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Synthesis and Properties of Fluorine-Containing Heterocyclic Compounds. 8. α-(2-Pyridyl)- and α-(2-Piperidyl)-2-(trifluoromethyl)-4-azaphenanthrenemethanols

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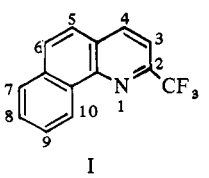
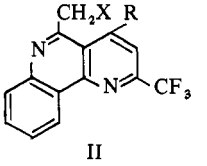
Some α-(2-pyridyl)- and α-(2-piperidyl)-2-(trifluoromethyl)-4-azaphenanthrenemethanols were synthesized as potential antimalarials. These compounds were prepared by a route involving the condensation of aminonaphthalenes or aminoquinolines with ethyl trifluoroacetoacetate. The resulting 2-(trifluoromethyl)azaphenanthren-4-ols were converted to the corresponding 4-chloro and 4-bromo derivatives. The 4-bromo derivatives exchanged rapidly with *n*-butyllithium. The lithio derivatives thus obtained were treated with 2-pyridinecarboxaldehyde or converted to the parent 4-carboxylic acids which were then treated with 2-lithiopyridine. The products of these reactions were reduced to the desired amino alcohols with hydrogen and platinum oxide. α-(2-Piperidyl)-2-(trifluoromethyl)-4-benzo[*h*]quinolinemethanol and its 6-chloro derivative were found to be curative in mice infected with *Plasmodium berghei* and active in chicks infected with *Plasmodium gallinaceum*. These compounds exhibited higher antimalarial activity than the corresponding 2-(trifluoromethyl)-4-quinolinemethanols but were also phototoxic. The α-(2-pyridyl)-4-azaphenanthrenemethanols were inactive.

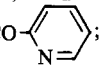
Quinolinemethanols have long been known as active antimalarial agents.[1] Unfortunately, many of these compounds are also photosensitizers.[2] In a search for useful antimalarial chemotherapeutic agents, we investigated the synthesis of some 2-(trifluoromethyl)-4-azaphenanthrenemethanols. These compounds incorporate both a quinoline nucleus and a phenanthrene nucleus in a single structure. Such nuclei[3,4] have shown antimalarial activity when appropriately substituted with amino or amino alcohol groups. Suitable amino alcohol substituents such as the α-(2-piperidyl)-methanol group were introduced at the 4 position to impart the desired activity. It was hoped that the 2-trifluoromethyl group would prevent metabolic oxidation at the 2 position and would decrease the phototoxic side effects associated with similar structures.[2] The 2-(trifluoromethyl)azaphenanthrenes previously synthesized in our laboratory were chosen as the parent nuclei for these potential antimalarials.[5,6] They included 2-trifluoromethyl derivatives of the following heterocycles: benzo[*h*]quinoline (I), benzo[*h*]-1,6-naphthyridine (II), 1,7-phenanthroline (III), 1,8-phenanthroline (IV), and 1,10-phenanthroline (V).



I



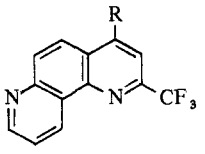
II

17, R = Br; X = H
18, R = Br; X = Br
33, R = CO-  ; X = H

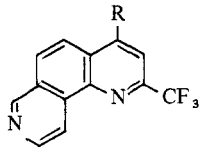
Chemistry. The synthetic routes used to prepare α-(2-pyridyl)- and α-(2-piperidyl)-2-(trifluoromethyl)-4-azaphenanthrenemethanols are outlined in Schemes I and II.

The 2-(trifluoromethyl)azaphenanthren-4-ols† were formed by a Conrad–Limpach-type condensation of the appropriate amine and ethyl trifluoroacetoacetate in polyphosphoric acid. 2-(Trifluoromethyl)benzo[*h*]quinolin-4-ol (**1**), 6-chloro-2-(trifluoromethyl)benzo[*h*]quinolin-4-ol (**9**), 6-cyano-2-(trifluoromethyl)benzo[*h*]quinolin-4-ol (**10**), 7-nitro-2-(trifluoromethyl)benzo[*h*]quinolin-4-ol (**11**), 2-(trifluoromethyl)-1,7-phenanthrolin-4-ol (**12**), 2-(trifluoromethyl)-1,8-phenanthrolin-4-ol (**13**), 2-(trifluoromethyl)-1,10-phenanthrolin-4-ol (**14**), 5-methoxy-2-(trifluoromethyl)-1,10-phenanthrolin-4-ol (**15**), and 5-methyl-2-(trifluoromethyl)benzo[*h*]-1,6-naphthyridin-4-ol (**16**) were prepared from 1-naphthylamine, 4-chloro-1-naphthylamine, 4-amino-1-naphthalenecarbonitrile, 5-nitro-1-naphthylamine, 5-aminoisoquinoline, 8-aminoisoquinoline, 8-amino-6-methoxyquinoline, and 4-aminoquinaldine, respectively. The conversion of the 4-hydroxy compounds into the corresponding 4-bromo derivatives was accomplished with either phosphorus pentabromide, phosphorus oxybromide,[8] phosphorus tribromide, or a mixture of phosphorus oxybromide and

†The 4-hydroxy derivatives of azaphenanthrenes exist in equilibrium with their keto tautomers which are believed to be the predominant form.[7] For convenience, however, we refer to them simply as azaphenanthren-4-ols.

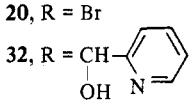


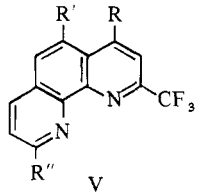
III



IV

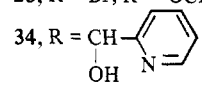
20, R = Br
21, R = Br
30, R = CO_2H

32, R = 



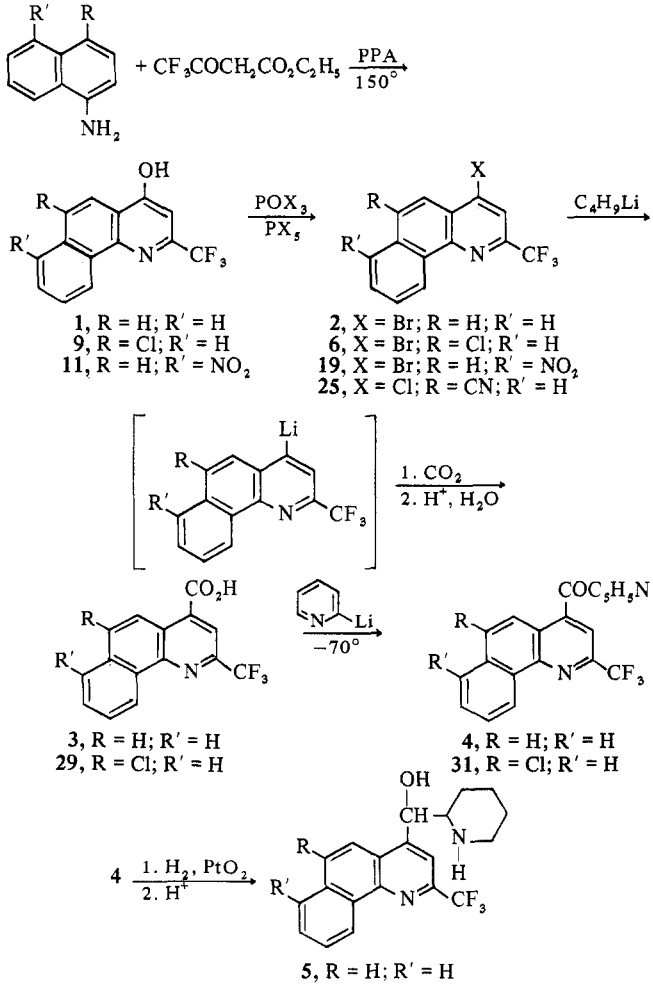
V

15, R = OH; R′ = H; R″ = H
22, R = Br; R′ = H; R″ = H
23, R = Br; R′ = OCH_3; R″ = H

34, R =  ; R′ = OCH_3; R″ = C_4H_9

phosphorus pentabromide. Phosphorus oxybromide[8] and phosphorus tribromide proved to be unsuitable reagents. The most effective reagent was the mixture of phosphorus oxybromide and phosphorus pentabromide. For the benzo[*h*]-1,6-naphthyridine and 1,8- and 1,10-phenanthroline systems, the final product was the hydrobromide salt. These salts were easily converted to the corresponding free

Scheme I



1, R = H; R′ = H
9, R = Cl; R′ = H
11, R = H; R′ = NO_2

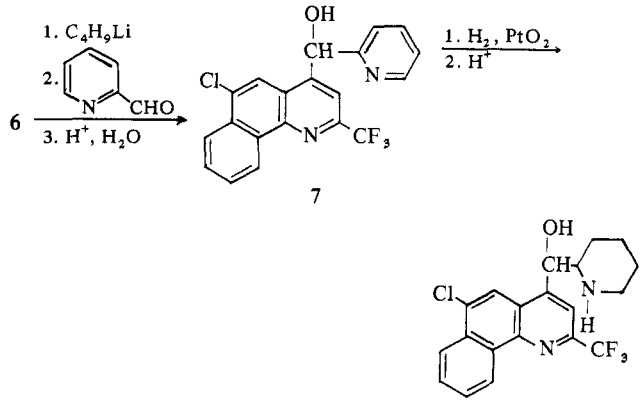
2, X = Br; R = H; R′ = H
6, X = Br; R = Cl; R′ = H
19, X = Br; R = H; R′ = NO_2
25, X = Cl; R = CN; R′ = H

3, R = H; R′ = H
29, R = Cl; R′ = H

4, R = H; R′ = H
31, R = Cl; R′ = H

5, R = H; R′ = H

Scheme II

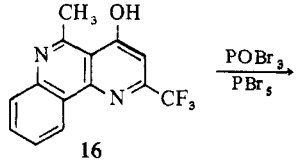


7

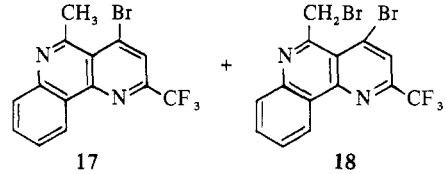
8

bases. When 5-methyl-2-(trifluoromethyl)benzo[*h*]-1,6-naphthyridin-4-ol (**16**) was treated with phosphorus oxybromide and phosphorus pentabromide, monobromination of the methyl side chain occurred affording 4-bromo-5-(α-bromomethyl)-2-(trifluoromethyl)benzo[*h*]-1,6-naphthyridine (**18**). The expected 4-bromo derivative **17** was also formed (Scheme III). 4-Bromo-2-(trifluoromethyl)benzo-

Scheme III



16



17 18

[*h*]quinoline (**2**), 4-bromo-6-chloro-2-(trifluoromethyl)-benzo[*h*]quinoline (**6**), 4-bromo-7-nitro-2-(trifluoromethyl)-benzo[*h*]quinoline (**19**), 4-bromo-2-(trifluoromethyl)-1,7-phenanthroline (**20**), 4-bromo-2-(trifluoromethyl)-1,8-phenanthroline (**21**), 4-bromo-2-(trifluoromethyl)-1,10-phenanthroline (**22**), and 4-bromo-5-methoxy-2-(trifluoromethyl)-1,10-phenanthroline (**23**) were prepared from compounds **1**, **9**, **11**, **12**, **13**, **14**, and **15**, respectively, *via* the same procedure.

Several 4-chloro derivatives were also prepared from the corresponding 2-(trifluoromethyl)azaphenanthrene-4-ols.[5] When compounds **1**, **10**, **12**, **15**, and **16** were treated with phosphorus oxychloride and phosphorus pentachloride, 4-chloro-2-(trifluoromethyl)benzo[*h*]quinoline (**24**), 4-chloro-6-cyano-2-(trifluoromethyl)benzo[*h*]quinoline (**25**), 4-chloro-2-(trifluoromethyl)-1,7-phenanthroline (**26**), 4-chloro-5-methoxy-2-(trifluoromethyl)-1,10-phenanthroline (**27**), and 4-chloro-5-methyl-2-(trifluoromethyl)benzo-[*h*]-1,6-naphthyridine (**28**) were obtained.

Although there are many ways to introduce amino alcohol side chains in aromatic or heterocyclic nuclei, only two methods were used in this investigation. The first method (Scheme I) involved the conversion of the 4-halo derivative to the corresponding carboxylic acid *via* the 4-lithio derivative. Treatment of the carboxylic acid with 2-lithiopyridine gave the corresponding ketone[9] which could then be reduced with either hydrogen and platinum oxide or sodium borohydride[10] to the desired amino alcohol.

The synthesis of 4-lithio-2-(trifluoromethyl)azaphenanthrenes was investigated. Lithium exchange was found to be successful only with the 4-bromo derivatives. 2-(Trifluoromethyl)benzo[*h*]quinoline-4-carboxylic acid (**3**), 6-chloro-2-(trifluoromethyl)benzo[*h*]quinoline-4-carboxylic acid (**29**), and 2-(trifluoromethyl)-1,8-phenanthroline-4-carboxylic acid (**30**) were prepared by first mixing the corresponding 4-bromo derivatives with 2 equiv of *n*-butyllithium at −70°[11] and then treating the resulting 4-lithio derivatives *in situ* with solid carbon dioxide.

One of the routes to 2-(trifluoromethyl)-4-azaphenanthrenemethanols involved the reaction of 4-lithio-2-(trifluoromethyl)azaphenanthrenes with 2-pyridinecarboxaldehyde and subsequent reduction of the resultant products (Scheme II). Although this method was used to prepare a number of 4-azaphenanthrenemethanols, α-(2-pyridyl)-6-chloro-2-(trifluoromethyl)benzo[*h*]quinoline-4-methanol (**7**), and α-(2-pyridyl)-2-(trifluoromethyl)-1,7-phenanthroline-4-methanol (**32**), yields were generally low and isolation of the products difficult. The reaction between the 4-lithioazaphenanthrenes and 2-pyridinecarboxaldehyde was often incomplete, causing appreciable contamination of the product with unreacted starting materials. Compound **17** yielded only trace amounts of the desired product **33**. Large amounts of the corresponding 4-unsubstituted product were found. The 5-methyl group undoubtedly inhibited addition of the aldehyde as a result of steric hindrance The reaction of 4-lithio-5-methoxy-2-(trifluoromethyl)-1,10-phenanthroline with 2-pyridinecarboxaldehyde yielded α-(2-pyridyl)-9-*n*-butyl-5-methoxy-2-(trifluoromethyl)-1,10-phenanthroline-4-methanol (**34**) in very low yields. This product indicates that nucleophilic attack at the 9 position of the 1,10-phenanthroline ring is one of the side reactions.

2-Pyridyl 2-(trifluoromethyl)benzo[*h*]quinolin-4-yl ketone (**4**) and 2-pyridyl 6-chloro-2-(trifluoromethyl)-benzo[*h*]quinolin-4-yl ketone (**31**) were prepared by the reaction of compounds **3** and **29** with 2 equiv of 2-lithiopyridine. When compound **30** was treated with this reagent, however, only starting material was recovered.

α-(2-Piperidyl)-2-(trifluoromethyl)benzo[*h*]quinoline-4-methanol (**5**) was obtained by the reduction of compound **4** with hydrogen and platinum dioxide. Although the stereochemistry of this product was not determined, similar reductions have been shown to be stereospecific.[12] α-(2-Piperidyl)-6-chloro-2-(trifluoromethyl)benzo[*h*]quinoline-4-methanol (**8**) was prepared from compound **7** by the same method.

Biological Results. The antimalarial tests were performed with mice and chicks as previously described.[13] All the compounds mentioned have been submitted for testing against *Plasmodium berghei* in mice. The antimalarial test data for the α-(2-piperidyl)-2-(trifluoromethyl)benzo[*h*]quinoline-4-methanols **5** and **8** and the corresponding α-(2-piperidyl)-2-(trifluoromethyl)quinoline-4-methanols[3] **5a** and **8a** are listed in Table I. The benzo[*h*]quinolines **5** and **8** are more active than the quinolines **5a** and **8a**. All of the active compounds, however, are phototoxic. The other compounds tested were found inactive.

Rothe and Jacobus[2] have investigated the phototoxic response of mice to various quinolinemethanols. Compound **5** produced phototoxic responses at 100 mg/kg when injected intraperitoneally and 50 mg/kg when administered orally. The corresponding α-(2-pyridyl) compounds did not cause photosensitization but were inactive in the antimalarial test.

Table I. Antimalarial Activity[a]

Compd no.	Test dosage (mg/kg), ΔMST[b] or C[c]							
	Mice, *P. berghei*						Chicks, *P. gallinaceum*	
	20	40	80	160	320	640	100	120
5a	5.3	17.5	21.5	C	C	C	6.0	
5a[d]	Inactive at all dosage levels							
8	0.6	7.6	8.4	C	C	C		10.0
8a[e]				7.5	8.7	C		

[a]Tests were performed by Dr. Leo Rane of the University of Miami, Fla. The results were provided through the Walter Reed Army Institute of Research. [b]MST = mean survival time (days) of five treated animals − mean survival time (days) of five control animals. [c]C = curative; mice survived at least 60 days. For compound **5**, four of the test animals were cured at a dosage of 160 mg/kg. All test animals were cured at dosages of 320 and 640 mg/kg. For compound **8**, three of the test animals were cured at a dosage of 160 mg/kg, four were cured at a dosage of 320 mg/kg, and all of the test animals were cured at a dosage of 640 mg/kg. For compound **8a**, one of the test animals was cured at a dosage of 640 mg/kg. [d]α-(2-Piperidyl)-2-(trifluoromethyl)-4-quinolinemethanol hydrochloride. [e]α-(2-Piperidyl)-2-(trifluoromethyl)-6-chloro-4-quinolinemethanol hydrochloride.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, West Germany. All analytical results (C, H, N, and X) were within 0.3% of the theoretical values. Melting points, recrystallization solvents, percentage yields, and molecular formulas for all new compounds are given in Table II. The structures assigned to these compounds were supported by infrared spectra recorded on Perkin-Elmer 137 or 521 spectrophotometers and nuclear magnetic resonance spectra recorded on Varian A-60A or HA-100 spectrometers.

2-(Trifluoromethyl)azaphenanthren-4-ols 1 and 9–16 (Scheme I). The synthesis of these compounds was based upon a procedure developed by Dey and Joullié[5] as illustrated in the preparation of 6-chloro-2-(trifluoromethyl)benzo[*h*]quinolin-4-ol (**9**). Ethyl trifluoroacetoacetate (8.85 g, 0.048 mol) was added dropwise to a

Table II. 2-(Trifluoromethyl)azaphenanthrenes

Compd no.	Formula	Yield, %	Solvent	Mp, °C
	2-(Trifluoromethyl)benzo[*h*]quinolines			
9	$C_{14}H_7ClF_3NO$	80	95% ethanol	202–203
11	$C_{14}H_7F_3N_2O_3 \cdot H_2O$	5	Ethanol–water	197–198
25	$C_{15}H_6ClF_3N_2$	80	Ethanol	197–199
2	$C_{14}H_7BrF_3N$	64	Ethanol–water	107–109
6	$C_{14}H_6BrClF_3N$	76	Ethanol	143–145
19	$C_{14}H_6BrF_3N_2O_2$	82	95% ethanol	175–176.5
3	$C_{15}H_8F_3NO_2$	89	Ethanol–water	262–263.5
29	$C_{15}H_7ClF_3NO_2$	68	Methanol–water	242–244
4	$C_{20}H_{11}F_3N_2O$	50	Ethanol–water	116–117
31	$C_{20}H_{10}ClF_3N_2O$	39	Ethanol	174–175
7	$C_{20}H_{12}ClF_3N_2O$	67	Ethanol	181–182.5
5	$C_{20}H_{19}F_3N_2O$	49	95% ethanol	196–197.5
8	$C_{20}H_{18}ClF_3N_2O$	93	Acetonitrile	183.5–184.5
	2-(Trifluoromethyl)benzo[*h*]-1,6-naphthyridines			
17	$C_{14}H_8BrF_3N_2$	56	95% ethanol	126–127.5
18	$C_{14}H_7Br_2F_3N_2$	13	95% ethanol	195–196
33	$C_{20}H_{12}F_3N_3O$		Ethanol–water	173–174.5
	2-(Trifluoromethyl)-1,7-phenanthrolines			
20	$C_{13}H_6BrF_3N_2$	56	95% ethanol	148–149
32	$C_{19}H_{12}F_3N_3O$	38	95% ethanol	182–184
	2-(Trifluoromethyl)-1,8-phenanthrolines			
21	$C_{13}H_6BrF_3N_2$	82	Methanol	216–217
30	$C_{14}H_7F_3N_2O_2$	20	Methanol	318 dec
	2-(Trifluoromethyl)-1,10-phenanthrolines			
15	$C_{13}H_7F_3N_2O \cdot 0.5H_2O$	80	95% ethanol	153–155
22	$C_{13}H_6BrF_3N_2$	80	Ethanol	165–166
23	$C_{14}H_8BrF_3N_2O$	30	95% ethanol	239–240
34	$C_{20}H_{14}F_3N_3O_2$	3	Benzene–hexane	204–205.5

mixture of 8.13 g (0.046 mol) of 4-chloro-1-naphthylamine in 75 ml of polyphosphoric acid heated at 100–110°. The temperature was then raised to 130° and maintained for 2.5 hr. The reaction mixture was then poured slowly, with stirring, into 2500 ml of ice–water. The resulting mixture was stirred overnight. The solid that formed was collected and washed with water. It was then dissolved in 10% aqueous sodium hydroxide and treated with decolorizing carbon. The carbon was removed by filtration and the solution was acidified with glacial acetic acid to give a tan solid **(9)**. For heterocyclic systems II–V, appropriate heterocyclic amines were used as described by Dey and Joullié[5] and Nyquist and Joullié.[6]

4-Bromo-2-(trifluoromethyl)azaphenanthrenes 2, 6, and 19–23 (Scheme I). These compounds were synthesized by a procedure illustrated for the preparation of 4-bromo-6-chloro-2-(trifluoromethyl)benzo[*h*]quinoline **(6)**. A mixture of 11.0 g (0.037 mol) of 6-chloro-2-(trifluoromethyl)benzo[*h*]quinolin-4-ol **(9)**, 31.8 g (0.11 mol) of phosphorus oxybromide, and 17.7 g (0.04 mol) of phosphorus pentabromide was heated at 130° for 2 hr. After the mixture cooled, it was poured into 2000 ml of ice–water. The resulting solution was stirred overnight. The solid that formed **(6)** was collected, washed with water, and dried. In some instances, the products were the hydrobromide salts rather than the free bases. These salts were converted to the free bases by heating them in dilute alkali on a steam bath. 5-Methyl-2-(trifluoromethyl)benzo[*h*]-1,6-naphthyridin-4-ol **(16)** yielded a mixture of two products, **17** and **18**. These compounds were separated by fractional crystallization from 95% ethanol. 4-Bromo-5-(α-bromomethyl)-2-(trifluoromethyl)benzo[*h*]-1,6-naphthyridine (18) was the less soluble product.

4-Chloro-2-(trifluoromethyl)azaphenanthrenes 24–28. These compounds were prepared by the procedure described for the preparation of 4-chloro-6-cyano-2-(trifluoromethyl)benzo[*h*]quinoline **(25)**. A mixture of 5.17 g (0.018 mol) of 6-cyano-2-(trifluoromethyl)benzo[*h*]quinolin-4-ol, 3.75 g (0.018 mol) of phosphorus pentachloride, and 8.3 g (0.054 mol) of phosphorus oxychloride was heated at 130° for 1 hr. The mixture was cooled and poured into 500 ml of ice–water. The resulting suspension was stirred overnight. The solid **(25)** was collected, washed with water, and dried.

Lithium Exchange Reactions. The 4-lithio derivatives synthesized in this investigation (Scheme I) were not isolated but were treated *in situ* with suitable reagents. These reactions were conducted in a flame-dried, wide-mouth, four-necked reaction flask equipped with a coil condenser and drying tube, a nitrogen inlet system, a rubber septum, and a glass stopper. Teflon sleeves were used instead of silicone grease. Liquid reagents were introduced with a syringe; solids were added *via* a powder funnel after removal of the glass stopper. Nitrogen was passed continuously through the system during the course of the reaction. All reaction mixtures were stirred magnetically.

2-(Trifluoromethyl)azaphenanthrenecarboxylic Acids 4, 29, and 30 (Scheme I). These compounds were synthesized by the procedure described for the preparation of 2-(trifluoromethyl)benzo[*h*]-quinoline-4-carboxylic acid **(3)**. To 0.04 mol of *n*-butyllithium in 25 ml of diethyl ether at −70° was added 6.0 g (0.018 mol) of 4-bromo-2-(trifluoromethyl)benzo[*h*]quinoline **(2)**. The reaction mixture was kept under nitrogen and stirred for 1 hr. An excess of powdered Dry Ice was then added to it with stirring. After 3 hr, the solvent was removed by evaporation under reduced pressure. The solid that formed was dissolved in a dilute aqueous sodium hydroxide solution. Insoluble impurities were removed by filtration. Acidification of the filtrate with glacial acetic acid precipitated the product **(3)** which was then collected, washed with water, and dried.

2-Pyridyl 2-(Trifluoromethyl)azaphenanthren-4-yl Ketones 4 and 31 (Scheme I). These compounds were synthesized by the following general procedure illustrated for the preparation of 2-pyridyl 6-chloro-2-(trifluoromethyl)benzo[*h*]quinolin-4-yl ketone **(31)**. To a stirred solution of 0.031 mol of *n*-butyllithium in 150 ml of anhydrous diethyl ether, under nitrogen at −70°, was added 4.74 g (0.03 mol) of 2-bromopyridine. After the solution was stirred for 1 hr, 3.26 g (0.01 mol) of 4-chloro-2-(trifluoromethyl)benzo[*h*]quinolin-4-carboxylic acid **(29)** was added to it. The mixture was stirred an additional 3 hr at −70° and then allowed to warm to 0–5°. Aqueous diethyl ether (~50%) was added to the reaction. The ether layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed by evaporation under reduced pressure to afford the product **(31)**.

α-(2-Pyridyl)-2-(trifluoromethyl)azaphenanthrene-4-methanols 7 and 32 (Scheme II). These compounds were synthesized by a procedure illustrated for the preparation of α-(2-pyridyl)-2-(trifluoromethyl)-1,7-phenanthrolin-4-methanol **(32)**. To a solution of 1.56 g (0.024 mol) of *n*-butyllithium in 75 ml of anhydrous diethyl ether, under nitrogen, at −70° was added 4.0 g (0.012 mol) of 4-bromo-2-(trifluoromethyl)-1,7-phenanthroline **(20)**. The dark reaction mixture was stirred for 1 hr. 2-Pyridinecarboxaldehyde (3.14 g, 0.029 mol) was then added to it. After the solution was stirred for 3 hr, its temperature was allowed to rise to 25°. The reaction was quenched with aqueous diethyl ether (~50%). The ether layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give a brown oil. After standing in 95% ethanol overnight, the oil solidified affording the yellow crystalline product **(32)**. In the case of 4-bromo-5-methoxy-2-(trifluoromethyl)-1,10-phenanthroline **(23)**, a black gum formed upon removing the solvent. This gum was washed with water and extracted with boiling hexane. The combined hexane extracts were concentrated under reduced pressure. The resulting oil was triturated with diethyl ether to yield the product, α-(2-pyridyl)-9-*n*-butyl-5-methoxy-2-(trifluoromethyl)-1,10-phenanthroline-4-methanol **(34)**.

α-(2-Piperidyl)-2-(trifluoromethyl)azaphenanthrene-4-methanols 5 and 8 (Schemes I and II). These compounds were prepared by the reduction of the corresponding ketones as illustrated in the preparation of α-(2-piperidyl)-2-(trifluoromethyl)benzo[*h*]quinoline-4-methanol **(5)** or by the reduction of the α-pyridylmethanol as illustrated in the preparation of α-(2-piperidyl)-6-chloro-2-(trifluoromethyl)benzo[*h*]quinoline-4-methanol **(8)**. To 2.0 g (5.67 mol) of 2-pyridyl 2-(trifluoromethyl)benzo[*h*]quinolin-4-yl ketone **(4)** and 0.2 g of platinum oxide was added 150 ml of absolute ethanol and 1 ml of concentrated hydrochloric acid. The mixture was shaken in a Parr hydrogenator (50 lb, room temperature) until the theoretical amount of hydrogen was consumed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. A saturated aqueous sodium bicarbonate solution was added to the residue and the resulting solution was extracted with diethyl ether. The ether layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was treated with 95% ethanol to precipitate the product **(5)**.

A mixture of 3.0 g (7.7 mol) of α-(2-pyridyl)-6-chloro-2-(trifluoromethyl)benzo[*h*]quinoline-4-methanol **(7)**, 0.25 g of platinum oxide, and 2 ml of concentrated hydrochloric acid was shaken in a Parr hydrogenator (50 lb, room temperature) until the theoretical amount of hydrogen was consumed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. A saturated aqueous sodium bicarbonate solution was added to the residue and the resulting solution was warmed on a steam bath. When the solution was cooled the desired product **(8)** crystallized.

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