Synthesis of Substituted Quinoline-4-carboxylic Acids

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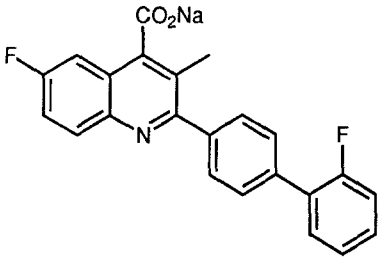
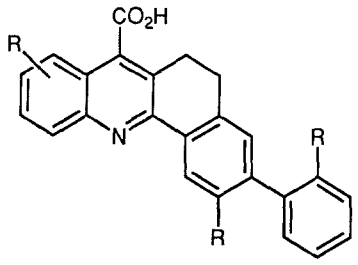
A high yielding synthesis of a variety of quinoline-4-carboxylic acids has been accomplished using a modified Pfitzinger approach involving the condensation of a ketone with an isatin derivative employing aqueous acid conditions. A convenient synthesis of the substituted isatin precursor is also described.

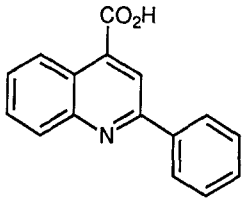
Quinoline-4-carboxylic acids are of general synthetic interest due to a wide variety of medicinal applications including their reported anti-tumor and anti-viral activity. In particular Dupont reported Brequinar Sodium **(I)** and related analogs as dihydroorotate dehydrogenase inhibitors.[1] The carboxylic acid at C4 (among other restrictions) was essential for good enzyme inhibition. More recently, Dupont Merck Pharmaceuticals reported 3-phenyl-5,6-dihydrobenz[*c*]acridine-7-carboxylic acid derivatives **(II)** for use in treating auto-immune disease, psoriasis, graft versus host disease, organ transplant rejection and chronic inflammation.[2] A much older member of this class of compounds, chinchophen **(III)**,[3] was formerly used in the treatment of gout, as an antirheumatic, and more recently as an analgesic.[4]



I, Brequinar Sodium



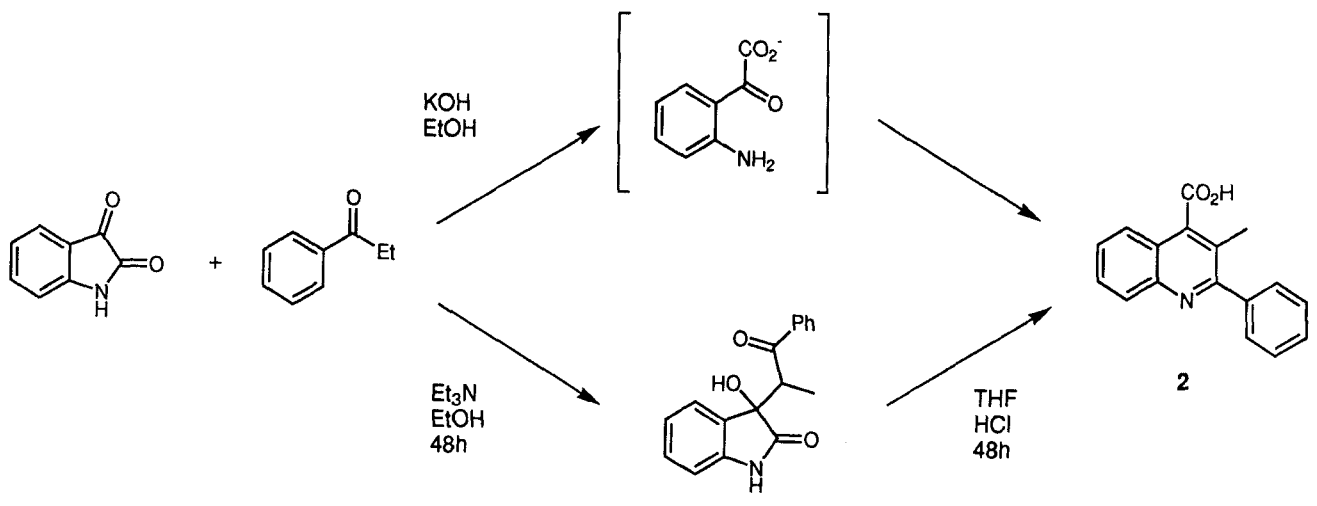
II



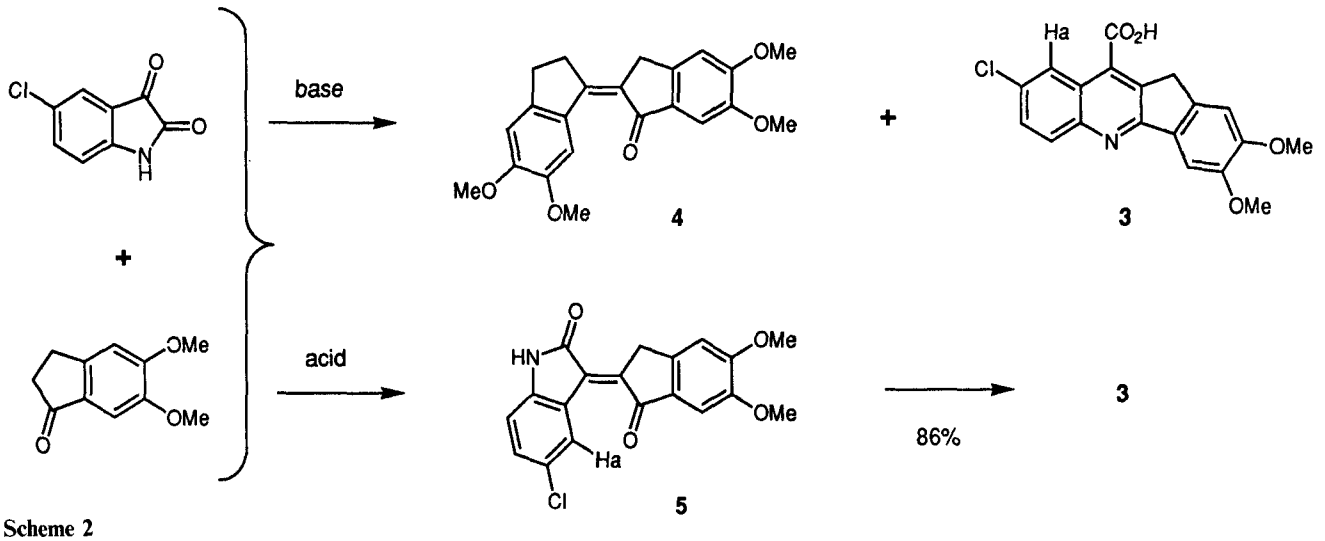
III, Cinchophen

During a program to synthesize substituted quinolines, the Pfitzinger reaction was investigated. The original conditions[5] and subsequent reported modifications[6] all involve treating a mixture of a ketone and an isatin derivative with base. The proposed mechanism involves a base induced ring opening of an isatin derivative to the isatic acid followed by condensation with an appropriate ketone. A similar approach utilizes an aldol condensation under basic conditions followed by treatment with acid to afford quinolines. The yields of these reactions vary between 37 and 55%.[1] For many of our targeted molecules, the basic conditions were not applicable. Herein, we report the high yield synthesis of several substituted quinoline-4-carboxylic acids employing straightforward aqueous acid conditions.

Condensation of 5-chloroisatin and 5,6-dimethoxyindanone under basic conditions according to Buu-Hoi [33% KOH (aq) in ethanol][6a,d,e] at reflux for 16 hours produced the desired compound **3** in 38% yield. The competing byproduct, the aldol adduct **4**, was unavoidable under these conditions. It was found that when this coupling



Scheme 1



Scheme 2

was carried out using aqueous acid conditions compound **3** was formed in 86% yield with no evidence of the aldol byproduct. In general, substituted quinoline-4-carboxylic acids may be formed by condensation of an isatin with a ketone using various solvent mixtures such as glacial acetic acid and concentrated hydrochloric acid or dimethoxyethane and 2 M sulfuric acid (aq). A probable mechanism involves the formation of a mixed aldol product followed by dehydration to the lactam. This lactam is subsequently hydrolyzed and rotation around the carbon–carbon bond allows a facile second irreversible condensation leading to the aromatic system.

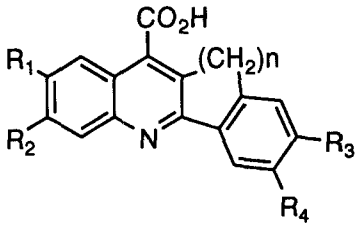
The intermediacy of the aldol product **5** (Scheme 2) was demonstrated by its isolation although it was not necessary to do so at this point. Elimination occurred readily when forming an exocyclic double bond for the five-membered-ring ketones forming structures as in scheme 2 in less than 2 hours. Most of the other ketones we tried could be isolated prior to the elimination as a mixture of diastereomers. Further, the isatin showed no evidence of ring opening to the isatic acid prior to the aldol reaction under these conditions, nor was there any decomposition.

At the outset we made no provisions to control the double bond geometry of the aldol condensation. However, the formation of only one isomer was observed which was assigned the *E*-geometry at the double bond. This was inferred by the downfield shift of the aromatic hydrogen (H_a) which presumably is due to the deshielding region of the carbonyl. A similar downfield shift of the same aromatic hydrogen was also observed in the quinoline-4-carboxylic acid. Further support for this *E*-geometry was obtained from molecular modeling calculations where a simple energy minimization was applied to both the *E*- and *Z*-conformer. The *Z*-geometry showed a less favorable oxygen–oxygen electrostatic interaction.

With a general procedure for the synthesis of the quinoline-4-carboxylic acid in place, the effect of substitution on the isatin was examined. The yields were consistently good, however an effect was observed in the reaction times. Isatins substituted with electron-withdrawing groups (e.g. nitro) react significantly faster than those substituted with electron-donating groups (e.g. methylenedioxy). In most cases the initial mixed aldol product precipitated from solution, and the reaction was continued as a heterogenous mixture. These reactions also produced highly colored solids.

Various types of ketones were also explored. Table I shows the quinoline-4-carboxylic acids derived from bicyclic aromatic ketones and a variety of substituted isatins. The yields are generally good and the purifications were all simple filtrations. The methodology was applied

Table 1. Synthesis of Tetracyclic Quinoline Derivatives

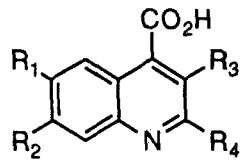


Product	R_1	R_2	n	R_3	R_4	Method[a]	Yield (%)
3[b]	Cl	H	1	OMe	OMe	A	86
6[b]	NO_2	H	1	OMe	OMe	A	91
7		OCH_2CH_2O	1	OMe	OMe	B	87
8	I	H	1	OMe	OMe	A	92
9	H	H	1	OMe	OMe	A	94
10	Cl	H	2	H	H	B	71
11[b]	F	H	2	H	H	B	85
12		OCH_2O	2	H	H	B	88
13	H	H	2	H	H	B	89
14	I	H	1	H	H	A	95
15	NO_2	H	1	H	H	A	71
16	Cl	H	1	H	H	A	88

[a] Methods: A, HOAc, Conc. HCl, 105°C, 16 h; B, DME, H_2SO_4 (aq), reflux 16 h.

[b] The intermediate aldol product has been characterized for these compounds. The intermediate aldol product of **3** is compound **5**, the intermediate of **6** is **6a**, and the intermediate of **11** is **11a**.

Table 2. Synthesis of Quinoline-4-Carboxylic Acid Derivatives

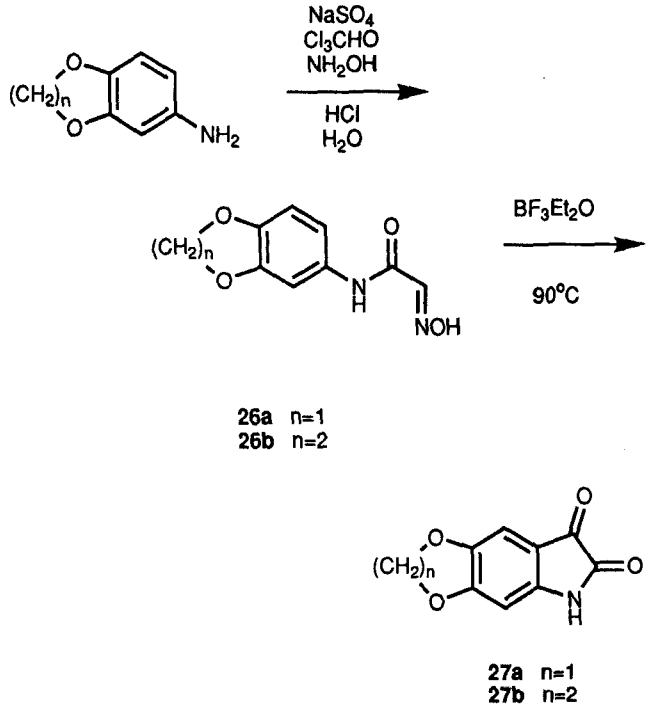


Product	R_1	R_2	R_3	R_4	Yield[a] (%)
17[b]	Cl	H	Me	Ph	92
18	NO_2	H	Me	Ph	82
19	OCH_2O		Me	Ph	65
20	H	H	Me	Ph	94
21	OCH_2CH_2O		$(CH_2)_4$		48
22	Cl	H	$(CH_2)_4$		51
23	H	H	$(CH_2)_4$		56

[a] Reaction conditions: HOAc, Conc. HCl, 105 °C, 16 h.
[b] The intermediate aldol product has been characterized for this compound and is referred to as **17a**.

to acyclic ketones and cyclic alkyl ketones as shown in Table 2. These data show that the aqueous acid conditions also worked well, but did give lower yields on condensation with cyclohexanone.

It was also found that many different types of aqueous acid conditions worked well with little variation in reaction times and yields. However, no reaction was observed if only a catalytic amount of acid was used or when non-aqueous conditions were used. Two sets of aqueous acid conditions were utilized: (a) glacial acetic with concentrated hydrochloric acid, and (b) dimethoxyethane with various concentrations of aqueous sulfuric acid (2–8 M). Our choice typically reflected the solubility of the starting reagents.



Scheme 3

The synthesis of isatin is well known.[7] Following this procedure, the α-oximinoanilide precursor could be made from chloral, hydroxylamine and a substituted aniline. Some modifications in temperature and addition order were necessary to push the reaction to completion presumably because of solubility. However, we noted poor yields and deterioration of substituents on the phenyl ring when attempting ring closure with sulfuric acid. Taylor reported less than a 1% overall yield using this method to synthesize dimethoxyisatin.[8] We found that heating the α-oximinoanilide at 90 °C with $BF_3 \cdot Et_2O$ as a solvent provided a high yielding alternative. Furthermore, with unsymmetrical anilides only one regioisomer was observed.

This brief investigation into the formation of quinoline-4-carboxylic acids has shown a high yielding alternative to the Pfitzinger reaction done under basic conditions. Unlike the proposed mechanism for the basic conditions, we have demonstrated that, in aqueous acid, the aldol condensation followed by elimination occurs before the hydrolysis of the isatin.

All reagents were obtained from Aldrich and were used without further purification. Melting points were determined on a Mel-Temp II melting point apparatus and were uncorrected. NMR spectra were determined on a Varian VXR 300 in DMSO-d_6 (unless otherwise noted) and were referenced to residual DMSO (2.49 ppm, ^{1}H). Microanalyses were performed by Atlantic Microlab, Inc in GA. Compounds **3-23**, **26** and **27** gave C ± 0.4, H ± 0.4, N ± 0.4, except: **14** · 1.5 H_2O, H ± 0.66; **22** · 0.5 H_2O, C ± 2.16, N ± 0.56; **27a**, C ± 0.43. Mass spectra were obtained from either a Hewlett Packard 5988A GC/mass spectrometer or a JEOL SX102 mass spectrometer with chemical, electrospray, or fast atom bombardment ionization.

Method A: 6-Chloro-3-methyl-2-phenylquinoline-4-carboxylic Acid (17):

5-Chloroisatin (200 mg, 1.10 mmol) was slurried in glacial AcOH (3 mL) at r.t. Propiophenone (148 mg, 1.10 mmol) was added and the reaction mixture was placed in a preheated oil bath set to 75 °C. The reaction was stirred for 5 min before the addition of conc. HCl (1.0 mL). The reaction was heated to 105 °C and stirred for 16 h. The reaction was then cooled to r.t. and water (5 mL) was added. The cream colored solid was collected by filtration, and was washed with EtOH (3 mL) and Et_2O (6 mL). The solid was dried under high vacuum to afford **17** (302 mg, 92%) mp 314 °C.

^{1}H NMR: δ = 2.39 (s, 3 H, CH_3), 7.51 (m, 3 H, ph), 7.61 (m, 2 H, Ph), 7.78 (s, 1 H, H-5), 7.80 (dd, 1 H, H-8), 8.04 (d, 1 H, H-9).

Electrospray MS: m/z = 298 (MH^+), 300 (MH^+, chlorine isotope).

Intermediate Aldol 17a:

The above reaction was stopped after 1.0 h by cooling it to r.t. and precipitating an orange solid with the addition of water (5 mL). The solid was washed with Et_2O and dried in vacuo to afford **17a** as a mixture of diastereomers (4:1) (333 mg, 96%): mp 219–221 °C.

Diastereomer (a): ^{1}H NMR: δ = 1.00 (d, 3 H), 4.24 (m, 1 H), 6.75 (d, 1 H), 7.40 (dd, 1 H), 7.47 (m, 3 H), 7.68 (s, 1 H), 7.95 (d, 2 H), 10.42 (s, 1 H, NH).

Diastereomer (b): ^{1}H NMR: δ = 1.37 (d, 3 H), 4.19 (m, 1 H), 6.78 (d, 1 H), 7.25 (dd, 1 H), 7.29 (s, 1 H), 7.60 (m, 3 H), 7.83 (d, 2 H), 10.33 (s, 1 H, NH).

FAB MS: m/z = 316 (MH^+), 317 (MH^+ for Cl isotope).

Method B: 9-Chloro-5,6-dihydrobenz[*c*]acridine-7-carboxylic Acid (10):

5-Chloroisatin (200 mg, 1.10 mmol), α-tetralone (161 mg, 1.10 mmol) and dimethoxyethane (2.0 mL) were combined at r.t. The mixture was gently warmed until complete dissolution occurred

and 2M H_2SO_4 (aq, 2 mL) was added. This was placed in a preheated oil bath set to 105 °C and refluxed for 16 h. The mixture was cooled to r.t., water (5 mL) was added and the precipitate was collected by filtration. The solid was washed with DME (5 mL) and Et_2O (5 mL), and dried in vacuo to provide a cream colored solid **10** (242 mg, 71%): mp 301–302 °C.

^{1}H NMR: δ = 3.00 (m, 2 H, CH_2), 3.08 (m, 2 H, CH_2), 7.40 (m, 3 H, ArH), 7.79 (d, 1 H, ArH), 7.80 (s, 1 H, H-8), 8.11 (d, 1 H, ArH), 8.40 (m, 1 H, ArH).

Electrospray MS: m/z = 310 (MH^+), 311 (MH^+ CI isotope).

8-Chloro-2,3-dimethoxy-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (3):

Yield: 86%, method A, bright orange solid: mp > 300 °C.

^{1}H NMR: δ = 3.92 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.98 (s, 2 H, CH_2), 7.26 (s, 1 H), 7.58 (s, 1 H), 7.60 (d, 1 H), 7.95 (d, 1 H), 8.34 (s, 1 H).

Electrospray MS: m/z = 356 (MH^+), 357 (MH^+ CI isotope).

Sideproduct 4 Formed Under Basic Conditions:

5,6-Dimethoxyindanone (407 mg, 2.12 mmol) and 5-chloroisatin (385 mg, 2.12 mmol) were combined with EtOH (5 mL). Aq KOH (33%, 1 mL) was added dropwise. The reaction was refluxed for 12 h and cooled to r.t. The solid was collected by filtration, washed with EtOH (5 mL), Et_2O (5 mL) and dried in vacuo to afford **4** as a golden yellow solid (240 mg, 62%): mp 225 °C (decomp.).

^{1}H NMR: δ = 2.99 (t, 2 H, CH_2), 3.38 (t, 2 H, CH_2), 3.80 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.89 (s, 6 H, OMe), 3.98 (s, 2 H, CH_2), 7.06 (s, 1 H), 7.12 (s, 1 H), 7.20 (s, 1 H), 7.30 (s, 1 H).

Electrospray MS: m/z = 367 (MH^+). The remaining dark filtrate was acidified using conc. aq HCl to precipitate 8-chloro-2,3-dimethoxy-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic acid (**3**). (See direct preparation).

Aldol Adduct 5 Formed as Intermediate Under Acid Conditions:

5-Chloroisatin (200 mg, 1.04 mmol) and 5,6-dimethoxyindanone (211 mg, 1.10 mmol) were slurried in glacial AcOH (3 mL). Conc. HCl (1.0 mL) was added and the reaction mixture was placed in a preheated oil bath set to 100 °C for 1.25 h. This was then cooled to r.t. and water (5 mL) was added to precipitate a red solid that was washed with water (5 mL), acetone (5 mL), and Et_2O (5 mL). Compound **5** was dried in vacuo (383 mg, 98%): mp 294 °C.

^{1}H NMR: δ = 3.80 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 4.18 (s, 2 H, CH_2), 6.85 (d, 1 H), 7.21 (s, 1 H), 7.23 (s, 1 H), 7.40 (d, 1 H), 9.16 (s, 1 H), 10.88 (s, 1 H, NH).

Electrospray MS: m/z = 356 (MH^+), 357 (MH^+ CI isotope).

2,3-Dimethoxy-8-nitro-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (6):

Yield: 91%, method A, yellow solid: mp 316 °C (decomp.).

^{1}H NMR (trifluoroacetic acid): δ = 3.52 (s, 3 H, OMe), 3.60 (s, 3 H, OMe), 3.89 (s, 2 H, CH_2), 6.62 (s, 1 H), 6.80 (s, 1 H), 7.01 (s, 1 H), 7.88 (dd, 1 H), 9.30 (s, 1 H), 9.60 (s, 1 H, exchangeable).

Electrospray MS: m/z = 367 (MH^+).

Intermediate Aldol Product 6a:

Yield: 94%, orange solid: mp 316 °C (decomp.).

^{1}H NMR: δ = 3.90 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 4.28 (s, 2 H, CH_2), 7.13 (d, 1 H), 7.37 (s, 1 H), 7.39 (s, 1 H), 8.38 (m, 1 H), 10.19 (s, 1 H), 11.58 (s, 1 H, NH).

Electrospray MS: m/z = 367 (MH^+).

7,8-Ethylenedioxy-2,3-dimethoxy-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (7):

Yield: 87%, method B, tan solid: mp > 300 °C (decomp.).

^{1}H NMR (acetone-d_6): δ = 3.90 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 4.19 (s, 2 H, CH_2), 4.28 (m, 2 H, CH_2), 4.37 (m, 2 H, CH_2), 6.40 (s, 1 H), 7.20 (s, 1 H), 7.24 (s, 1 H), 8.97 (s, 1 H, H-9).

Electrospray MS: m/z = 380 (MH^+).

8-Iodo-2,3-dimethoxy-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (8):

Yield: 92%, method A, red solid: mp 321 °C (decomp.).

^{1}H NMR (trifluoroacetic acid): δ = 3.50 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.80 (s, 2 H, CH_2), 6.34 (d, 1 H), 6.60 (s, 1 H), 6.93 (s, 1 H), 7.19 (d, 1 H), 8.82 (s, 1 H), 8.94 (s, 1 H, exchangeable).

FAB MS: m/z = 448 (MH^+).

2,3-Dimethoxy-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (9):

Yield: 94%, method A, red-orange solid: mp 308 °C (decomp.).

^{1}H NMR (trifluoroacetic acid): δ = 2.80 (s, 3 H, OMe), 2.90 (s, 3 H, OMe), 3.12 (s, 2 H, CH_2), 5.81 (d, 1 H, ArH), 5.90 (s, 1 H, ArH), 6.00 (m, 1 H, ArH), 6.22 (m, 2 H, ArH), 6.99 (d, 1 H, ArH), 8.64 (s, 1 H, exchangeable).

Electrospray MS: m/z = 322 (MH^+).

9-Fluoro-5,6-dihydrobenz[*c*]acridine-7-carboxylic Acid (11): Yield: 85%, method B, yellow-orange solid: mp 310 °C (decomp.).

^{1}H NMR: δ = 2.98 (m, 2 H, CH_2), 3.10 (m, 2 H, CH_2), 7.44 (m, 2 H), 7.65 (m, 2 H), 7.82 (m, 1 H), 8.18 (m, 1 H), 8.41 (m, 1 H).

FAB MS: m/z = 312 (MH^+).

Intermediate Aldol Product 11a:

Mixture of diastereomers. Yield: 91%, grey solid (yellow in solution), mp 208 °C (decomp.).

^{1}H NMR: δ = 2.20 (m, 1 H), 2.68 (m, 1 H), 3.03 (m, 3 H), 3.32 (m, 1 H), 6.80 (m, 1 H), 6.97 (m, 1 H), 7.08 (m, 1 H), 7.27 (m, 1 H), 7.39 (m, 1 H), 7.50 (m, 1 H), 7.61 (m, 1 H), 10.32 (s, 1 H, NH).

FAB MS: m/z = 312 (MH^+), 293 ($MH^+ - H_2O$).

9,10-Methylenedioxy-5,6-dihydrobenz[c]acridine-7-carboxylic Acid (12):

Yield: 88%, method B, tan solid: mp 296 °C (decomp.).

^{1}H NMR: δ = 3.00 (m, 2 H), 3.11 (m, 2 H), 6.27 (s, 2 H), 7.25 (m, 1 H), 7.38 (m, 1 H), 7.42 (m, 1 H), 7.59 (m, 1 H), 8.31 (s, 1 H), 8.54 (s, 1 H).

FAB MS: m/z = 320 (MH^+).

5,6-Dihydrobenz[c]acridine-7-carboxylic Acid (13):

Yield: 89%, method B, orange solid, mp 249 °C.

^{1}H NMR: δ = 2.98 (m, 2 H, CH_2), 3.03 (m, 2 H, CH_2), 7.40 (m, 3 H, ArH), 7.63 (m, 1 H, ArH), 7.80 (m, 2 H, ArH), 8.09 (d, 1 H, ArH), 8.45 (m, 1 H, ArH).

FAB MS: m/z = 276 (MH^+).

8-Iodo-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (14):

Yield: 95%, method A, brick-red solid: mp 277 °C (decomp.).

^{1}H NMR: δ = 4.35 (s, 2 H, CH_2), 7.59 (m, 2 H), 7.68 (d, 1 H), 7.90 (d, 1 H), 8.02 (d, 1 H), 8.13 (m, 1 H), 8.91 (s, 1 H).

^{13}C NMR: δ = 35.2, 93.4, 121.6, 125.1, 125.9, 126.0, 127.7, 131.0, 131.2, 131.3, 134.1, 135.7, 137.6, 138.7, 145.7, 147.0, 167.2.

Electrospray MS: m/z = 388 (MH^+).

FAB HRMS: calc. for $C_{17}H_{11}NO_2I$: 387.9835. Found: 387.9848.

8-Nitro-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (15):

Yield: 71%, method A, yellow solid: mp > 320 °C.

^{1}H NMR (trifluoroacetic acid): δ = 3.95 (s, 2 H, CH_2), 6.50 (d, 1 H), 6.60 (m, 3 H), 7.10 (d, 1 H), 7.95 (dd, 1 H), 9.22 (s, 1 H), 9.45 (s, 1 H).

Electrospray MS: m/z = 307 (MH^+).

8-Chloro-11*H*-indeno[1,2-*b*]quinoline-10-carboxylic Acid (16):

Yield: 88%, method A, cream colored solid: mp > 294 °C.

^{1}H NMR: δ = 4.37 (s, 2 H, CH_2), 7.55 (m, 2 H), 7.71 (d, 1 H), 7.82 (d, 1 H), 8.19 (m, 1 H), 8.60 (s, 1 H).

Electrospray MS: m/z = 296 (MH^+), 297 (MH^+ CI isotope).

3-Methyl-6-nitro-2-phenylquinoline-4-carboxylic Acid (18):

Yield: 82%, method A, cream colored solid: mp 325 °C (decomp.–froths).

^{1}H NMR: δ = 2.47 (s, 3 H, CH_3), 7.55 (m, 3 H, Ph), 7.63 (m, 2 H, Ph), 8.22 (d, 1 H, 9-H), 8.44 (dd, 1 H, 8-H), 8.63 (d, 1 H, H-6).

Electrospray MS: m/z = 309 (MH^+).

3-Methyl-6,7-methylenedioxy-2-phenylquinoline-4-carboxylic Acid (19):

Yield: 65%, method A, tan solid: mp > 225 °C (decomp.).

^{1}H NMR: δ = 2.35 (s, 3 H, CH_3), 6.03 (s, 2 H, MDO), 7.3 (s, 1 H, H-9), 7.5 (m, 3 H, Ph), 7.6 (m, 2 H, Ph), 8.0 (s, 1 H, H-6).

FAB MS: m/z = 308 (MH^+).

3-Methyl-2-phenylquinoline-4-carboxylic Acid (20):

Yield: 94%, method A, light yellow solid, mp 306 °C.

^{1}H NMR: δ = 2.40 (s, 3 H, CH_3), 7.5 (m, 3 H), 7.6 (m, 2 H), 7.68 (m, 1 H), 7.8 (m, 2 H), 8.04 (d, 1 H, H-5).

FAB MS: m/z = 310 (MH^+).

6,7-Ethylenedioxy-1,2,3,4-tetrahydroacridine-9-carboxylic Acid (21):

Yield: 48%, method A, tan solid: mp 318 °C (decomp.).

^{1}H NMR: δ = 1.63 (m, 2 H), 1.8 (m, 2 H), 2.81 (t, 2 H), 3.03 (t, 2 H), 4.18 (m, 2 H), 4.40 (m, 2 H), 6.39 (s, 1 H), 7.40 (s, 1 H).

Electrospray MS: m/z = 286 (MH^+).

7-Chloro-1,2,3,4-tetrahydroacridine-9-carboxylic Acid (22):

Yield: 51%, method A, brick-red solid: mp 233 °C (decomp.).

^{1}H NMR: δ = 1.72–1.91 (m, 4 H), 2.90 (t, 2 H), 3.13 (t, 2 H), 6.82 (d, 1 H), 7.51 (m, 1 H), 7.98 (s, 1 H).

FAB MS: m/z = 262 (MH^+), 263 (MH^+ CI isotope).

1,2,3,4-Tetrahydroacridine-9-carboxylic Acid (23):

Yield: 56%, method A, tan yellow solid: mp 224 °C (decomp.).

^{1}H NMR: δ = 1.70–1.90 (m, 4 H), 2.91 (t, 2 H), 3.10 (t, 2 H), 7.38 (d, 1 H), 7.79 (m, 1 H), 7.96 (m, 1 H), 8.18 (d, 1 H).

FAB MS: m/z = 228 (MH^+).

3′,4′-Methylenedioxy-2-hydroxyiminoacetanilide (26a):

Chloral hydrate (2.68 g, 16.2 mmol) was dissolved in water (40 mL) with Na_2SO_4 (23.3 g, 121 mmol). The solution was warmed to 60 °C before the solution of hydroxylamine hydrochloride (3.19 g, 45.9 mmol) in water (20 mL) was added. In a separate flask, a slurry of molten methylenedioxyaniline (2.0 g, 14.6 mmol) in water (22 mL) with conc. HCl (1.2 mL) was prepared at 80 °C. Poor yields were obtained if this solution was prepared at lower temperatures. The two reaction mixtures were combined and the reaction temperature was increased to 95 °C for 20 min. It was removed from the heat and cooled in an ice bath for 15 min. The solids were collected by filtration, washed with water (30 mL) and dried in a vacuum oven for 15 h at 60 °C to afford **26a** (2.58 g, 86%) as a tan solid: mp 167 °C.

^{1}H NMR: δ = 5.97 (s, 2 H, CH_2), 6.83 (d, 1 H, ArH), 7.08 (dd, 1 H, ArH), 7.33 (d, 1 H, ArH), 7.59 (s, 1 H, OH), 10.08 (s, 1 H, CH), 12.10 (s, 1 H, NH).

FAB MS: m/z = 209 (MH^+).

3′,4′-Ethylenedioxy-2-hydroxyiminoacetanilide (26b):

Yield: 97%, prepared as in **26a**, mp 88 °C.

^{1}H NMR: δ = 4.20 (s, 4 H, EDO), 6.77 (d, 1 H, ArH), 7.03 (d, 1 H, ArH), 7.30 (s, 1 H, ArH), 7.60 (s, 1 H, OH), 10.02 (s, 1 H, CH), 12.08 (s, 1 H, NH).

FAB MS: m/z = 223 (MH^+).

5,6-Methylenedioxyisatin (27a):

$BF_3 \cdot Et_2O$ (2.5 mL) was placed in a flask at r.t. under N_2. Using a solid addition funnel, **26a** (1.0 g, 4.81 mmol) was added portionwise so as to not disrupt stirring. The deep-purple reaction mixture was placed in a preheated oil bath set at 85 °C and stirred for 30 min at which point it turned red. This was cooled to r.t. before water (30 mL) was added dropwise. Three extractions with EtOAc (25 mL each) were combined, dried (Na_2SO_4), and volatiles removed in vacuo to afford a rose colored solid, **27a** (0.68 g, 74%): mp 218 °C.

^{1}H NMR: δ = 6.11 (s, 2 H, CH_2), 6.56 (s, 1 H, ArH), 7.02 (s, 1 H, ArH), 10.82 (s, 1 H, NH).

Electrospray MS: m/z = 192 (MH^+).

5,6-Ethylenedioxyisatin (27b):

Prepared as in **27a** using **26b** in warm $BF_3 \cdot Et_2O$. Rose colored solid, 82%, mp 196 °C.

^{1}H NMR: δ = 4.20 (m, 2 H, CH_2), 4.40 (m, 2 H, CH_2), 6.38 (s, 1 H, ArH), 7.01 (s, 1 H, ArH), 10.77 (s, 1 H, NH).

CI MS: m/z = 206 (MH^+).

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