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A convenient synthetic pathway to benzo[g]quinolines (1-azaanthracenes) has been developed. The nickel catalyzed coupling of methyl 2-chloronicotinate (**3a**) with benzylic organo zinc reagents **2a-e** led to the methyl 2-benzylic substituted nicotinates **4a-e**. Treatment of methyl 2-chloro-6-methylnicotinate (**3b**)with **2a** in a similar manner led to methyl 2-benzyl-6-methylnicotinate (**4f**). The coupling of 2-chloro-3-acetylpyridine (**5**) with benzyl zinc bromide (**2a**) led to 2-benzyl-3-acetylpyridine (**4g**). The coupling of the 2,5-dichlorobenzylic organic zinc reagent (**2f**) with methyl 2-choronicotinate (**3a**) was unselective but readily coupled with methyl 2-bromonicotinate (**6**) to yield methyl 2-(2,5-dichlorobenzyl)nicotinate (**4h**). The esters **4a-f,h** on reduction with lithium aluminum hydride led to the corresponding alcohols **7a-f,h** which were subsequently oxidized with manganese dioxide to the respective 2-benzylic substituted pyridine-3-carboxaldehydes **8a-f,h.** In one case the coupling of benzy] zinc bromide (**2a**) with 2-chloropyridine-3-carboxaldehyde (**9**) led directly to 2-benzylpyridine-3-carboxaldehyde (**8a**), but in poor yield. Cyclizations of the aldehydes **8a-d,f,h** or the ketone **4g** with polyphosphoric acid afforded the benzo[g]quinolines **10a-d,f-h** in high yields. Aldehyde **8e** was cyclized to **10e** using a solution of sulfuric acid in methanol. Several of the benzo[g]quinolines **10c,d** could be readily converted into the benzo[q]quinoline-5,10-diones **11c,d** on treatment with ammonium ceric nitrate.

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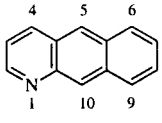
Introduction.

During the course of a program dealing with the synthesis of heterocyclic antitumor agents, we required benzo[g]-quinoline and several of its substituted analogues. An examination of the literature revealed no convenient synthetic pathway which would lead to multi-gram quantities of these substrates.



Benzo[g]quinoline
1-Azaanthracene

Benzo[f]quinoline
4-Azaphenanthrene

Many of the early reports on benzo[g]quinoline have dealt with spectroscopic studies [1-3] analytical techniques for detection in coal tars [4], crude oils [5] and tobacco smoke [6]. Polarographic [7] and thermodynamic data [8] along with some theoretical studies dealing with aromaticity [9,10] and energy transitions [11-12] have also been reported.

Few chemical investigations on benzo[g]quinoline have appeared in the literature. The photolysis to a dimer [13-15], cycloadditions with maleamide [14] and photooxidations [14] have been documented. Phenylations by Grignard reactions [16] and nucleophilic substitutions with the carbanion derived from dimethyl sulfoxide [17] (leading to mono or dimethylated substrates) have been reported. The preparation of the *N*-oxide [17], Reissert reactions [17] and the formation of *N*-alkylated products [18] have been studied. Substitutions dealing with free radical or electrophilic species have not been evaluated.

In general, most of the reported synthetic strategies which lead to the benzo[g]quinoline skeleton have been adapted from the venerable reactions which lead to quinolines (or modifications) as the Skraup, Doebner-Miller, Combes, Conrad-Limpach, Knorr or Pfitzinger methodologies [19-23].

The application of the Skraup reaction [24] to 2-aminonaphthalene led predominantly to the angular product benzo[f]quinoline. In 2-aminonaphthalenes, where the α-position is blocked by a bromo- or nitro group, angular products result with the loss of the substituent. The use of 1-methyl-2-aminonaphthalene led to 10-methylbenzo[g]-quinoline (25% yield). In the case of 1-chloro-2-aminonaphthalene, benzo[f]quinoline was formed from displacement of chloride, although the linear 10-chlorobenzo[g]quinoline was also formed in an equal amount [25-27]. The conversion of this chloro derivative to benzo[g]quinoline (50% yields) has been reported by passage through a long tube at 350-370° containing zinc granules and dust [14].

The oxidation of the 10-chloro analogue to the corresponding benzo[g]quinoline-5,10-dione followed by reduction of the quinone with zinc, zinc chloride and sodium chloride at 200-330° led to benzo[g]quinoline (53%) [14]. Although this reduction strategy might be applicable for the synthesis of substituted benzo[g]quinolines, the synthesis of the diones are, in general, quite difficult. In addition the reduction conditions will not tolerate certain substituents such as halides. The preparation of benzo[g]quinoline-5,10-dione *via* cyclization of 3-benzoylpicolinic acid led to low yields (6%) [28]. While cycloadditon pathways of dienes with quinoline-5,8-diones have led to substituted benzo[g]quinoline-5,10-diones, the cycloadditions lack regiochemical control and product separation occasionally requires tedious separations [29-32]. The reactions of azadienes with naphthoquinones

also lead to benzo[*g*]quinolines-5,10-diones [33-34]. For example, the cycloaddition reactions involving 1-dimethylamino-3-alkyl-1-aza-1,3-butadienes led to 3-alkylbenzo[*g*]quinoline-5,10-diones.

Both angular and linear products can be formed in the Combes reaction and the reactions conditions can be varied in some cases to favor either product. Treatment of 2-aminonaphthalene with malondialdehyde followed by cyclization of the intermediate β-(2-naphthylamino)acrolein with polyphosphoric acid afforded benzo[*g*]quinoline (23%) along with benzo[*f*]quinoline (56%). The former compound was isolated *via* a tedious chromatographic separation over silica gel [17]. On the other hand, the reactions of 2-aminonaphthalene with 3-oxobutanal, 2-methyl-3-oxobutanal, and 2,4-pentanedione followed by cyclization of the resultant Schiff bases with hydrogen fluoride led to 4-methyl-, 3,4-dimethyl- and 2,4-dimethylbenzo[*g*]quinoline, respectively [35]. Cyclization of these Schiff bases with zinc chloride led to the angular products. The mechanisms of these divergent results have been discussed [36,37].

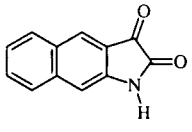
The oxidation of 2,4-dimethylbenzo[*g*]quinoline to the corresponding diacid followed by thermal decarboxylation yielded benzo[*g*]quinoline [38].

The Doebner-Miller and Conrad-Limpach procedures when applied to 2-aminonaphthalene lead predorninantly to angular cyclization products although benzo[*g*]quinolines can be obtained if the 1-position is blocked by groups such as chloro, bromo or methyl [22].

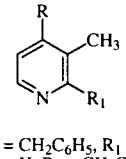
The Pfitzinger reaction applied to 5,6-benzisatin with acetone or pyruvic acids yields 2-methyl- 4-carboxy- or 2,4-dicarboxybenzo[*g*]quinoline which on thermolysis undergo decarboxylation in the presence of copper chromite at 240-280° to yield 2-methyl- and benzo[*g*]quinoline (50% yields) respectively [39].

Dehydrocyclizations of methyl-substituted 2- or 4-benzylpyridines (obtained as mixtures from the Ladenberg reaction) at temperatures of 560° over catalyst led to mixtures of benz[*g*]isoquinolines and benzo[*g*]quinolines which apparently could be separated in some cases [40].

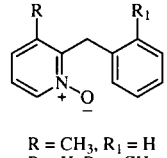
Flash vacuum pyrolysis (800°) of the 2-methylbenzylpyridine-1-oxide or 2-benzyl-3-methylpyridine 1-oxide led to benzo[*g*]quinoline in 35 and 53% yields, respectively, along with several additional products [41].



5,6-benzisatin



R = $CH_2C_6H_5$, R_1 = H
R = H, R_1 = $CH_2C_6H_5$

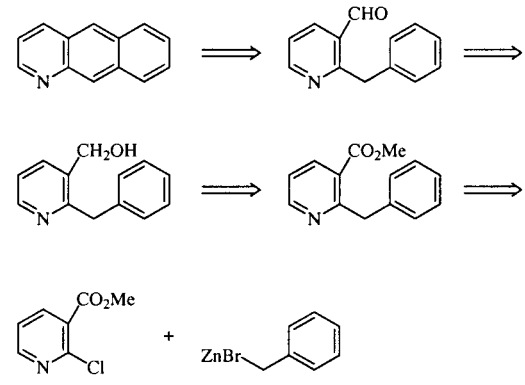


R = CH_3, R_1 = H
R = H, R_1 = CH_3

Results and Discussion.

We wish to report a convenient synthetic pathway which not only leads to benzo[*g*]quinoline but is quite adaptable to the synthesis of analogues with a variety of substituents. The retro-synthetic pathway leading to benzo[*g*]quinoline is outlined in Scheme 1.

Scheme 1



Benzo[*g*]quinoline was prepared by cyclization and subsequent aromatization of the aldehyde on treatment with polyphosphoric acid. The aldehyde was acquired from reduction of methyl 2-benzylnicotinate to the corresponding alcohol followed by oxidation. The methyl 2-benzylnicotinate was prepared by regiospecific C-C bond formation [42-44] between methyl 2-chloronicotinate and benzyl zinc bromide catalyzed by bis(triphenylphosphine)-nickel(II) chloride (Scheme 1).

The preparations of the methyl 2-benzylic substituted nicotinates are shown in Scheme 2.

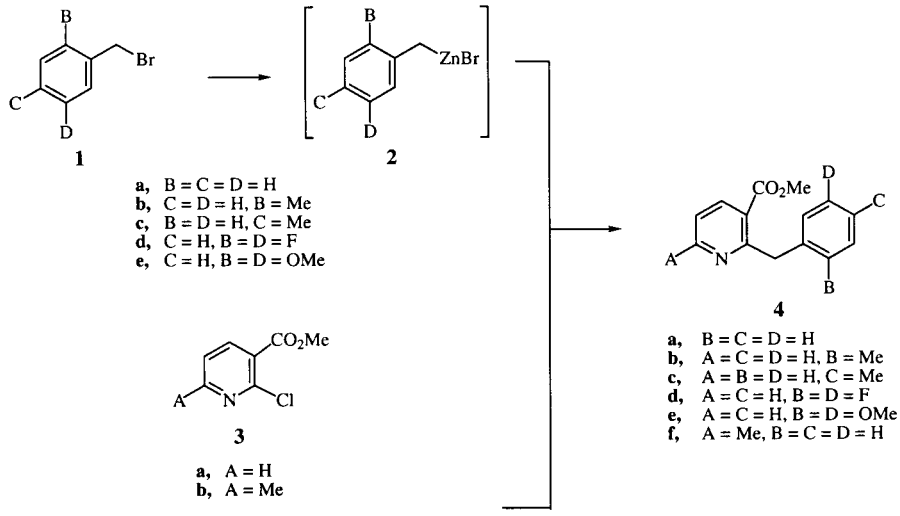
Treatment of the benzylic bromides **1a-e** with zinc dust in tetrahydrofuran at room temperature led to the corresponding benzylic zinc bromides **2a-e**. The addition of solutions of the benzylic zinc bromides **2a-e** in tetrahydrofuran (some unreacted zinc usually remained) *via* carmulation to methyl 2-chloronicotinate (**3a**) in tetrahydrofuran containing a catalytic amount of bis(triphenylphosphine)-nickel(II) chloride led to the corresponding coupled products **4a-e**. Since a two fold-molar excess of the benzyl bromides were used, some 1,2-diphenylethane (δ 2.92, methylene protons) was formed as a by-product which could readily removed on chromatography. Small amounts of triphenylphosphine were formed from decomposition of the nickel catalyst and could also be readily removed.

Compound **4f** was synthesized by the addition of **2a** to methyl-2-chloro-6-methylnicotinate (**3b**) in the presence of the nickel catalyst.

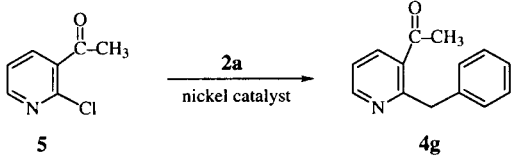
This methodology was also utilized for the coupling of 2-chloro-3- acetylpyridine (**5**) with benzylic zinc bromide (**2a**). (Scheme 3).

The nickel coupling of 2,5-dichlorobenzyl zinc bromide (**2f**) with methyl 2-chloronicotinate (**3a**) led to impure **4h** in a poor yield (20%). A multitude of coupling products were formed, probably arising from competitive interaction of the nickel catalyst with the chloride on the benzyl

Scheme 2



Scheme 3



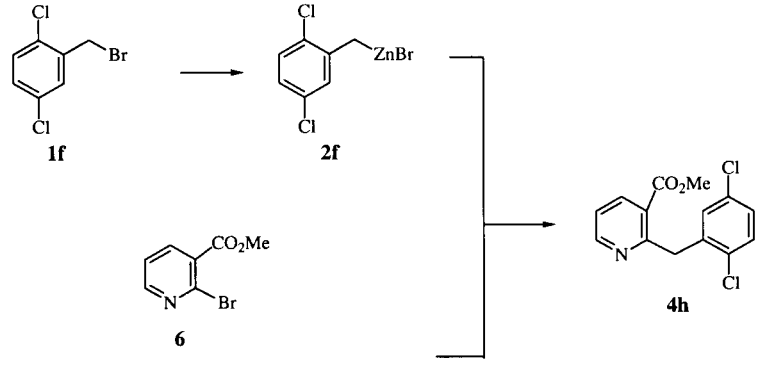
or pyridine moieties which led to a non-selective product distribution. However, catalytic nickel coupling of 2,5-dichlorobenzyl zinc bromide (**2f**) (prepared from **1f**) with methyl 2-bromonicotinate (**6**) led to **4h** (28%) in modest yield (Scheme 4).

using excess manganese dioxide in dichloromethane at room temperature led to the corresponding aldehydes **8a-f,h** (Scheme 5).

The aldehyde **8a** could be prepared in a one-step process by coupling benzyl zinc bromide (**2a**) with 2-chloropyridine-3-carboxaldehyde (**9**) effected by bis(triphenylphosphine)nickel(II) chloride (Scheme 6). However, the low yield of **8a** (25%) made the use of the esters as the more practical route to the aldehydes

The conversions of the aldehydes **8a-d,f,h** and the acetylpyridine **4g** to the corresponding benzo[*g*]quinolines **10a-d,f-h** in excellent yield (84-95%) were accomplished by heating in polyphosphoric acid for 1.5 hours at 140° (Scheme 7) [45]. However, under simlar conditions aldehyde

Scheme 4



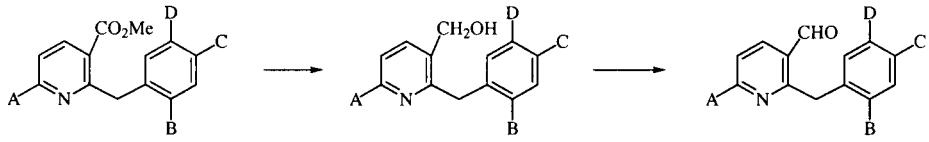
The esters **4a-f,h** were then converted *via* a two-step process into the corresponding aldehydes (Scheme 5).

Treatment of **4a-f,h** with lithium aluminum hydride in diethyl ether yielded the corresponding primary alcohols **7a-f,h** (58-95%). Oxidation of the primary alcohols **7a-f,h**

8e led to poor yields of **10e**. Aldehyde **8e** was readily cyclized into **10e** using a methanol solution of sulfuric acid.

The benzo[*g*]quinolines **10c,d** were converted into the corresponding benzo[*g*]quinoline-5,10-diones **11c,d** by oxidation with ammonium cerium(IV) nitrate (Scheme 8).

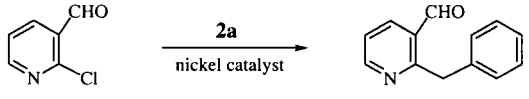
Scheme 5



4 **7** **8**

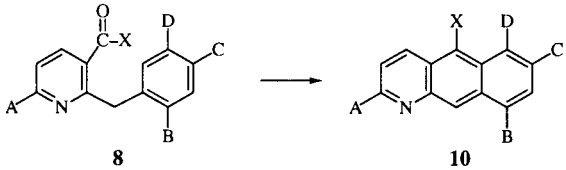
a, A = B = C = D = H
b, A = C = D = H, B = CH_3
c, A = B = D = H, C = CH_3
d, A = C = H, B = D = F
e, A = C = H, B = D = OMe
f, B = C = D = H, A = CH_3
h, A = C = H, B = D = Cl

Scheme 6



9 **8a**

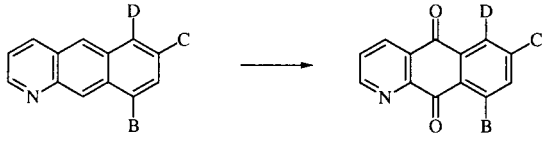
Scheme 7



8 **10**

a, X = A = B = C = D = H
b, X = A = C = D = H, B = CH_3
c, X = A = B = D = H, C = CH_3
d, X = A = C = H, B = D = F
e, X = A = C = H, B = D = OMe
f, X = B = C = D = H, A = CH_3
4g, A = B = C = D = H, X = CH_3
h, X = A = C = H, B = D = Cl

Scheme 8



10 **11**

c, B = C = H, C = CH_3
d, B = D = F, C = H

Conclusions.

The methodology should be quite adaptable for the synthesis of analogues with substituents at position 2,3 or 4 on the pyridine ring and might be limited to those moieties where in the cyclodehydration stage two unsubstituted positions are present in the 2-benzylic moiety of the substituted nicotinates. This could lead to regioisomeric mixtures. In additon, the facile oxidations of the benzo[*g*]-quinolines afford a synthetic pathway to the benzo[*g*]-quinoline-5,10-diones.

EXPERIMENTAL

The benzylic bromides **1a-d** were purchased from Aldrich and **1e** was prepared by a known route [46]. Zinc dust (Aldrich, 32,493-0, 99.998% purity) was used as received. The catalyst bis(triphenylphosphine)nickel(II) chloride was purchased from Lancaster and used as received. Esters **3a** and and **3b** were prepared from the commercially available acids on treatment with ethereal diazomethane. Compound **5** was prepared following a modified literature procedure for the conversion of esters to methyl ketones [47]. Ester **6** was prepared following a literature procedure [48]. Tetrahydrofuran was freshly distilled from potassium metal. All reactions were performed under a nitrogen atmosphere using standard septa techniques. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Proton, carbon-13 and fluorine-19 nmr were recorded on a Bruker WM-250 or ARX-500 pulsed spectrometer. Microanalyses were performed by Robertson Microlit Laboratories, Inc., Madison, N.

2,5-Dichlorobenzyl Bromide (**1f**).

To a solution of 2,5-dichlorobenzyl alcohol (501 mg, 2.83 mmoles) and *N*-bromosuccimide (824 mg, 4.63 mmoles) in dichloromethane (20 ml) was added triphenylphosphine (904 mg, 3.45 mmoles) at 0°. The resultant yellow solution was warmed to room temperature and allowed to stir for 2 hours. The solvent was removed under reduced pressure to yield a dark yellow oil. Purification by flash chromaotgraphy (silica gel) eluting with hexane: dichloromethane (3:1) yielded **1f** as a clear oil (574 mg, 85%); ^{1}H nmr (deuteriochloroform): δ 7.43 (d, 1H, J = 2.49 Hz), 7.31 (d, 1H, J = 8.55 Hz), 7.22 (dd, 1H, J = 8.54 Hz, J = 2.49 Hz), 4.52 (s, 2H) [49].

2-Chloro-3-acetylpyridine (**5**).

A solution of **3a** (305 mg, 1.78 mmoles) in anhydrous toluene (25 ml) was treated with anhydrous triethylamine (2.9 ml, 20.8 mmoles) and methyl magnesium bromide (1.3 ml, 10*M* in diethyl ether, 3.9 mmole) at -10° for 6 hours under a nitrogen atmosphere. The reaction mixture was quenched into saturated ammonium chloride (5 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic layers were dried over magnesium sulfate. Removal of the solvent under reduced pressure yielded a yellow oil which on purification by chromatography (silica gel) eluting with dichloromethane:ethyl acetate (8:2) yielded **5** (183 mg, 66%) as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 8.48 (m, 1H), 7.93 (m, 1H), 7.37 (m, 1H), 2.70 (d, 3H, J = 1.01 Hz); lit nmr [50].

Table 1

Properties, Yields and ^{1}H NMR Data for Analogues **4**

4	mp, °C	% yield	^{1}H NMR δ, deuteriochloroform (tetramethylsilane)
a	oil	88	8.68 (dd, 1 H, J = 4.79,1.81 Hz), 8.15 (dd, 1H, J = 7.88, 1.82 Hz), 7.23 (m, 5H), 7.14 (m, 1H), 4.58 (s, 2H), 3.85 (s, 3H)
b	oil	93	8.67 (dd, 1 H, J = 4.78, 1.70 Hz), 8.18 (dd, 1H, J = 7.87, 1.78 Hz), 7.23 (m, 1H), 7.15 (d, 1H, J = 7.35 Hz), 7.09 (m, 2H), 6.81 (d, 1H, J = 7.45 Hz), 4.56 (s, 2H), 3.81 (s, 3H), 2.30 (s, 3H)
c	oil	83	8.68 (dd, 1 H, J = 4.79, 1.82 Hz), 8.15 (dd, 1 H, J = 7.86, 1.83 Hz), 7.21 (dd, 1H, J = 7.86, 4.80 Hz), 7.14 (d, 2H, J = 8.02 Hz), 7.05 (d, 2H, J = 7.92 Hz), 4.53 (s, 2H), 3.86 (s, 3H), 2.28 (s, 3H)
d	oil	94	8.65 (dd, 1 H, J = 4.79, 1.82 Hz), 8.20 (dd, 1 H, J = 7.90, 1.83 Hz), 7.23 (dd, 1 H, J = 7.90, 4.79 Hz), 6.96 (m, 1H), 6.82 (m, 1H), 6.75 (m, 1H), 4.58 (s, 2H), 3.86 (s, 3H)
e	oil	46	8.64 (dd, 1H, J = 4.79, 1.84), 8.12 (dd, 1H, J = 7.86, 1.84), 7.19 (dd, 1H, J = 7.86, 4.80), 6.75(d, 1H, J = 8.83), 6.68 (dd, 1H, J = 8.82, 3.06), 6.54 (d, 1H, J = 3.04), 4.51 (s, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H)
f	oil	93	8.06 (d, 1H, J = 8.02), 7.23 (m, 4H), 7.14 (m, 1H), 7.07 (d, 1H, J = 8.02 Hz), 4.55 (s, 2H), 3.81 (s, 3H), 2.59 (s, 3H)
g	oil	71	8.60 (dd, 1H, J = 4.84, 1.74 Hz), 7.82 (dd, 1H, J = 7.81, 1.75 Hz), 7.21 (d, 4H, J = 4.49 Hz), 7.18 (m, 1H), 4.43 (s, 2H), 2.37 (s, 3H)
h	79-80	20 [i] 28 [j]	8.68 (dd, 1H, J = 4.78,1.78), 8.25 (dd, 1H, J = 7.91, 1.79), 7.28 (m, 2H), 7.12 (dd, 1H, J = 8.51, 2.48), 6.92 (d, 1H, J = 2.43), 4.64 (s, 2H), 3.88 (s, 3H)

[i] Yield from **3a** coupled with **2f** (impure product). [j] Yield from **6** coupled with **2f**.

Table 2

Properties, Yields and ^{1}H NMR Data for Analogues **7**

7	mp, C°	% yield	^{1}H NMR δ, deuteriochloroform (tetramethylsilane)
a	88-89	80	8.39 (d, 1H, J = 4.03 Hz), 7.74 (d, 1H J = 7.32 Hz), 7.15 (m, 6H), 4.60 (s, 2H), 4.16 (s, 2H), 3.04 (s, 1H)
b	82-83	93	8.44 (dd, 1H, J = 4.84, 1.59 Hz), 7.75 (m, 1H), 7.19 (dd, 1H, J = 7.64, 4.89 Hz), 7.15 (d, 1H, J = 7.24 Hz), 7.09 (t, 1H, J = 7.41 Hz), 7.02 (t, 1H, J = 7.44 Hz), 6.71 (d, 1H, J = 7.57 Hz), 4.56 (s, 2H), 4.14 (s, 2H), 2.51(brs, 1H), 2.29 (s, 3H)
c [l]	oil	79	8.44 (dd, 1H, J = 4.80, 1.39 Hz), 7.73 (d, 1H, J = 7.65 Hz), 7.15 (dd, 1H, J = 7.67, 4.89 Hz), 7.04 (s, 4H), 4.62 (s, 2H), 4.15 (s, 2H), 2.47 (br s, 1H), 2.27 (s, 3H)
d	83-84	95	8.46 (dd, 1H, J = 4.84, 1.61 Hz), 7.78 (dd, 1H, J = 6.96, 0.90 Hz), 7.20 (dd, 1H, J = 7.69, 4.86 Hz), 6.97 (m, 1H), 6.83 (m, 1H), 6.76 (m, 1H), 4.70 (d, 2H, J = 4.80 Hz), 4.18 (s, 2H), 2.35 (t, 1H, J = 5.28 Hz)
e [m]	118-119	58	8.50 (dd, 1H, J = 4.81, 1.68 Hz), 7.71 (dd, 1H, J = 7.67,1.62 Hz), 7.16 (dd, 1H, J = 7.64, 4.85 Hz), 6.79 (d, 1H, J = 8.83 Hz), 6.70 (dd, 1H, J = 8.81, 3.08 Hz), 6.66 (d, 1H, J = 3.04 Hz), 4.68 (d, 2H, J = 5.61 Hz), 4.18 (s, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 2.18 (t, 1H, J = 5.86 Hz), 7.59 (d,
f	71-72	94	1H, J = 7.78 Hz), 7.23 (m, 2H), 7.14 (m, 3H), 7.02 (d, 1H, J = 7.77 Hz), 4.55 (s, 2H), 4.17 (s, 2H), 2.53 (s, 3H)
h [n]	110-111	75	8.47 (dd, 1H, J = 4.84, 1.65 Hz), 7.78 (dd, 1H, J = 7.67,1.01 Hz), 7.29 (d, 1H, J = 8.52 Hz), J = 7.22 (dd, 1H, J = 7.71, 4.86 Hz), 7.12 (dd, 1H, J = 8.52, 1.01 Hz), 6.94 (d, 1H, J = 2.49 Hz), 4.67 (s, 2H), 4.25 (s, 2H) 2.32 (s, 1H)

[l] Purification using flash chromatography eluting with dichloromethane:ethyl acetate (8:2). [m] Purification using flash chromatography eluting with hexane:ethyl acetate (3:1). [n] Purification using flash chromatography eluting with dichloromethane:ethyl acetate (8:2).

Typical Coupling Preparative Procedure.

Methyl 2-(2-Methylbenzyl)nicotinate (**4b**).

To a suspension of zinc dust (222 mg, 3.41 mmoles) and freshly distilled tetrahydrofuran (3 ml) was added a solution of **2b** (428 mg, 2.31 mmoles) in tetrahydrofuran (2 ml), dropwise at 0° over 5 minutes. The reaction mixture was allowed to stir for 3 hours at 0° at which time the stirring was stopped to allow for excess zinc to settle. A solution of **3a** (254 mg, 2.31 mmoles) in tetrahydrofuran (8 ml) was added *via* cannulation to a solution of bis(triphenylphosphine)nickel(II) chloride (254 mg, 0.387 mmole) in tetrahydrofuran (12 ml). This mixture was allowed to stir at room temperature for 5 minutes, at which time the benzylic zinc bromide solution was added *via* cannulation over 5 minutes.

Table 3

Properties, Yields and ^{1}H NMR Data for Analogues **8**

8	mp °C	% yield	^{1}H NMR δ, deuteriochloroform (tetramethylsilane)
a	oil	93	10.3 (s, 1H), 8.75 (dd, 1H, J = 4.81, J = 1.80 Hz), 8.12 (dd, 1H, J = 7.77, 1.82 Hz), 7.34 (dd, 1H, J = 7.76, 4.82 Hz), 7.25 (m, 4H), 7.19, (m, 1H), 4.59, (s, 2H)
b [p]	oil	94	10.3 (s, 1H), 8.75 (dd, 1H, J = 4.81, 1.87 Hz), 8.17 (dd, 1H, J = 7.78, 1.87 Hz), 7.37 (dd, 1H, J = 7.76, 4.81 Hz), 7.18 (d, 1H, J =7.47 Hz), 7.12 (m, 1H), 7.06 (m, 1H), 6.78 (d, 1H, J = 7.53 Hz), 4.57 (s, 2H), 2.35 (s,3H)
c	oil	88	10. 3 (s, 1H), 8.72 (dd, 1H, J = 4.80, 1.79 Hz), 8.08 (dd, 1H, J = 7.77,1.83 Hz), 7.30 (dd, 1H, J = 7.76, 4.82 Hz), 7.11 (d, 2H, J = 8.01 Hz), 7.05 (d, 2H, J = 8.10 Hz), 4.53 (s,2H), 2.26 (s, 3H).
d	oil	88	10.3 (s, 1H), 8.73 (dd, 1H, J = 4.61, 1.65 Hz), 8.14 (dd, 1H, J = 7.70, 1.65 Hz), 7.38 (dd, 1H, J = 7.68, 4.80 Hz), 7.00 (m, 1H), 6.85 (m, 2H), 4.58 (s, 2H)
e	84-85	84	10.5 (s, 1H), 8.70 (dd, 1H, J = 4.77,1.89 Hz), 8.12 (dd, 1H, J = 7.81, 1.90 Hz), 7.27 (dd, 1H, J = 7.41, 4.80 Hz), 6.71 (m, 3H), 4.49 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H)
f	oil	94	10. 3 (s, 1H), 8. 01 (d, 1H, J = 7.92 Hz), 7.21 (m, 6H), 4.55 (s, 2H), 2.63 (s, 3H).
h	oil	95	10.3 (s, 1H), 8.73 (dd, 1H, J = 4.81, 1.86 Hz), 8.17 (dd, 1H, J = 7.78, 1.88 Hz), 7.40 (dd, 1H, J = 7.76, 4.82 Hz), 7.30 (d, 1H, J = 4.82 Hz), 7.15 (dd, 1H, J = 8.52, 2.54 Hz), 7.02 (d, 1H, J = 2.54 Hz), 4.66 (s, 2H)

[p] The reaction mixture was allowed to stir for 2 hours.

The color of the reaction mixture changed from green to purple over the course of the addition. The reaction mixture was allowed to stir at room temperature for 48 hours. The mixture was poured into aqueous ammonium chloride (10%, 25 ml) and allowed to stir for 30 minutes. The product was extracted with ethyl acetate (25 ml) and the extract washed with brine (3 x 25 ml). The extract was dried over magnesium sulfate and removal of the solvent left an oil which on purification by flash chromatography (silica gel) by elution with hexane:ethyl acetate 3:1 yielded **4b** (332 mg, 93%) as a clear oil.

Analogues **4a,c-h** were prepared from the appropriate reactants in a similar manner. The properties, yields and ^{1}H nmr data for **4a-h** are tabulated in Table 1.

Typical Reduction Procedure.

2-(2-Methylbenzyl)-3-(hydroxymethyl)pyridine (**7b**).

A solution of **4b** (250 mg, 1.04 mmoles) in diethyl ether (10 ml) was added dropwise to a suspension of lithium aluminum hydride (97 mg, 2.55 mmoles) in diethyl ether (10 ml) at -78° over a period of 5 minutes under a nitrogen atmosphere. The reaction mixture was allowed to stir at -78° for 60 minutes. Ethyl acetate (2 ml) was added and the temperature was warmed to 0° over 30 minutes. Water (2 ml) was added upon which a white solid formed. The mixture was filtered, the ether layer was separated and dried over magnesium sulfate. Removal of the solvent yielded **7b** (204 mg, 93%) as a white solid.

Table 4

Properties, Yields and ^{1}H NMR Data for Analogues **10**

10	Mp °C	yield %	1H NMR δ, deuteriochloroform (tetramethylsilane)
a	108-109	96	8.99 (dd, 1H, J = 3.80), 8.70 (s, 1H), 8.38 (s, 1H), 8.31 (d, 1H, J = 8.51 Hz), 8.09 (m, 1H), 8.02 (m, 1H), 7.51 (m, 2H), 7.36 (dd, 1H, J = 8.54 Hz)
b	53-54	82	8.90 (dd, 1H, J = 3.70, 1.33 Hz), 8.78 (s, 1H), 8.23 (s, 1H), 8.16 (d, 1H, J = 8.40 Hz), 7.78 (d, 1H, J = 8.43 Hz), 7.36-7.25 (m, 3H), 2.77 (s, 3H)
c [q]	140-141	78	8.90 (dd, 1H, J = 3.87, 1.65 Hz), 8.61 (s, 1H), 8.15 (d, 1H, J = 8.52 Hz), 8.13 (s, 1H), 7.93 (d, 1H, J = 8.66 Hz), 7.66 (s, 1H), 7.30 (dd, 1H, J = 8.66, 1.41 Hz), 7.24 (dd, 1H, J = 8.52, 3.91 Hz), 2.49 (s, 3H)
d	142-143	83	9.01 (dd, 1H, J = 3.88, 1.69 Hz), 8.84 (s, 1H), 8.51 (s, 1H), 8.26 (d, 1H, J = 8.54 Hz), 7.39 (dd, 1H, J = 8.55, 3.92 Hz), 7.02 (m, 2H)
e [r]	118-119	49	9.04 (s, 1H), 8.89 (dd, 1H, J = 3.90, J = 1.69 Hz), 8.72 (s, 1H), 8.31 (d, 1H, J = 8.45 Hz), 7.35 (dd, 1H, J = 8.49, 3.94 Hz), 6.64 (m, 2H), 4.02 (s, 3H), 4.01 (s, 3H)
f [s]	129-130	85	8.55 (s, 1H), 8.16 (s, 1H), 8.00 (m, 2H), 7.89 (d, 1H, J = 8.10 Hz), 7.41 (m, 2H), 7.09 (d, 1H, J = 8.64 Hz), 2.71 (s, 3H)
g	92-93	715	8.98 (dd, 1H, J = 3.74, 1.37 Hz), 8.61 (m, 2H), 8.27 (dd, 1H, J = 8.42, 0.85 Hz), 8.08 (m, 1H), 7.53 (m, 2H), 7.37 (dd, 1H, J = 9.01, 3.83 Hz), 3.07 (s, 3H)
h	169-170	73	9.08 (s, 1H), 8.73 (s, 1H), 8.33 (d, 1H, J = 8.43 Hz), 7.50-7.42 (m, 3H)

[q] Previously reported in reference 40. [r] Cyclization and aromatization procedure was done with methanol, 10% sulfuric acid (see experimental section). [s] Purification using flash chromatography eluting with dichloromethane:ethyl acetate (8:2).

Table 5

^{13}C NMR Data for Analogues **10a-c,e-h** and ^{19}F Data for **10d**

10	δ, deuteriochloroform (tetramethylsilane)
a	151.5, 144.7, 136.3, 133.8, 131.7, 128.5, 128.0, 127.4, 126.6, 126.5, 126.2, 126.0, 120.4
b	151.2, 144.4, 135.9, 134.6, 133.4, 131.8, 126.9, 126.3, 126.2, 125.9, 125.7, 123.9, 120.3, 19.6
c	150.9, 144.3, 136.0 135.6, 132.4, 131.9, 129.0, 128.1, 127.0, 126.5, 126.1, 125.4, 120.2, 21.8
d	F19; -80.78 (d, 1F, J = 22.7 Hz), -79.93 (d, 1F, J = 22.5 Hz)
e	151.5, 149.6, 149.3, 144.9, 136.7, 128.0, 126.3, 125.7, 122.2, 121.4, 120.6, 102.1, 101.7, 55.8, 55.6
f	159.7, 144.2, 136.1, 133.7, 131.1, 128.2, 127.9, 126.2, 126.1, 125.9, 125.4, 124.9, 121.6, 25.6
g	150.7, 144.3, 133.4, 132.7, 130.9, 129.9, 129.1, 126.0, 125.6, 125.6, 124.8, 124.4, 119.7, 13.2
h	152.8, 145.2, 136.5, 131.6, 131.3, 130.8, 129.4, 127.2, 125.8, 125.7, 125.3, 125.1, 121.7

Alcohols **7a,c-f,h** were prepared from the appropriate esters following the typical procedure. The properties, yields, modifications of the typical procedure and ^{1}H nmr data for **7a-f,h** are recorded in Table 2.

Table 6

Microanalytical Data

	Molecular Formula	Calcd. %C	%H	%N	Found %C	%H	%N
7a	$C_{13}H_{13}NO$	78.36	6.58	7.03	78.15	6.57	6.91
7b	$C_{14}H_{15}NO$	78.84	7.09	6.57	78.65	6.99	6.46
7d	$C_{13}H_{11}NOF_2$	66.38	4.71	5.95	66.37	4.94	5.73
7e	$C_{15}H_{17}NO_3$	69.48	6.61	5.40	69.30	6.60	5.23
7f	$C_{14}H_{15}NO$	78.84	7.09	6.57	78.80	7.14	6.52
7h	$C_{13}H_{11}NOCl_2$	58.23	4.13	5.22	57.98	4.36	4.99
10b	$C_{14}H_{11}N$	87.01	5.74	7.25	86.66	5.49	7.06
10c	$C_{14}H_{11}N$	87.01	5.74	7.25	86.91	5.78	7.21
10d	$C_{13}H_7NF_2$	72.56	3.28	6.51	72.28	3.46	6.28
10e	$C_{15}H_{13}NO_2$	75.30	5.48	5.85	74.76	5.76	5.49
10f	$C_{14}H_{11}N$	87.01	5.74	7.25	87.02	5.75	7.30
10g	$C_{14}H_{11}N$	87.01	5.74	7.25	86.99	6.01	7.12
10h	$C_{13}H_7NCl_2$	62.93	2.84	5.65	62.57	2.94	5.45

Typical Oxidation Procedure

2-(2-Methylbenzyl)pyridine-3-carboxaldehyde (**8c**).

A mixture of **7c** (170 mg, 0.80 mmole) and manganese dioxide (1230 mg, 12.1 mmoles) in dichloromethane (28 ml) was stirred at room temperature for 1 hour under a nitrogen atmosphere. The reaction mixture was filtered through a celite bed and the celite washed repeatedly with dichloromethane. Removal of the solvent under reduced pressure yielded **8c** (148 mg, 88%) as a clear oil.

The aldehydes **8a,b,d-f,h** were prepared in a simliar fashion from the respective alcohols. The properties, yields, any modifications of this procedure and ^{1}H nmr data are tabulated in Table 3.

Typical Procedure for the Synthesis of Benzo[g]quinolines

9-Methylbenzo[g]quinoline (**10b**).

A mixture of **8b** (151 mg, 0.715 mmole) and polyphosphoric acid (4.8 g) was heated at 140° for 1.5 hours. Water (10 ml) was added to the cooled reaction mixture and it was neutralized with sodium hydroxide (5*M*). The aqueous mixture was extracted with dichloromethane (3 x 20 ml) and the organic layers were combined and dried over magnesium sulfate. Removal of the solvent under reduced pressure yielded **10b** (113 mg, 82%) as a dark yellow solid. Addition purification can be performed by sublimation; however, the product darkens over a few days on standing at room temperature in the ambient atmosphere. All the benzo[g]-quinolines **10a-h** exhibited an intense bluish fluorescence when observed under long uv light.

Modified Procedure for the Synthesis of 6,9-Dimethoxybenzo[g]-quinoline (**10e**).

A mixture of 2-(2,5-dimethoxybenzyl)pyridine-3-carboxaldehyde (**8e**, 55 mg, 0.215 mmole), methanol (2.5 ml) and sulfuric acid (10%, 4 ml) was heated at 100° for 12 hours. The reaction mixture was cooled and the methanol removed under reduced pressure. The aqueous portion was basified using sodium hydroxide (5*M*) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulfate. Removal of the solvent yielded a green solid. Purification by flash chromatography (silica gel) eluting with dichloromethane: ethyl acetate yielded **10e** as a yellow solid (25 mg, 49%).

The benzo[g]quinolines **10a,c-d,f,h** were prepared in a similar cyclization procedure from the respective aldehydes. The cyclization of ketone **4g** was similarly accomplished. The properties, yields and ^{1}H nmr data for these substrates are tabulated in Table 4. The ^{13}C (**10a-c,e-h**) and ^{19}F (**10d**) data are tabulated in Table 5.

7-Methylbenzo[g]quinoline-5,10-dione(**11c**).

A mixture of **10c** (20 mg, 0.104 mmole) and ammonium cerium(IV) nitrate (570 mg, 1.04 mmoles) in a tetrahydrofuran: water (75:25, 4 in]) was stirred at room temperature for 1.5 hours. The reaction mixture was poured into water (5 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic layers were dried over magnesium sulfate and removal of the solvent under reduced pressure afforded an orange solid. Purification by flash chromatography (silica gel), eluting with dichloromethane: methanol (95:5) yielded **11c** (19.7 mg, 85%), mp 215-216°; lit mp 201-204° [29]; ^{1}H nmr (deuteriochloroform): δ 9.11 (dd, 1H, J_{HH} = 4.57 Hz, J_{HH} = 1.74 Hz), 8.63 (dd, 1H, J_{HH} = 7.91 Hz, J_{HH} = 1.74 Hz), 8.33 (d, 1H, J_{HH} = 7.92 Hz), 8.12 (s, 1H), 7.72 (dd, 1H, J_{HH} = 7.92 Hz, J_{HH} = 4.59 Hz), 7.66 (d, 1H, J_{HH} = 7.92 Hz), 2.56 (s, 3H).

6,9-Difluorobenzo[g]quinoline-5,10-dione (**11d**).

A mixture of **10d** (27 mg, 0. 123 mmole) and ammonium cerium(IV)nitrate (679 mg, 1.24 mmoles) in a tetrahydrofuran: water (75:25, 5H) was stirred at room temperature for 1.5 hours. The reaction mixture was poured into water (5 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic layers were dried over magnesium sulfate and removal of the solvent under reduced pressure afforded a pale yellow solid. Purification by flash chromatography (silica gel), eluting with dichloromethane:methanol (90:10) yielded **11d** (26 mg, 85%), mp 248-249°, lit mp 250-251° and ^{1}H nmr [44].

Microanalytical Data.

The elemental analysis for most intermediates and all final benzo[g]isoquinolines are tabulated in Table 6.

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