A. Paul Krapcho* and Timothy P. Gilmor

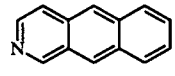
Department of Chemistry, University of Vermont, Burlington, VT 05405
Received January 17, 1998

Benzylic zinc reagents add with high regioselectivity to 1-(phenoxycarbonyl) salts derived from pyridine-3-carboxaldehyde (**1a**) or 3-acetylpyridine (**1b**) to yield 1-(phenoxylcarbonyl)-4-benzyl-1,4-dihydropyridine-3-carboxaldehydes **5a**, **5c** or ketones **5b**, **5d**. Aromatizations of these dihydro analogues with sulfur led to the corresponding aldehydes **6a**, **6c** or ketones **6b**, **6d**. An alternate synthesis to the aldehydic precursors involved additions of benzylic zinc reagents to 1-(phenoxycarbonyl) salts formed from methyl nicotinates which led to the corresponding methyl 1-(phenoxycarbonyl)-4-benzyl-1,4-dihydronicotinates **7a**, **7b**. Aromatizations of **7a**, **7b** led to the corresponding pyridine esters **8a**, **8b** which on reduction with lithium aluminum hydride yielded the corresponding carbinols **9a**, **9b**. Oxidation of **9a**, **9b** by manganese dioxide afforded aldehydes **6e**, **6f**. Aldehydes **6a-f** were readily converted into the benz[*g*]isoquinolines **10a-f** on heating in polyphosphoric acid.

J. Heterocyclic Chem., **35**, 669 (1998).

Introduction.

As part of a program dealing with the synthesis of heterocyclic antitumor agents [1], we required benz[*g*]isoquinoline (2-azaanthracene) and its substituted congeners. It was surprising to discover that no facile pathways have been reported for the preparation of these aza chemotypes [2,3].



Benz[*g*]isoquinoline
2-Azaanthracene

The first synthesis was reported over a century ago by reduction of benz[*g*]isoquinoline-5,10-dione using zinc and ammonium hydroxide to yield the product in poor yield [4,5]. In addition, the preparation of the starting dione is quite difficult [6,7] and although commercially available, it is extremely expensive [8].

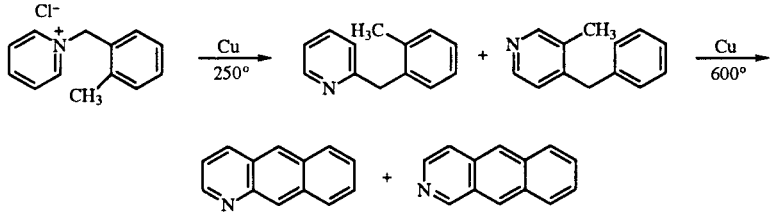
In 1937 von Braun and Nelles [9] reported that treatment of pyridines with benzyl halides or substituted benzyl halides led to the corresponding pyridinium salts which could be rearranged (Ladenburg rearrangement) [10] into mixtures of 2- and 4-benzylated pyridines on being heated with a trace of copper powder at 250°. Upon heating these mixtures over copper turnings to 600°, dehydrogenations occurred to produce low yields of mixtures of benzo[*g*]quinolines (1-azaanthracenes) and benz[*g*]isoquinolines (2-azaanthracenes) which could be separated in a few cases (Scheme 1). This procedure was subsequently utilized by others for the synthesis of benz[*g*]isoquinoline [11,12].

More recently a Russian group reinvestigated the von Braun procedure and described the preparation of a number of substituted benz[*g*]isoquinolines [13-15]. The mixtures of benzyl pyridines in benzene were dehydrogenated by *passage* over a *K-16* catalyst for a 4 hour period at a *temperature* of 560° to afford mixtures which could be separated by crystallization. Clearly these thermal processes lack stereochemical control and require extremely high temperatures which are quite difficult to achieve in a typical laboratory setting.

The preparation of benz[*g*]isoquinoline was described *via* a 5-step cycloaddition pathway which required the use of $Fe_2(CO)_9$ in the terminal deoxygenation step [16]. A related cycloaddition pathway led to 9,10-diphenylbenz[*g*]isoquinoline [17]. A zeolite-catalyzed isomerization of 1-amino- or 2-aminoanthracene in the presence of ammonia and high pressure led to poor yields of methylazaanthracenes [18].

We have reported that benzyl and substituted benzylic zinc bromides, undergo highly regioselective additions to 1-(phenoxycarbonyl)pyridinium salts formed from methyl nicotinate to yield methyl 4-benzyl substituted-1,4-dihydronicotinates. Aromatizations of these dihydropyridines

Scheme 1

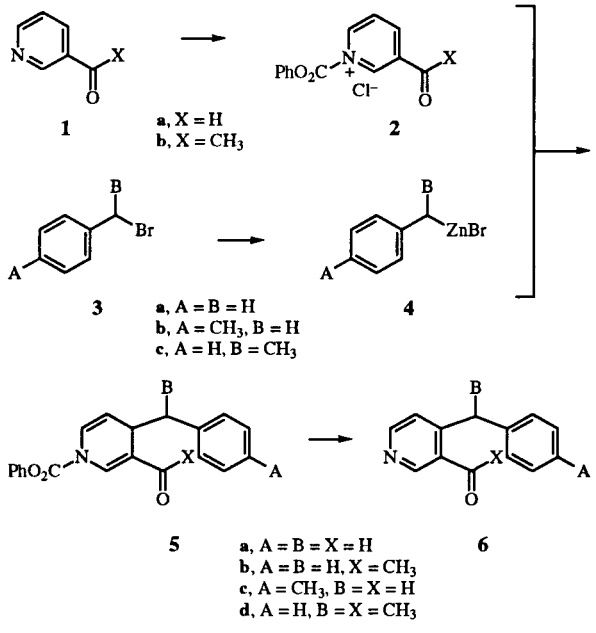


leads to the corresponding methyl 4-benzylnicotinates [19]. These intermediates on hydrolysis to the corresponding acids followed by cyclization and concomitant oxidation lead to the corresponding benz[*g*]isoquinoline-5,10-diones [20].

Results and Discussion.

We now wish to report an adaptation of this procedure which leads to benz[*g*]isoquinoline and its substituted analogues. This methodology is based on the regioselective addtions of benzyl zinc bromides to pyridine 3-carboxaldehyde (**1a**) [21] or 3-acetylpyridine (**1b**) followed by aromatizations and cyclizations of the resultant aldehydes or ketones with polyphosphoric acid [22]. The preparative methodology is illustrated in Scheme 2.

Scheme 2



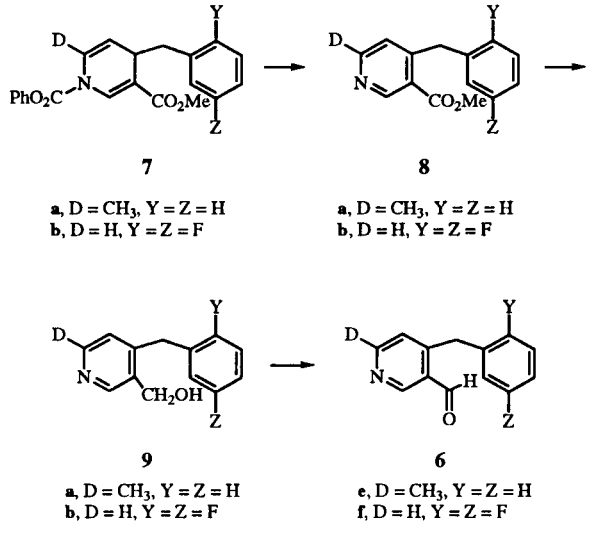
Pyridine-3-carboxaldehyde (**1a**) and 3-acetylpyridine (**1b**) in tetrahydrofuran at 0° were converted into the corresponding pyridinium chlorides **2a** and **2b** by treatment with phenylchloroformate. The benzylic bromides **3a-c** on treatment with zinc dust in tetrahydrofuran at room temperature were converted into the respective benzylic zinc bromides **4a-c**.

Addition of the solution of **4a** (small amounts of unreacted Zn were usually present) *via* cannula under nitrogen pressure to the pyridinum salts **2a** and **2b** held at 0°, followed by an aqueous workup afforded dihydropyridines **5a** and **5b**, respectively. In a similar manner, reaction of **2a** with **4b**, led to **5c** while treatment of **2b** with **4c** led to **5d**.

The dihydropyridines **5a-d** on being heated with sulfur in refluxing decalin led to the corresponding pyridines **6a-d** in good yields.

The synthesis of the pyridinealdehydes **6e** and **6f** commenced by regioselective additions of benzyl zinc bromides to pyridiniums salts derived from methyl nicotinates. Aromatizations led to the corresponding pyridine esters which were reduced with lithium aluminum hydride to the alcohols, followed by oxidation to yield the desired substituted pyridine-3-carboxaldehydes (Scheme 3).

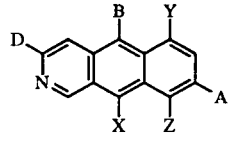
Scheme 3



Treatment of benzyl zinc bromide or 2,5-difluorobenzyl zinc bromide with the pyridinium salts derived from methyl 6-methylnicotinate or methyl nicotinate led to the dihydro esters **7a** and **7b**, respectively. Aromatizations of **7a** and **7b** led to the pyridine esters **8a** and **8b**. Reduction of these esters by lithium aluminum hydride led to the corresponding alcohols **9a** and **9b**, respectively, Oxidation of these benzylic alcohols with manganese dioxide led to the aldehydes **6e** and **6f.**

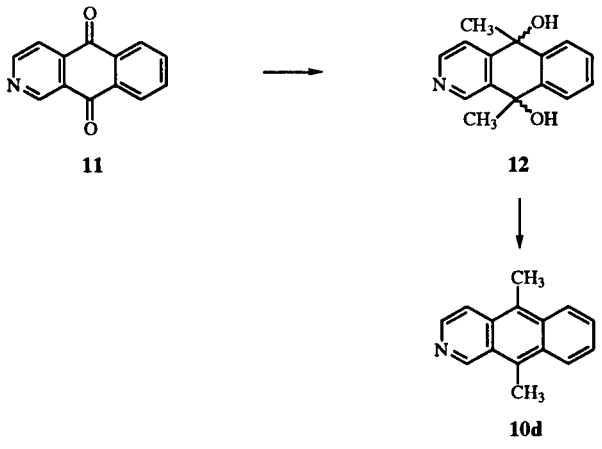
Upon heating aldehydes **6a-f** in polyphosphoric acid the benz[*g*]isoquinolines **10a-f** which are tabulated in Table 1 were obtained. The structural assignments are based on ^{1}H, ^{13}C and ^{19}F (for **10f**) data.

Table 1



10	A	B	D	X	Y	Z
a	H	H	H	H	H	H
b	H	H	H	CH_3	H	H
c	CH_3	H	H	H	H	H
d	H	CH_3	H	CH_3	H	H
e	H	H	CH_3	H	H	H
f	H	H	H	H	F	F

Scheme 4



The structure of **10d** was verified by an alternate synthetic route which is illustrated in Scheme 4.

Treatment of dione **11** with methyllithium led to the diol **12**. Upon heating this diol to 140° with 57% aqueous hydriodic acid in acetic acid [23], **10d** was obtained in a good yield.

Conclusions.

The pathways described constitute valuable preparative routes to benz[*g*]isoquinoline and substituted derivatives. This procedure should prove quite useful in the synthesis of other substituted derivatives. The facile oxidation of these chemotypes to benz[*g*]isoquinoline-5,10-diones also opens up a new synthetic avenue to these analogues.

Table 2

Properites, Yields and ^{1}H NMR Data for Analogues **5**

5	mp, °C	% yield	^{1}H NMR δ, deuteriochlroroform (tetramethylsilane)
a	99-100	25	9.48 (s, 1H), 7.72 (s, 1H), 7.43-6.87 (m, 11H), 5.14 (s, 1H), 3.70 (m, 1H), 3.10 (dd, 1H), 2.67 (dd, 1H)
b [k]	oil	96	7.91 (s, 1H), 7.41-7.39 (m, 2H), 7.27-7.12 (m, 9H), 5.14 (s, 1H), 3.74 (m, 1H), 2.97 (m, 1H), 2.68-2.60 (m, 1H), 2.37 (s, 3H)
c [l]	97-98	28	9.46 (s, 1H), 7.71 (s, 1H), 7.43-7.40 (m, 2H), 7.30-7.25 (m, 1H), 7.15 (m, 2H), 7.14-7.06 (m, 4H), 6.88 (m, 1H), 5.14 (s, 1H), 3.67 (m, 1H), 3.06 (m, 1H), 2.63 (m, 1H), 2.33 (s, 3H)
d [m]	oil	87	product was not isolated in pure form

[k] Purification was performed on a silica gel column using dichloromethane as an eluent. [l] Purification on a silica gel column using dichloromethane as an eluent, dissolved sample in hexane/ethyl acetate and placed in freezer to yield a solid material. *Anal.* Calcd. for $C_{21}H_{19}NO_3$: C, 75.55; H, 5.75; N, 4.20. Found C, 75.81; H, 5.78; N, 4.03. [m] Several attempts to purify *via* silica gel column chromatography led to impure material (nmr) which was used in the next step.

Table 3

Properties, Yields and ^{1}H NMR Data for Analogues **6**

6	mp, °C	% yield	^{1}H NMR δ, deuteriochloroform (tetramethylsilane)
a	oil	64	10.30 (s, 1H), 8.98 (s, 1H), 8.66 (d, 1H, J = 5.1 Hz), 7.34-7.14 (m, 6H), 4.47 (s, 2H)
b [n]	oil	51	8.92 (s, 1H), 8.56 (d, 1H, J = 5.1 Hz), 7.30 (m, 2H), 7.27 (m, 1H), 7.13 (m, 3H), 4.30 (s, 2H), 2.55 (s, 3H)
c [p]	oil	54	10.2 (s, 1H), 8.93 (s, 1H), 8.61 (d, 1H, J = 5.1 Hz), 7.12 (d, 1H, J = 5.1 Hz), 7.09-7.01 (m, 4H), 4.37 (s, 2H), 2.29 (s, 3H)
d [q]	oil	44	8.77 (s, 1H), 8.59 (d, 1H, J = 5.3 Hz), 7.29 (m, 3H), 7.25-7.16 (m, 2H), 7.15 (d, 1H, J = 5.1 Hz), 4.96 (q, 1H, J = 7.1 Hz), 2.43 (s, 3H), 1.61 (d, 3H, J = 7.2 Hz)
e [r]	84-85	97	10.2 (s, 1H), 8.84 (s, 1H), 7.32-7.15 (m, 5H), 6.98 (s, 1H), 4.41 (s, 2H), 2.56 (s, 3H)
f [s]	oil	85	10.3 (s, 1H), 8.99 (s, 1H), 8.68 (d, 1H, J = 4.9 Hz), 7.14 (d, 1H, J = 4.6 Hz), 7.05 1H), 6.95 (m, 1H), 6.85 (m, 1H), 4.46 (s, 2H)

[n] Refluxed in decalin for 4.5 hours. Purification performed on a silica gel column using dichloromethane:methanol (95:5) as an eluent to yield a red oil. [p,q] Refluxed sample **6c** for 4.5 hours and **6d** for 5 hours in decalin. Purification performed on a silica gel column using dichloromethane:ethyl acetate (80:20) as an eluent to yield a red oil. [r,s] Both **6e** and **6f** were refluxed for 5 hours in decalin. Purification performed on a flash silica gel column using dichloromethane:ethyl acetate (80:20) as an eluent to yield a yellow solid for **6e** and a red oil for **6f**.

Table 4

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

10	mp°C	% yield	^{1}H NMR δ, deuteriochloroform (tetramethylsilane)
a	169-171	66	9.42 (s, 1H), 8.55 (s, 1H), 8.35 (d, 1H, J = 6. 0 Hz), 8.30 (s, 1H), 7.97 (d, 1H, J = 8.3 Hz), 7.91 (d, 1H, J = 8.4 Hz), 7.7 (d, 1H, H = 6.1 Hz),7.5 (m, 2H)
b [t]	75-77	61	9.81 (s, 1H), 8.43 (d, 1H, J = 5.9 Hz), 8.30 (m, 1H), 8.22 (s, 1H), 7.98 (m, 1H), 7.71 (d, 1H, J = 5.9 Hz), 7.57-7.53 (m, 2H), 3.15 (s, 3H)
c [u]	208-209	44	9.50 (s, 1H), 8.69 (s, 1H), 8.53 (s, 1H), 8.37 (d, 1H, J = 5.9 Hz), 8.05 (d, 1H, J = 8.7 Hz), 7.94 (s, 1H), 7.89 (d, 1H, J = 6.0 Hz), 7.49 (d, 1H, J = 8.7 Hz), 2.52 (s, 3H)
d [v]	152-153	86	9.84 (s, 1H), 8.48 (d, 1H, J = 6.3 Hz), 8.38 (d, 1H, J = 8.4 Hz), 8.31 (d, 1H, J = 8.7 Hz), 7.98 (d, 1H, J = 6.4 Hz), 7.65-7.57 (m, 2H), 3.20 (s, 3H), 3.03 (s, 3H)
e [w]	194-195	98	9.42 (s, 1H), 8.55 (s, 1H), 8.26 (s, 1H), 8.05 (d, 1H, J = 8.4 Hz), 7.99 (d, 1H, J = 8.5 Hz), 7.57 (s, 1H), 7.55-7.52 (m, 1H), 7.50-7.47 (m, 1H), 2.72 (s, 3H)

Table 4 (continued)

Melting Points, Yields and ^1H NMR Data for Analogues **10**

10	mp°C	% yield	^1H NMR δ, deuteriochloroform (tetramethylsilane)
f [x]	127-128	85	9.35 (s, 1H), 8.59 (s, 1H), 8.38 (m, 2H), 7.63 (d, 1H, J = 6.0 Hz), 6.99-6.89 (m, 2H)

[t] Reaction time was increased to 1.5 hours at 140°. Purification using silica gel column chromatography eluting with 95:5 dichloromethane:-ethyl acetate followed by sublimation yielded a yellow solid. Sample darkened rapidly over time in the freezer and could not be analyzed. [u] Reaction time was increased to 1.5 hours at 140°. Purificaton using flash silica gel chromatography eluting with 80:20 dichloromethane:ethyl acetate yielded a light yellow solid, lit. mp [13] 194-196°; NMR solvent:methyl-d_3 alcohol-d. [v] Reaction time was increased to 1.5 hours. Reaction workup yielded a yellow soild which readily sublimed, lit mp [23)] 160-161.5°. [w] Reaction time was increased to 1.5 hours at 140°. Purificaton using flash silica gel chromatography eluting with 9:1 dichloromethane:methanol yielded a light yellow solid. [x] Purificaton using flash silica gel chromatography eluting with 80:20 dichloromethane:ethyl acetate yielded a light yellow solid. *Anal.* Calcd. for $C_{13}H_7F_2N$: C, 72.56; H, 3.28; N, 6.51. Found: C, 72.10; H, 3.00; N, 6.30

Table 5

^{13}C NMR Data for Analogues **10a-e** and ^{19}F for **10f**

10	^{13}C NMR δ, deuteriochloroform (tetramethylsilane)
a	154.5, 140.7, 134.3, 132.2, 131.9, 128.9, 128.1, 127.6, 127.4, 126.8, 126.1, 124.8, 119.9
b	151.3, 139.8, 133.8, 133.0, 131.7, 130.7, 128.8, 126.7, 125.7, 124.8, 124.7, 123.6, 120.3, 13.0
c [m]	154.1, 140.2, 135.6, 132.4, 132.0, 130.9, 130.3, 127.9, 126.7, 126.5, 126.4, 124.5, 119.8, 21.4
d	152.1, 139.9, 132.4, 131.2, 130.5, 130.5, 127.6, 126.7, 125.6, 125.4, 125.2, 124.8, 117.0, 13.5, 13.2
e	154.0, 149.3, 134.5, 132.9, 131.8, 128.9, 128.0, 127.6, 127.3, 125.6, 125.4, 123.9, 117.3, 24.2
f	^{13}F nmr (deuteriochloroform): δ, 4-fluorobenzaldehyde 80.9 (d, 1F, J = 23.0 Hz), 80.3 (d, 1F, J = 23.0 Hz)

[m] NMR solvent methyl-d_3 alcohol-d.

EXPERIMENTAL

Benzyl bromides were purchased from Aldrich. Zinc dust (Aldrich, 32,493-0, 99.998% purity) was used as received. 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 and carbon-13 and fluorine-19 nmr were recorded on a Bruker WM-250 or ARX-500 pulsed spectrometer.

Typical Dihydropyridine Preparative Procedure

1-(Phenoxycarbonyl)-4-(benzyl)-1,4-dihydropyridine-3-carboxaldehyde (**5a**).

A solution of **3a** (2.7 g, 16.1 mmoles) in tetrahydrofuran (10 ml, freshly distilled from potassium metal) was added dropwise over a 5-minute period to a suspension of zinc dust (1.13 g, 17.3 mmoles) in tetrahydrofuran (15 ml). The mixture was kept in a water bath at room temperature and allowed to stir for 4 hours. To a solution of **1a** (1.72 g, 16.1 mmoles) in tetrahydrofuran (15 ml) held in an ice bath, phenyl chloroformate (2.5 g, 16.1 mmoles) in tetrahydrofuran (2 ml) was added dropwise over a 5 minute period. The mixture was stirred for 1 hour in an ice bath. The organo zinc bromide **4a** was added to the cold phenoxycarbonyl pyridinium chloride solution **2a** over 10 minute period *via* a cannula and the mixture was stirred for 1 hour. The mixture was warmed to room temperature and quenched into aqueous ammonium chloride (20%, 6 ml). The product was extracted with ethyl acetate (2 x 50 ml) and the extract washed with aqueous sodium bicarbonate (10%, 30 ml), water (50 ml), aqueous ammonium chloride (20%, 30 ml) and then water (20 ml). The extract was dried over sodium sulfate, decanted from the drying agent and concentrated by rotary evaporation to yield a viscous orange oil (4.09 g). Hexane (10 ml) was added to the oil and the mixture boiled followed by the addition of ethyl acetate (7 ml). A dark brown oil remained undissolved. The solution was decanted and hexane added to induce turbidity. The solution was placed in the freezer overnight. The resultant solid was collected by filtration to afford **5a** (0.64 g). Additional product could be obtained from the filtrate to yield a total of 1.14 g (25%); mp 99-100°.

Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.62; H, 5.10; N, 4.22.

Analogues **5b-d** were prepared from the appropriate reactants in a similar fashion. The properties, yields, modification of the typical procedure and ^1H nmr data for the dihydropyridine **5a-d** are tabluated in Table 2.

Typical Aromatization Procedure.

4-Benzylpyridine-3-carboxaldehyde (**6a**).

Dihydropyridine **5a** (0.51 g, 1.60 mmoles) and sulfur (0.092 g, 2.88 mmoles) in decalin (8 ml) were refluxed for 24 hours. The mixture was allowed to cool to room temperature and steam distilled to remove the decalin. The residue was extracted with dichloromethane (4 x 30 ml), the extracts dried over sodium sulfate and the solvent removed by rotary evaporation to leave a dark red oil (0.20 g, 64%) which was used in the next step without further purification.

Analogues **6b-d** were prepared from the appropriate reactants in a similar fashion. The properties, yields, modification of the typical procedure and ^1H nmr data for the pyridine-3-carboxaldehydes **6a-d** are tabluated in Table 3.

Methyl 1-(Phenoxycarbonyl)-4-benzyl-6-methyl-1,4-dihydronicotinate (**7a**).

The procedure was similar to that described for the synthesis of **5a**. Benzyl zinc bromide was allowed to react with the pyridinium salt derived from methyl 6-methylnicotinate. The crude viscous oil was purified by column chromatography over silica

gel with dichloromethane:hexane (3:1) as eluent to give **7a** as a yellow oil, which upon standing in the freezer yielded a white solid (63%), mp 68-70°; ^{1}H nmr (deuteriochloroform): δ 8.0 (s, 1H), 7.40-7.13 (m, 10H), 6.79 (m, 1H), 4.98 (d, 1H), 3.78 (s, 3H), 3.06 (m, 1H), 2.70 (m, 1H), 2.17 (s, 3H).

Anal. Calcd. for $C_{22}H_{21}NO_4$: C, 72.91; H, 5.56; N, 3.86. Found: C, 75.81; 5.78; N, 4.03.

Methyl 1-(Phenoxycarbonyl)-4-(2,5-difluorobenzyl)dihydronicotinate (**7b**).

The procedure was similar to that described for the synthesis of **5a**. The 2,4-difluorobenzyl zinc bromide was allowed to react with the pyridinium salt derived from methyl nicotinate. The crude viscous oil was purified by column chromatography over silica gel with dichloromethane:hexane (3:1) as eluent to give **7b** as a clear oil, which upon standing in the freezer formed a white solid (77%), mp 62-64°; ^{1}H nmr (deuteriochloroform): δ 8.03 (s, 1H), 7.42 (m, 2H), 7.39 (m, 1H), 7.26 (m, 2H), 7.10-6.97 (m, 4H), 5.10 (s, 1H), 3.79 (s, 3H), 3.71 (m, 1H), 2.92 (m, 1H), 2.86 (m, 1H).

Anal. Calcd. for $C_{21}H_{17}F_2NO_4$: C, 65.45; H, 4.45; N, 3.63. Found: C, 65.28; H, 4.44; N, 3.43.

Methyl 4-Benzyl-6-methylnicotinate (**8a**).

A mixture of **7a** (1.04 g, 2.9 mmoles) and sulfur (0.13 g, 4 mmoles) in decalin (5 ml) was heated in an oil bath held at 190° for 5 hours. The mixture was cooled to room temperature and steam distilled to remove the decalin. The residue was extracted with dichloromethane (3 x 20 ml) and dried over magnesium sulfate. Removal of the solvent under reduced pressure yielded a brown oil (0.77 g). Purification by flash chromatography over silica gel using dichloromethane:ethyl acetate (4:1) as eluent afforded **8a** as a reddish oil (0.56 g, 80%) which was not further purified; ^{1}H nmr (deuteriochloroform): δ 8.96 (s, 1H), 7.28-7.24 (m, 2H), 7.21 (m, 1H), 7.13 (m, 2H), 6.92 (s, 1H), 4.34 (s, 2H), 3.85 (s, 3H), 2.50 (s, 3H).

Methyl 4-(2,4-Difluorobenzyl)nicotinate (**8b**).

Treatment of **7b**, with sulfur in decalin following a similiar procedure to that for the aromatization of **7a** to **8a** led to **8b**, as a reddish oil. A mixture of **7b** (1.51 g, 3.9 mmoles) and sulfur (0.18 g, 5.6 mmoles) in decalin (6 ml) was heated in an oil bath held at 190° for 5 hours. The mixture was cooled to room temperature and steam distilled to remove the decalin. The residue was extracted with dichloromethane (3 x 20 ml) and dried over magnesium sulfate. Removal of the solvent under reduced pressure yielded a brown oil (1.19 g). Purification by flash chromatography over silica gel using dichloromethane:ethyl acetate (4:1) as eluent afforded **8b** as a reddish oil which solidified upon standing to yield an orange solid (0.70 g, 64%), mp 82-83°; ^{1}H nmr (deuteriochloroform): δ 9.13 (s, 1H), 8.61 (d, 1H, J = 5.2 Hz), 7.09 (d, 1H, J = 5.1 Hz), 7.04 (m, 1H), 6.90-6.81 (m, 1H), 6.79 (m, 1H), 4.41 (s, 2H), 3.92 (s, 3H).

Anal. Calcd. for $C_{14}H_{11}F_2NO_2$: C, 63.88; H, 4.21; N, 5.32. Found: C, 63.92; H, 4.52; N, 5.16.

4-Benzyl-3-hydroxymethyl-6-methylpyridine (**9a**).

A solution of **8a** (52 mg, 0.22 mmole) in ether (2 ml) was added dropwise over a period of 5 minutes to a suspension of lithium aluminum hydride (15 mg, 0.41 mmole) in ether (2 ml) which was cooled in a dry ice acetone bath at -78°. The reaction mixture was stirred at -78° for 30 minutes. Ethyl acetate (0.5 ml) was then added to the mixture and the temperature allowed to rise to 5° over 20 minutes. Water (0.5 ml) was added and the white solid which separated was collected by filtration and washed with ethyl acetate. The layers in the filtrate were separated and the ethyl acetate layer was concentrated under reduced pressure to leave a reddish-brown oil (43 mg). Purification by flash chromatography over slica gel using dichloromethane:-methanol (9:1) as eluent afforded **9a** as a white solid (32 mg, 70%), mp 99-100°; ^{1}H nmr (deuteriochloroform): δ 8.27 (s, 1H), 7.28 (m, 2H), 7.24 (m, 1H), 7.21 (m, 2H), 6.85 (s, 1H), 4.62 (s, 2H), 4.04 (s, 2H), 2.16 (s, 3H).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.62; H, 6.77; N, 6.33.

4-(2,5-Difluorobenzyl)-3-(hydroxymethyl)pyridine (**9b**).

A solution of **8b** (201 mg, 0.77 mmoles) in tetrahydrofuran (7 ml) was added dropwise over a period of 5 minutes to a suspension of lithium aluminum hydride (60.4 mg, 1.59 mmoles) in ether (8 ml) which was cooled in a dry ice acetone bath at -78°. The reaction mixture was stirred at -78° for 60 minutes. Ethyl acetate (5 ml) was then added to the mixture and the temperature allowed to rise to 0° over 30 minutes. Water (4 ml) was added and the white solid which separated was collected by filtration and washed with ethyl acetate. The layers in the filtrate were separated and the ethyl acetate layer was concentrated under reduced pressure to leave a clear oil (201 mg). Purification by flash chromatography over slica gel using dichloromethane:methanol (9:1) as eluent afforded **9b** as a clear oil (135 mg, 75%); ^{1}H nmr (deuteriochloroform): δ 8.50 (s, 1H), 8.41 (d, 1H, J = 5.0 Hz), 7.05 (m, 1H), 6.98 (d, 1H, J = 5.0 Hz), 6.94 (m, 1H), 6.79 (m, 1H), 4.75 (s, 2H), 4.10 (s, 2H).

4-Benzyl-6-methylpyridine 3-carboxaldehyde (**6e**).

A mixture of **9a** (32 mg, 0.15 mmole) and manganese dioxide (234 mg, 2.3 mmoles) in dichloromethane (6 ml) was stirred at room temperature for 1 hour. The mixture was filtered through a celite bed and the celite was washed thoroughly with dichloromethane. The removal of the solvent under rotary evaporation led to **6e** as a light yellow solid.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.19; H, 6.18; N, 6.46.

4-(2,5-Difluorobenzyl)pyridine 3-carboxaldehyde (**6f**).

The procedure for the preparation of **6e** was adapted for the conversion of **9b** to yield an oil which was not further purified but used directly in the next step. The properties, yields, modification of the typical procedure and ^{1}H nmr data for the pyridine-3-carboxaldehydes **6e-f** are tabluated in Table 3.

Typical Cyclization Procedure.

Benz[g]isoquinoline (**10a**).

A mixture of **6a** (0.13 g, 0.66 mmole) and polyphosphoric acid (1.9 g) was heated in an oil bath held at 140° for 1 hour. Water (6 ml) was added to the cool reaction mixture and it was extracted with dichloromethane (2 x 20 ml). The aqueous layer was neutralized with aqueous sodium hydroxide (2*N*) and extracted with dichloromethane (3 x 20 ml). The extracts were dried over magnesium sulfate and removal of the solvent left a brown solid. Additional product was otained by a continuous extraction of the aqueous phase to yield a total of 0.08 g (66%) of **10a**, mp 169-171°; lit mp [16] 179-180°; the color could easily be removed by sublimation although the yellow material darkened over a few days in standing at room temperature.

The cyclization procedure utilized for the preparation of **10a** was adapted to the pyridines **6b-f**, to afford the benz[*g*]isoquinolines **10b-f**, respectively. The properties, yields, modification of the typical procedure and ^{1}H nmr data for benz[*g*]isoquinolines **10a-f** are tabulated in Table 4.

All the benz[*g*]isoquinolines showed intense fluorescence when observed under long uv light.

The ^{13}C nmr data for **10a-e** and ^{19}F data for **10f** are listed in Table 5.

5,10-Dimethyl-5,10-dihydro-5,10-dihydroxybenz[*g*]isoquinoline (**12**).

A solution of methyllithium (1.4 *M* in diethyl ether, 2.0 ml, 2.80 mmoles) was added to a mixture of **11** (252 mg, 1.20 mmoles) and tetrahydrofuran (25 ml) under nitrogen at -78° over 5 minutes. The mixture was allowed to stir at -78° for 30 minutes, allowed to warm to room temperature over 4 hours and quenched over crushed ice (8 g) and ammonium chloride (755 mg). The product was extracted with methylene chloride (3 x 20 ml) and the extracts dried over magnesium sulfate. The dark brown solid which was obtained upon removal of the solvent under reduced pressure was dissolved in hot ethyl acetate (10 ml). The white solid which formed was collected by filtration and washed with ethyl acetate to afford **12** (128 mg, 44% yield), mp 202-203°; ^{1}H nmr (methyl-d_3 alcohol-d): δ 8.9 (s, 1H), 8.51-8.49 (d, 1H, J = 5.16 Hz), 7.80-7.78 (m, 2H), 7.68-7.66 (d, 1H, J = 5.06 Hz), 7.41-7.38 (m, 2H), 1.59 (s, 3H), 1.53 (s, 3H).

9,10-Dimethylbenz[*g*]isoquinoline (**10d**).

A mixture of **12** (25 mg, 0.102 mmole), hydriodic acid (57% aqueous, 0.06 ml) and acetic acid (2 ml) were heated at 140° for 5 hours. The reaction mixture was quenched into sodium bisulfite (1%, 5 ml). The solid which separated was collected by filtration (57 mg) and purified by flash chromatography (silica-gel) eluting with methylene chloride:methanol (98:2) to give **10d** as a yellow solid (12.5 mg, 59%) which was identical in all respects to the product prepared *via* the cyclization procedure.

REFERENCES AND NOTES

[1] A. P. Krapcho, M. E. Petry, Z. Getahun, J. J. Landi, Jr., J. Stallman, J. F. Polsenberg, C. E. Gallagher, M. J. Maresch, M. P. Hacker, F. C. Giuliani, G. Beggiolin, G. Pezzoni, E. Menta, C. Manzotti, A. Oliva, S. Spinelli and S. Tognella, *J. Med. Chem.*, **37**, 828 (1994).

[2] C. V. Wilson, Azaanthracene in The Chemistry of Heterocyclic Compounds, Six-Membered Heterocyclic Nitrogen Compounds with Three Condensed Rings, C. F. H. Allen, ed, **12**, 1958, Interscience Publishers, Inc., NY, pp 1-164, for a review of the early literature and the difficulties of obtaining 2-azaanthracene.

[3] A. Etienne, *Ann. Chim. (Paris)*, **12**, 5 (1946), a review of the older literature with a focus on 1-azanthracene.

[4a] A. Philips, *Ber.*, **27**, 1923 (1894); [b] A. Philips, *Ber.*, **28**, 1658 (1895); attempts to repeat this experiment (zinc, copper sulfate, ammonium hydroxide, reflux, 4 hours) were quite difficult; -tlc showed mainly starting material and small amounts of desired product which is highly fluorescent under UV light.

[5] T. Vo-Dinh, G. H. Miller, D. W. Abbott, R. L. Moody, C. Y. Ma and C.-H. Ho, *Anal. Chim. Acta*, **175**, 181 (1985).

[6] A. A. Artamonov, T. Shneider and N. V. Baranova, *Chem. Heterocylic Compd.*, English Translation, **16**, 397 (1980).

[7] S. P. Khanapure and E. R. Biehl, *Heterocycles*, **27**, 2643 (1988).

[8] Aldrich, 1996-1997 catalog price: 1 g at $606.

[9] J. von Braun and J. Nelles, *Ber.*, **70B**, 760 (1937).

[10] The Merck Index, 1996, 12th Ed., ONR-52, Merck Research Laboratories, Division of Merck & Co., Whitehouse Station, N. J.

[11] A. Etienne and J. Robert, Compt. Rend. *Acad. Sci. (Paris)* Series C, **223**, 331 (1946).

[12] J. Robert, *Ann. Chim. (Paris)*, **7**, 772 (1952).

[13] N. S. Prostakov, V. I. Kuznetsov and G. Datta Ray, *Khim. Geterotsikl Soedin.*, **5**, 673 (1980); *Chem. Heterocyclic Compd.*, English Translation, **5**, 525 (1980).

[14] N. S. Prostakov, *Russ. Chem. Rev.*, English Translation, **38**, 774 (1969).

[15] U. G. Alvarado, N. S. Prostakov and P. Ya. Manu, *Rev. Latinoam. Quim.*, **9**, 218 (1978); *Chem. Abstr.*, **90**, 151949a (1979).

[16] S. L. Crump, J. Netka and B. Rickborn, *J. Org. Chem.*, **50**, 2746 (1985).

[17] C. Bozzo and M. D. Pujol, *Heterocyclic Commun.*, **2**, 163 (1996).

[18] T. Stamm, H. W. Kouwenhoven, D. Seebach and R. Prins, *J. Catalysis*, **155**, 268 (1995).

[19] A. P. Krapcho, D. J. Waterhouse, A. Hammach, R. Di Domenico, E. Menta, A. Oliva and S. Spinelli, *Synth. Commun.*, **27**, 781 (1997).

[20] A. P. Krapcho, C. E. Gallagher, A. Hammach, M. Ellis, E. Menta and A. Oliva, *J. Heterocyclic Chem.*, **34**, 27 (1997).

[21] T.-L. Shing, W. L. Chia, M.-J. Shiao and T. Y. Chau, *Synthesis*, 849 (1991).

[22] C. K. Bradsher, *Chem. Rev.*, **87**, 1277 (1987).

[23] M. Konieczny and R. G. Harvey, *J. Org. Chem.*, **45**, 1308 (1980).

[24] E. Campaigne and J. Ashby, *J. Heterocyclic Chem.*, **8**, 487 (1971). The ^{1}H nmr reported in this manuscript for 9,10-dimethylbenz-[*g*]isoquinoline (**10d**) is incorrect.