M* at 25°: $[\theta]_{360}$ ±0, $[\theta]_{349}$ −124, $[\theta]_{332}$ −157, $[\theta]_{318}$ −122, $[\theta]_{316}$ −94.

(+)-**3a**·HCl. The CD measurements were obtained at a concentration of 9.44×10^{-3} *M* in MeOH at 25°: $[\theta]_{360}$ ±0, $[\theta]_{349}$ +132, $[\theta]_{332}$ +150, $[\theta]_{317}$ +115, $[\theta]_{314}$ +104.

(+)-**3b**·HCl. The CD measurements were obtained at a concentration of 8.96×10^{-3} *M* in MeOH at 25°: $[\theta]_{360}$ ±0, $[\theta]_{350}$ +39, $[\theta]_{334}$ +41, $[\theta]_{320}$ +26.

(−)-**3b**·HCl. The CD measurements were obtained at a concentration of 9.04×10^{-3} *M* in MeOH at 25°: $[\theta]_{360}$ ±0, $[\theta]_{350}$ −41, $[\theta]_{334}$ −40, $[\theta]_{320}$ −19.

(−)-**4a**·HCl. The CD measurements were obtained at a concentration of 1.84×10^{-2} *M* in MeOH at 25°: $[\theta]_{360}$ ±0, $[\theta]_{321}$ +293, $[\theta]_{313}$ −1059, $[\theta]_{299}$ −1631.

(+)-**4a**·HCl. The CD measurements were obtained at a concentration of 1.80×10^{-2} *M* in MeOH at 25°: $[\theta]_{360}$ ±0, $[\theta]_{321}$ −292, $[\theta]_{313}$ +1152, $[\theta]_{299}$ +1753.

(+)-**4b**·HCl. The CD measurements were obtained at a concentration of 1.59×10^{-2} *M* in MeOH at 25°: $[\theta]_{360}$ ±0, $[\theta]_{319}$ −897, $[\theta]_{308}$ −120, $[\theta]_{297}$ +561.

(−)-**4b**·HCl. The CD measurements were obtained at a concentration of 1.59×10^{-2} *M* in MeOH at 25°: $[\theta]_{360}$ ±0, $[\theta]_{319}$ +929, $[\theta]_{308}$ +125, $[\theta]_{197}$ −498.

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Folic Acid Analogs. Modifications in the Benzene-Ring Region. 4. 3′-Ethyl- and 3′-Isopropylfolic Acids†

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3′-Ethylfolic acid (**12a**) and 3′-isopropylfolic acid (**12b**) were synthesized as part of a program to obtain folic acid analogs, the reduced forms of which may have an altered ability to function as one-carbon transfer agents. The condensation of 2-acetamido-6-formylpteridin-4(3*H*)-one (**10**) with diethyl *N*-(4-amino-3-ethylbenzoyl)-L-glutamate (**9a**) and with diethyl *N*-(4-amino-3-isopropylbenzoyl)-L-glutamate (**9b**) afforded anils **11a** and **11b** which were reduced with sodium borohydride. Anaerobic alkaline hydrolysis of the reduction products gave the desired folic acid analogs **12a** and **12b**. Analogs **12a** and **12b** were inactive when tested against leukemia L1210 in mice and were not cytotoxic to KB cells in culture. Although **12a** and **12b** were noninhibitory toward pigeon liver dihydrofolate reductase, the dihydrofolate reductase enzyme was apparently stimulated by **12b** at higher concentrations. When tested *vs. Streptococcus faecium*, **12a** was an effective inhibitor while **12b** was growth-supporting. The differences in the behavior of **12a** and **12b** in the dihydrofolate reductase and *S. faecium* systems were rationalized as possibly being attributable to a combination of relative steric requirements and hydrophobic bonding.

Some of the folic acid analogs previously synthesized in this laboratory have been designed so that the electron density at N^{10} is decreased[1,2] or increased[3] relative to folic acid, and a mechanistic interpretation of the means by which these changes may potentially affect the participation of the reduced forms of the analogs in folate metabolism has been postulated.[1] We now wish to report the synthesis of *N*-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]-3-ethylbenzoyl]-L-glutamic acid (3′-ethylfolic acid, **12a**) and *N*-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]-3-isopropylbenzoyl]-L-glutamic acid (3′-isopropylfolic acid, **12b**) in which additional changes are effected relative to folic acid. Analogs **12a** and **12b** have a slightly increased electron density at N^{10} because of the positive *R* effect[4] of the ethyl and isopropyl groups attached to the benzene ring. The alkyl groups may provide steric hindrance to reactions at N^{10} during the formation of one-carbon transfer agents by the reduced forms of the analogs. Also, the relative bulk of the alkyl groups and the increased lipophilic character

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