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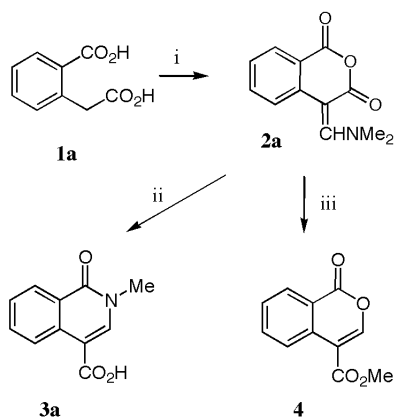
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Homophthalic acid and its pyrido and 8-methylquinolino analogues with dimethylformamide/phosphoryl chloride at 0° give the appropriate 4-(dimethylaminomethylene)isochroman-1,3-dione (**2a**, **2b**, **2c**, respectively). Under the literature conditions for conversion of **2a** to 2-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (**3a**), the aza analogues give instead 7-hydroxy-5-oxo-5*H*-pyrano[4,3-*b*]pyridine-8-carboxaldehyde (**5b**) and 3-hydroxy-6-methyl-1-oxo-1*H*-pyrano[4,3-*b*]quinoline-4-carboxaldehyde (**5c**), respectively. Modified conditions were required to isolate analogues **3b** and **3c**. Further, while reaction of **2a** with hydrogen chloride in methanol gave the known change to methyl 1-oxo-1*H*-isochromene-4-carboxylate (**4**), **2b** and **2c** gave only products of oxa-ring cleavage. Methyl 2-(*cis*-2-hydroxyvinyl)-8-methylquinoline-3-carboxylate (**8**) was the main product from **2c**, while a novel quinolizinium species (**11**) was formed in good yield from **2b**.

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Some time ago a novel synthesis of *N*-methylisoquinolones and isocoumarin-4-carboxylic acid esters was reported, arising from initial reaction of homophthalic acid (or the anhydride or ester **1a** derivatives) with Vilsmeier reagent (dimethyl formamide/phosphoryl chloride) [1]. Intermediate **2a** (Scheme 1), which was formed at 0°, when heated with this same reagent mixture or in neat phosphoryl chloride gave the isoquinolone **3a**, while reaction with methanol and hydrogen chloride gave isocoumarin **4** [2]. These reactions were extended to other substituted homophthalic acids [3] and the isoquinolone formation was reported for the pyridine analogue (**2b** to **3b**) [4]. We were attracted to this method of accessing the 1,6-naphthyridine system, but wish to report that in fact aza systems (*i.e.*, **2b**, Scheme 2 and **2c**, Scheme 3) show rather different chemistry from the benzenoid examples.

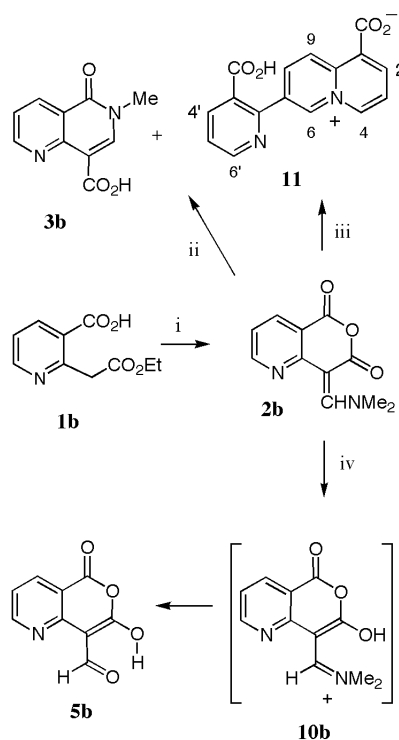
Scheme 1



(i) POCl<sub>3</sub>/DMF/0°. (ii) POCl<sub>3</sub>/reflux 3 h. (iii) MeOH/HCl<sub>(g)</sub>/reflux 2 h.

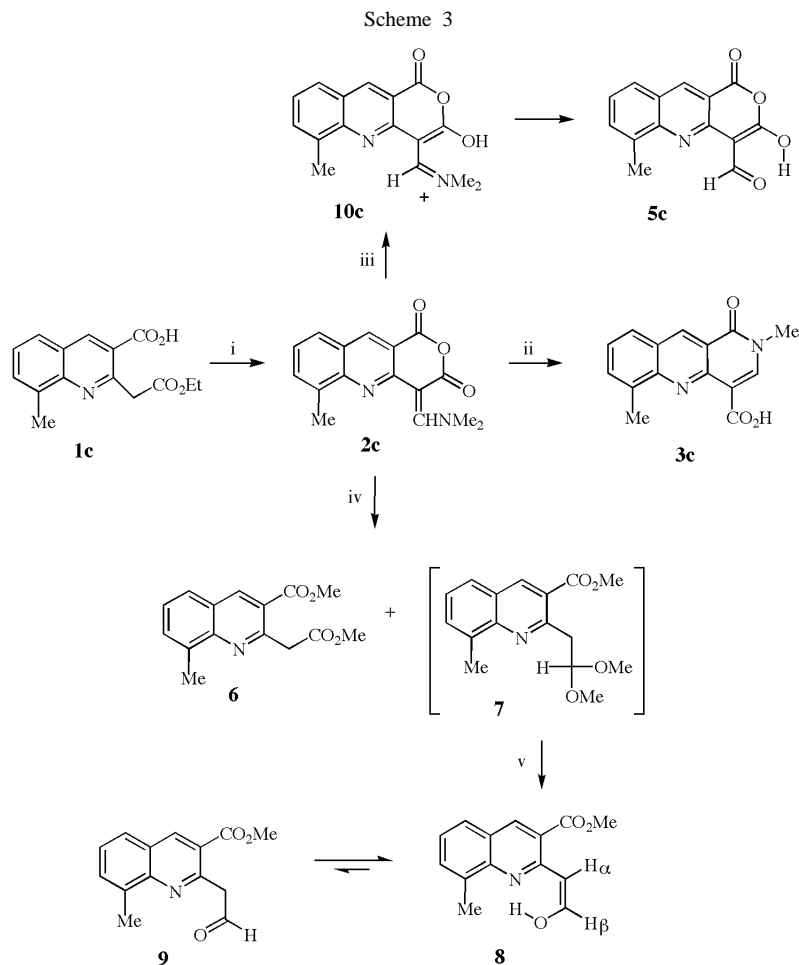
The initial reaction, *i.e.*, formation of **2** shows differences for the two classes. Compound **2a** is soluble in the reaction mixture and only separates when water is added, while **2b**

Scheme 2



(i) POCl<sub>3</sub>/DMF/0°. (ii) POCl<sub>3</sub>/reflux 16 h. (iii) MeOH/HCl<sub>(g)</sub>/reflux 2 h or c.HCl/reflux 2 h. (iv) Boil in HOAc or DMSO/100°

and **2c** precipitate directly [5]. The literature reports that if the dimethyl formamide/phosphoryl chloride reaction mixture containing **2b** is heated at 100° for 6 hours, then diluted with water and the product recrystallized from acetic acid, compound **3b** is formed [4]. We believe this to be incorrect and that the nmr data were misinterpreted. In our hands, the insoluble **2b** was unchanged during the heating process, but the attempted recrystallization resulted in formation of the



hydroxy-aldehyde **5b**. The same clean change could be seen when a solution in dimethyl sulfoxide in an nmr tube was heated at  $100^\circ$  for 2 hours. This might occur as the preferred reaction through hydrolysis of a possible iminium intermediate (**10**). The structure of **5b** followed from microanalysis, molecular weight and nmr data (Aldehyde: C, 186.9; H, 9.73. Hydroxy: deuterium oxide exchangeable H, 14.7 ppm).

Exactly parallel behaviour was found for the quinoline analogue **2c** though a slightly longer heating time in acetic acid was required, and **5c** was formed in quantitative yield.

Formation of the target **3** was achieved in all three cases by heating **2** in sufficient boiling phosphoryl chloride to achieve dissolution of **2**, but here too the details varied between compounds. For **2a**, reaction for 3 hours, followed by dilution with water, gave **3a** as reported [1]. However, the analogous **3b** is quite water soluble and requires a modified workup to achieve its isolation (further evidence that the previously reported product was not **3b**). In fact, the main product from this reaction of **2b** was the

highly water soluble quinolizinium species **11** (see further below). The quinoline compound **2c** required 48 hours heating for its complete conversion; **3c** was essentially insoluble in water and so was readily isolated like the benzo compound **3a**.

Intermediate **2a** undergoes a second interesting conversion, in methanol saturated with hydrogen chloride, when **4** is formed in high yield [2]. However, again the aza analogues show different behaviour and, in these cases, only products from isocoumarin ring cleavage were detected.

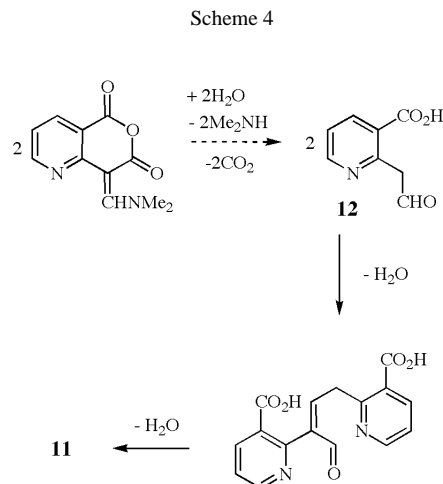
For example, reaction of **2c** in methanol saturated with hydrogen chloride followed by an aqueous acid workup gave a mixture of **8** and **6**. The ratio was variable and **8** appeared to be favoured by long, vigorous passage of hydrogen chloride (highest ratio found was 2:1). In one of the early reactions, a milder workup revealed the presence of a third product. A sample was separated by tlc and was assigned structure **7**, the acetal precursor of **8**, from characteristic  $^1\text{H}$  nmr peaks and a high resolution mass spectrum.

Nmr investigation led to the formulation of **8** in this enol form; the signal for the deuterium oxide exchangeable, hydrogen bonded hydroxyl proton ( $\delta$  16.2) in dilute solution in deuteriochloroform was a doublet, and the chemical shifts and splitting pattern of d (H- $\alpha$ ), t (H- $\beta$ ), d (OH) suggested this assignment. An HMBC experiment confirmed this structure, with  $^3J_{\text{CH}}$  coupling evident for C-3/H- $\alpha$ , C-2/H- $\beta$ , C- $\alpha$ /HO. Also of interest was additional  $^3J_{\text{CH}}$  coupling from HO to C-3 and C-4a, evidently transmitted through the NH hydrogen bond. Some of another compound, assigned as the keto tautomer **9** was also present in dimethyl sulfoxide solution; nmr peaks for the CH<sub>2</sub> and CHO groups were characteristic. The equilibrium position was dependent on temperature; the amount of **9** changed from c 10% at 20° to c 40% at 80°. This tautomerism was also reflected in the observation that H- $\alpha$  in **8** exchanged slowly with deuterium oxide.

The most unexpected reaction came from the methanol/hydrogen chloride treatment of the pyrido compound **2b**, with isolation of the novel quinolizinium species **11** (it can also be formulated as a zwitterionic form in the pyridine ring). This highly water soluble compound could be recrystallized from ethanol but underwent hydrate formation on the filter (became sticky and then hardened again) and microanalytical results were inconsistent. The electro-spray mass spectrum indicated that two molecules of **2b** had combined; molecular ion peaks were observed in both positive and negative ion modes, with the latter also containing a strong M-45 peak indicative of unusually facile decarboxylation. The structure was then assigned from nmr data. Nine aromatic hydrogens bound to carbons were present. In the  $^{13}\text{C}$  nmr spectrum, two quaternary carbons did not display while the two carbonyl carbons (one especially) were broadened, consistent with protonation equilibria involving the carboxy groups. From a COSY spectrum and characteristic splitting pattern in the  $^1\text{H}$  spectrum, the adjacent H-4',5',6' arrangement of the pendant pyridine ring was revealed. The remaining six CH groups had proton and carbon chemical shifts which agreed well with literature values for quinolizinium species [6]. COSY, HMQC and HMBC ( $^3J_{\text{CH}}$  coupling) experiments allowed for the assignment of these six hydrogens and the conclusion that the pyridine substituent was attached at position 7.

It seems almost essential for the mechanism to involve hydrolysis (Scheme 4); an intermediate such as **12** could dimerise by way of an aldol condensation, with subsequent dehydrative cyclization to **11**. The only source of water is the reaction workup, and it then transpired that the simplest means of obtaining **11** was to reflux **2b** in concentrated hydrochloric acid! It was at this point that a reinvestigation of the aqueous residue from the isolation of **3b** from the phosphoryl chloride reaction referred to above, revealed the presence of **11** here too.

The above results have revealed some surprising differences between the reactions of three variations on the



common **2** structure. Details of the mechanistic differences between the benzo and hetero molecules have not been elucidated but it seems clear that the presence of the aza function changes the bond of **2** which is cleaved in some of the reactions, relative to the situation in the benzo analogue.

## EXPERIMENTAL

Nmr spectra were recorded on a Bruker AM-300 spectrometer operating at 300.13 MHz ( $^1\text{H}$ ) and 75.47 MHz ( $^{13}\text{C}$ ) and a Bruker DRX-400 spectrometer operating at 400.13 MHz ( $^1\text{H}$ ) and 100.62 MHz ( $^{13}\text{C}$ ) and chemical shifts are reported as  $\delta$  values (ppm) relative to tetramethylsilane. COSY spectra were recorded on the AM-300 spectrometer using the pulse program COSY.AUR from the Bruker library. HMQC and HMBC spectra were recorded on the DRX-400 spectrometer using the pulse programs INV4GSTP and INV4GSLPLRND, respectively. Electro-spray mass spectra were obtained on VG Bio-Q or Perkin-Elmer Sciex API-300 triple quadrupole mass spectrometers, using methanol as mobile phase. EI and LSI (3-nitrobenzyl alcohol as liquid matrix) mode high-resolution mass spectra were obtained by Dr N. Davies, University of Tasmania. Microanalyses were carried out at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

Ethyl (3-Carboxy-8-methylquinolin-2-yl)acetate (**1c**).

2-Chloro-8-methylquinoline-3-carboxaldehyde [7] (3.0 g) was dissolved in hot *t*-butyl alcohol (300 ml), cooled to room temperature and 2-methylbut-2-ene (20 ml) was added. A solution of sodium chlorite (11.0 g) and sodium dihydrogen phosphate (11.0 g) in water (100 ml) was added dropwise, with stirring, over 10 minutes and the mixture was stirred at room temperature for a further 3 hours. Most of the solvent was removed at reduced pressure, water (200 ml) was added and the solution was acidified with concentrated hydrochloric acid. The precipitate was collected by filtration and washed with water to give 2-chloro-8-methylquinoline-3-carboxylic acid as a pale yellow solid (3.1 g, 96%), mp >298° (dec. after forming prisms above 270°);  $^1\text{H}$  nmr (dimethyl sulfoxide- $d_6$ ):  $\delta$  2.66 (s, 3H, CH<sub>3</sub>), 7.60 (t, 1H, J = 7.6 Hz), 7.77 (d, 1H, J = 6.9 Hz), 7.98 (d, 1H, J = 8.0 Hz), 8.86 (s, 1H).

This was reacted with ethyl acetoacetate, sodium ethoxide and copper acetate by the method reported for the pyrido analogue [8] to give **1c** as a pink solid (69%), mp 120-122° (from acetonitrile); <sup>1</sup>H nmr (deuteriochloroform): δ 1.28 (t, 3H, J = 7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.78 (s, 3H, C8-CH<sub>3</sub>), 4.21 (q, 2H, J = 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 4.47 (s, 2H), 7.47 (t, 1H, J = 7.5 Hz), 7.65 (d, 1H, J = 6.8 Hz), 7.74 (d, 1H, J = 8.1 Hz), 8.91 (s, 1H).

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>4</sub>: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.48; H, 5.88; N, 5.55.

#### 4-(Dimethylaminomethylene)isochroman-1,3-dione [1] (**2a**).

Phosphoryl chloride (2 ml) was added, with stirring, to a solution of homophthalic acid (2.0 g) in dimethylformamide (10 ml) at 0°. The mixture was stirred for a further 1 hour, then poured onto ice/water and the precipitate was collected by filtration and washed with water to give the product as a yellow solid (1.9 g, 86%), mp 142° (lit [1] 144-145°), sufficiently pure for further reaction; <sup>1</sup>H nmr (deuteriochloroform): δ 3.33 (s, 6H, CH<sub>3</sub>), 7.14-7.20 (m, 2H), 7.52 (t, 1H, J = 7.6 Hz), 7.87 (s, 1H), 8.12 (d, 1H, J = 8.5 Hz).

#### 8-Dimethylaminomethylene-8H-pyrano[4,3-*b*]pyridine-5,7-dione (**2b**).

This was prepared from **1b** [8], as for **2a**. The yellow solid which separated from the reaction mixture was collected by filtration and washed with little cold dichloromethane to give the product (86%), mp >170° (dec.) [9]; <sup>1</sup>H nmr (dimethyl sulfoxide-*d*<sub>6</sub>) [10]: δ 3.25 (s, 3H, CH<sub>3</sub>), 3.54 (s, 3H, CH<sub>3</sub>), 7.20 (dd, 1H, J = 7.8, 5.0 Hz, H-3), 8.27 (dd, 1H, J = 7.8, 1.5 Hz, H-4), 8.66 (dd, 1H, J = 5.0, 1.5 Hz, H-2), 8.75 (s, 1H, =CHN); <sup>13</sup>C nmr (dimethyl sulfoxide-*d*<sub>6</sub>): δ 44.8 (CH<sub>3</sub>), 48.5 (CH<sub>3</sub>), 85.7 (C-8), 113.2 (C-4a), 118.6 (C-3), 141.5 (C-4), 150.7 (C-2), 154.0 (C-8a), 156.9 (C-7), 161.3 (=CHN), 161.5 (C-5).

#### 4-Dimethylaminomethylene-6-methyl-4H-pyrano[4,3-*b*]quinoline-1,3-dione (**2c**).

This was prepared from **1c**, as for **2a**. The orange solid which separated from the reaction mixture was collected by filtration and washed with little cold dichloromethane to give the product (87%), mp >295° (dec. - after forming needles >280°) [9]; <sup>1</sup>H nmr (dimethyl sulfoxide-*d*<sub>6</sub>): δ 2.69 (s, 3H, CH<sub>3</sub>), 3.30 (s, 3H, NCH<sub>3</sub>), 3.59 (s, 3H, NCH<sub>3</sub>), 7.36 (t, 1H, J = 7.6 Hz, H-3), 7.68 (d, 1H, J = 7.0 Hz), 7.89 (d, 1H, J = 8.1 Hz), 8.81 (s, 1H), 8.93 (s, 1H).

#### 2-Methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid (**3a**).

Compound **2a** (0.5 g) in phosphoryl chloride (10 ml) was heated under reflux for 3 hours (dissolution occurred immediately on heating). The solution was poured onto crushed ice and the precipitate was collected by filtration to give the product as a white solid (0.35 g, 81%), mp >240° (dec. with decarboxylation) (lit [1] 262-263°); <sup>1</sup>H nmr (dimethyl sulfoxide-*d*<sub>6</sub>/deuteriochloroform): δ 3.57 (s, 3H, CH<sub>3</sub>), 7.42 (t, 1H, J = 7.9 Hz), 7.62 (t, 1H, J = 8.7 Hz), 8.19 (s, 1H, H-3), 8.29 (d, 1H, J = 7.9 Hz), 8.81 (d, 1H, J = 8.4 Hz).

#### 6-Methyl-5-oxo-5,6-dihydro-[1,6]naphthyridine-8-carboxylic Acid (**3b**).

Compound **2b** (0.5 g) in phosphoryl chloride (50 ml) was heated under reflux for 16 hours (dissolution occurred slowly during the heating). The phosphoryl chloride was removed at reduced pressure and water (30 ml) was added. The solution was neutralized with 10% sodium hydroxide and extracted with chloroform (× 5). The combined organic extracts were dried over magnesium sulfate and the solvent was removed at reduced pressure. The residual solid was recrystallized from toluene to give the product as a brown solid (0.09 g, 19%), mp >230° (dec. after forming needles >200°). <sup>1</sup>H nmr (deuteriochloroform): δ 3.70 (s, 3H, CH<sub>3</sub>), 7.57 (dd, 1H, J = 8.0, 4.6 Hz, H-7), 8.56 (s, 1H, H-3), 8.78-8.88 (m, 2H), 15.10 (s, 1H, COOH).

*Anal.* Calcd. for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>: C, 58.82; H, 3.95. Found: C, 59.17; H, 3.88.

The water of the aqueous layer of the above workup was removed at reduced pressure. Soxhlet extraction of the residue with ethanol gave **11** (0.25 g, 74%) (for data see below).

#### 2,6-Dimethyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxylic acid (**3c**).

Compound **2c** (0.15 g) in phosphoryl chloride (50 ml) was heated under reflux for 48 hours (dissolution occurred slowly during the heating). The phosphoryl chloride was removed at reduced pressure and water (30 ml) was added. The precipitate that formed was collected by filtration and recrystallized from dimethyl sulfoxide to give the product as a yellow solid (0.10 g, 70%), mp >300° (formed cubes >290°); <sup>1</sup>H nmr (dimethyl sulfoxide-*d*<sub>6</sub>): δ 2.75 (s, 3H, CH<sub>3</sub>), 3.67 (s, 3H, NCH<sub>3</sub>), 7.67 (t, 1H, J = 7.7 Hz, H-8), 7.95 (d, 1H, J = 6.6 Hz), 8.25 (d, 1H, J = 8.1 Hz), 8.83 (s, 1H), 9.52 (s, 1H), 16.03 (s, 1H, COOH).

*Anal.* Calcd. for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>·0.2H<sub>2</sub>O: C, 66.27; H, 4.60; N, 10.30. Found: C, 66.59; H, 4.40; N, 10.36.

#### Methyl 1-Oxo-1H-isochromene-4-carboxylate (**4**).

Dry hydrogen chloride gas was passed through a stirring solution of **2a** (0.5 g) in methanol (15 ml) at room temperature for 2 hours. The solution was heated under reflux for 2 hours and the solvent was removed at reduced pressure. Water was added to the residue and the mixture was extracted with chloroform (× 3). The combined organic extracts were dried over magnesium sulfate and the solvent was removed at reduced pressure to give the product as a white solid (0.37 g, 79%), mp 96° (from methanol/water) (lit [2] 97-98°); <sup>1</sup>H nmr (deuteriochloroform): δ 3.83 (s, 3H, CH<sub>3</sub>), 7.47 (t, 1H, J = 7.3 Hz), 7.71 (t, 1H, J = 7.4 Hz), 8.08 (s, 1H, H-3), 8.19 (d, 1H, J = 7.6 Hz), 8.51 (d, 1H, J = 8.2 Hz); <sup>13</sup>C nmr (deuteriochloroform): δ 51.9 (CH<sub>3</sub>), 109.6 (C), 120.1 (C), 125.1 (CH), 128.8 (CH), 129.6 (CH), 133.2 (C), 135.1 (CH), 152.4 (CH), 160.4 (C), 164.2 (C).

#### 7-Hydroxy-5-oxo-5H-pyrano[4,3-*b*]pyridine-8-carboxaldehyde (**5b**).

(a) A mixture of **2b** (0.2 g) and acetic acid (50 ml) was heated under reflux for 10 minutes. Solid was present throughout and, after cooling, this was collected by filtration to give the yellow product (0.15 g, 86%), mp >260° (dec.) (from methanol); <sup>1</sup>H nmr (dimethyl sulfoxide-*d*<sub>6</sub>) [10]: δ 7.36 (t, 1H, J = 6.8 Hz, H-3), 8.56 (dd, 1H, J = 6.2, 1.4 Hz, H-2), 8.69 (dd, 1H, J = 8.0, 1.4 Hz, H-4), 9.74 (s, 1H, CHO), 14.74 (broad s, 1H, OH); <sup>13</sup>C nmr (dimethyl sulfoxide-*d*<sub>6</sub>): δ 90.3 (C-8), 115.2 (C-4a), 117.4 (C-3), 144.2 (C-2), 145.3 (C-4), 150.1 (C-8a), 160.2 (C-5), 161.8 (C-7), 186.9 (CHO). ESMS: *m/z* 190 (M-1).

*Anal.* Calcd. for C<sub>9</sub>H<sub>5</sub>NO<sub>4</sub>: C, 56.55; H, 2.64; N, 7.33. Found: C, 56.59; H, 2.53; N, 7.38.

(b) Compound **2b** in dimethyl sulfoxide-*d*<sub>6</sub> in an nmr tube was heated at 100° for 16 hours to give an nmr spectrum identical with that above.

3-Hydroxy-6-methyl-1-oxo-1*H*-pyrano[4,3-*b*]quinoline-4-carboxaldehyde (**5c**).

Compound **2c** was treated as for the preparation of **5b**. Method (a) (20 min reflux-solid was present throughout) gave the product as a yellow solid (100%), mp >300° (from dimethyl sulfoxide); <sup>1</sup>H nmr (dimethyl sulfoxide-*d*<sub>6</sub>) [10]: δ 2.65 (s, 3H, CH<sub>3</sub>), 7.61 (t, 1H, J = 7.8 Hz, H-8), 7.94 (d, 1H, J = 7.2 Hz, H-7), 8.14 (d, 1H, J = 8.0 Hz, H-9), 9.36 (s, 1H, H-10), 9.86 (s, 1H, CHO), 14.94 (s, 1H, OH); <sup>13</sup>C nmr (dimethyl sulfoxide-*d*<sub>6</sub>): δ 15.3 (CH<sub>3</sub>), 91.3 (C-4), 113.6 (C-10a), 122.8 (C-9a), 126.0 (C-6), 126.1 (C-8), 128.6 (C-9), 136.1 (C-5a), 136.6 (C-7), 146.0 (C-10), 149.9 (C-4a), 159.0 (C-1), 160.5 (C-3), 187.9 (CHO). ESMS: *m/z* 254 (M-1).

Anal. Calcd. for C<sub>14</sub>H<sub>9</sub>NO<sub>4</sub>: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.94; H, 3.50; N, 5.54.

Method (b) (2 hours at 100°) gave the same result.

Methyl (3-Methoxycarbonyl-8-methylquinolin-2-yl)acetate (**6**), Methyl 2-(*cis*-2-Hydroxyvinyl)-8-methylquinoline-3-carboxylate (**8**) and Methyl 8-Methyl-2-(2-oxoethyl)quinoline-3-carboxylate (**9**).

Dry hydrogen chloride gas was passed through a stirring suspension of **2c** (0.50 g) in methanol (200 ml) at room temperature; a clear solution formed during 2 hours. This was heated under reflux for 2 hours and the solvent was removed at reduced pressure. Hydrochloric acid (10%) was added to the residue and stirred for 5 minutes. The solution was then neutralized with 10% sodium hydroxide and extracted with chloroform (× 3). The combined organic extracts were dried over magnesium sulfate and the solvent was removed at reduced pressure. The residual semisolid (0.40 g) was very predominantly **6** and **8** (1:2). Preparative tlc of a small sample (silica; chloroform) gave:

Compound **6** (R<sub>f</sub> = 0.45) as a white solid, mp 79-81°; <sup>1</sup>H nmr (deuteriochloroform): δ 2.76 (s, 3H, CH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.44 (s, 2H, CH<sub>2</sub>), 7.44 (t, 1H, J = 7.5 Hz, H-6), 7.62 (d, 1H, J = 6.9 Hz), 7.70 (d, 1H, J = 8.1 Hz), 8.79 (s, 1H, H-4). Hrms (EI): Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>4</sub> (M<sup>+</sup>): 273.1002. Found: 273.0997.

Compound **8** (R<sub>f</sub> = 0.25) as a bright orange solid, which contained 10% **9** at 20° (40% at 80°), and decomposed on standing over one week; <sup>1</sup>H nmr **8** (dimethyl sulfoxide-*d*<sub>6</sub>) [10]: δ 2.49 (s, 3H, CH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 6.40 (d, 1H, J = 4.2 Hz, H-α), 7.34 (t, 1H, J = 7.5 Hz, H-6), 7.66 (d, 1H, J = 7.1 Hz, H-7), 7.79 (d, 1H, J = 7.9 Hz, H-5), 8.53 (t, 1H, J = 3.7 Hz, H-β), 8.75 (s, 1H, H-4), 15.99 (s, 1-H, OH [11]); <sup>13</sup>C nmr **8** (dimethyl sulfoxide-*d*<sub>6</sub>): δ 16.7 (CH<sub>3</sub>), 52.5 (OCH<sub>3</sub>), 93.6 (C-α), 119.2 (C-3), 121.8 (C-4a), 124.6 (C-6), 126.9 (C-8), 127.4 (C-5), 134.1 (C-7), 138.9 (C-8a), 142.7 (C-4), 152.0 (C-2), 164.5 (CO), 176.3 (C-β).

Compound **9**, with <sup>1</sup>H nmr **9** (dimethyl sulfoxide-*d*<sub>6</sub>) (these signals could be seen at the 10% level in the mixture with **8**): δ 2.67 (s, 3H, CH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 4.41 (s, 2H, CH<sub>2</sub>), 7.55 (t, 1H, J = 7.4 Hz, H-6), 7.73 (d, 1H, J = 6.9 Hz), 7.97 (d, 1H, J = 8.0 Hz), 8.93 (s, 1H, H-4), 9.90 (s, 1H, CHO).

Methyl 2-(2,2-Dimethoxyethyl)-8-methylquinoline-3-carboxylate (**7**).

Compound **2c** was reacted as for the preparation of **8** but, after removal of the methanol, water was added to the residue and the solution was immediately neutralized with 10% sodium hydroxide. After extraction with chloroform (× 3), the combined organic extracts were dried over magnesium sulfate and the solvent was

removed at reduced pressure to give a mixture containing **6**, **7** and **8** (1:1:1). Preparative tlc of a small sample (silica; chloroform) gave **7** (R<sub>f</sub> = 0.5) as a colorless semi solid; <sup>1</sup>H nmr (deuteriochloroform): δ 2.92 (s, 3H, CH<sub>3</sub>), 3.40 (s, 6H, 2 × OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.02 (d, 2H, J = 5.1 Hz, C2-CH<sub>2</sub>), 5.07 (t, 1H, J = 5.1 Hz, C2-CH<sub>2</sub>-CH), 7.50 (t, 1H, J = 7.6 Hz, H-6), 7.68 (d, 1H, J = 6.9 Hz), 7.73 (d, 1H, J = 8.1 Hz), 8.76 (s, 1H, H-4). Hrms (LSI): Calcd. for C<sub>16</sub>H<sub>20</sub>NO<sub>4</sub> ((M+H)<sup>+</sup>): 290.1393. Found: 290.1380.

7-(3-Carboxypyridin-2-yl)quinolizinium-1-carboxylate Inner Salt (**11**).

(a) A solution of **2b** (0.50 g) in concentrated hydrochloric acid (5 ml) was heated under reflux for 2 hours, then neutralized with sodium hydroxide and evaporated to dryness at reduced pressure. Soxhlet extraction of the residue with ethanol gave the product as a brown solid (0.30 g, 89%), mp >240° (dec.) (from moist ethanol- the sample initially went sticky and then hardened); <sup>1</sup>H nmr (methanol-*d*<sub>4</sub>) [10]: δ 7.56 (dd, 1H, J = 7.5, 4.7 Hz, H-5'), 8.01 (t, 1H, J = 6.9 Hz, H-3), 8.17 (d, 1H, J = 7.6 Hz, H-4'), 8.58-8.61 (m, 2H, H-2, H-8), 8.71 (d, 1H, J = 3.1 Hz, H-6'), 9.25 (d, 1H, J = 6.4 Hz, H-4), 9.40 (d, 1H, J = 9.1 Hz, H-9), 9.47 (s, 1H, H-6); <sup>13</sup>C nmr (methanol-*d*<sub>4</sub>): δ 124.5 (C-3), 125.5 (C-5'), 126.5 (C-9), 137.3 (C-6), 137.7 (C-2), 138.2 (C-7), 138.5 (C-4), 138.68 (C-4'), 138.72 (C-8), 142.6 (C-9a), 150.7 (C-2', C-6'), 169.4 (C1-CO), 174.0 (C3'-CO) (C-1 and C-3' were not observed); ESMS: *m/z* (+ mode) 295 (M+1); (- mode) 293 (M-1), 249 (M-CO<sub>2</sub>-1).

Anal. Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>·2H<sub>2</sub>O: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.34; H, 3.42; N, 8.83.

(b) Dry hydrogen chloride gas was passed through a stirring suspension of **2b** (0.50 g) in methanol (150 ml) at room temperature; a clear solution formed during 2 hours. This was heated under reflux for 2 hours and the solvent was removed at reduced pressure. Water was added to the residue and the mixture was neutralized with 10% sodium hydroxide and evaporated to dryness at reduced pressure. Soxhlet extraction of the residue with ethanol gave the product (0.21 g, 62%), identical with that from (a).

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[9] Recrystallization was not attempted due to the low solubility and thermal instability of the compound.

[10] Nmr assignments were made from COSY (**11** only), HMQC and HMBC experiments.

[11] This signal appears as a doublet in dilute deuteriochloroform solution.