Synthesis of some Benzo[*b*][1,8] and [1,5]naphthyridines

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A series of carboxylic acid derivatives of the title compounds have been prepared as precursors of potential anti-tumor compounds, by annulation of 2-methylcyclohexanone to the appropriate aminopyridinecarboxaldehyde followed by aromatization and oxidation of the methyl group.

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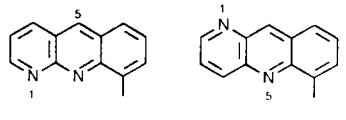
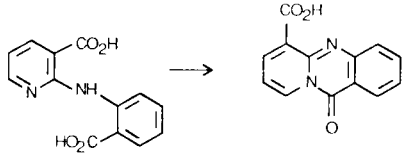
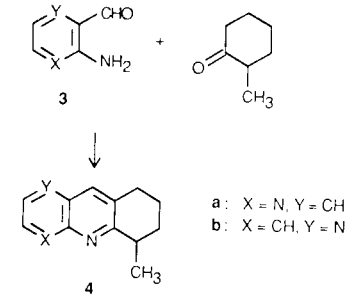
As part of a program on the preparation of potential anti-tumor heterocycles, we wished to include some "aza-acridines" in the series, specifically, compounds containing a carboxylic acid function peri to the acridine nitrogen. Series **1** and **2** are two of the isomeric possibilities but there were problems in applying the standard acridine synthesis through an intermediate *N*-hetarylanthranilic acid. For series **1**, the cyclization occurs preferentially onto the pyridine nitrogen, as shown, to give a pyridoquinazoline [1]. Also, attempts to prepare some analogous intermediates required for series **2** were unsuccessful [2]. This paper reports the results of a different strategy in which a methylcyclohexane ring is annulated to an aminopyridinecarboxaldehyde by the Friedländer synthesis, with subsequent aromatization and then manipulation of the methyl group. The synthesis of the two series confirms the generality of the method though there were some small but experimentally important differences between the two.



1 **2**



2-Aminopyridine-3-carboxaldehyde **3a** was prepared by a minor modification of a literature method [3]. The isomeric **3b** is known [4], but without detail, so a preparation is given in the Experimental. The literature suggested that the desired reaction was feasible; **3a** has been condensed with cyclohexanone under acid conditions [5] while the 6-position of 2-methylcyclohexanone is the reactive one in base-catalyzed aldol condensation [6]. In our hands, the reaction worked better in base conditions and the nature of the base, its concentration, and reaction time were important variables. The optimum conditions given in the Experimental gave excellent yields of **4a** and **4b**.



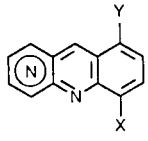
3 **4**

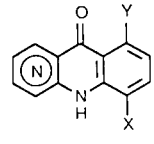
a: X = N, Y = CH
b: X = CH, Y = N

The key step to **1a** proved to be complex and very sensitive to a number of variables. The catalyst chosen was 10% palladium on carbon and the amount of catalyst, temperature, solvent, vigor of reflux and scale of reaction all affected the outcome. Direct nmr monitoring of the mixture indicated a sequence of reactions and, for complete conversion, boiling diphenyl ether was the solvent of choice. Initial oxidation of **4a** at the 8,9-positions to **5** is, surprisingly, the fastest step [evident from the first nmr spectral change from a doublet for the methyl signal (δ 1.5) to a singlet (δ 1.7), while signals for the saturated protons (H-6,7) were still evident] while full aromatization took considerably longer and seems not to involve direct oxidation at the 6,7-positions of **5**. Another intermediate was detected in the reaction mixture during this further heating (methyl singlet at δ 2.1 and additional two-proton singlet at δ 4.0, with loss of the complex of signals for H-6,7) which could be due to isomerism of **5** to **6** prior to the final dehydrogenation to **1a** (methyl singlet at δ 3.0). This sequence is compatible with the observation that acridans or acridines have been isolated from the dehydrogenation of tetrahydroacridines under different conditions [7]. Good yields of **1a** and, likewise, **2a** were only achieved on a 0.5 g scale and a series of these reactions was combined for the workup.

Attempts to oxidise the methyl groups directly to the carboxylic acids with standard strong oxidizing agents were unsuccessful, except for chromic acid oxidation of the nitromethyl compounds **1d** and **2d** (below). However, an alternative oxidation with selenium dioxide gave the appropriate aldehydes. This method of oxidation has occasionally been used with unactivated aryl methyl groups, but vigorous conditions are required. For example, 8-

methylquinoline gave a 49% yield of aldehyde on oxidation without solvent at 190° [8]. From many reactions, conveniently followed by ^{1}H nmr, we found that use of a solvent gave a cleaner oxidation, and the choice of solvent and ratio of reagents were important variables. There was no reaction in dioxan, in diphenyl ether the yields were poor, and vigorously refluxing *o*-dichlorobenzene gave the best results. Oxidation at the 5-position (10-position, series **2**) also occurred, though behaviour in the two series was different. Thus, **2a** with a 3.5 molar ratio of selenium





1a-e, 2a-e

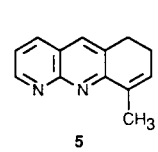
a: X = CH_3, Y = H
b: X = CHO, Y = H
c: X = CO_2H, Y = H
d: X = CH_3, Y = NO_2
e: X = CO_2H, Y = NO_2

1f-j, 2g-h

f: X = CH_3, Y = H
g: X = CHO, Y = H
h: X = CO_2H, Y = H
i: X = CO_2CH_3, Y = H
j: X = CO_2H, Y = NO_2

dioxide gave only **2b**, while 7 moles of selenium dioxide gave only **2g**, both yields being >60%. For **1a**, however, all conditions gave a mixture of **1b** and **1g**, and the best overall yield was achieved with only a 2-fold molar excess of selenium dioxide. The products were readily separated by making use of the greater basicity of **1b**. A noteworthy feature of the ^{1}H nmr spectra was the large difference in chemical shift for the aldehyde protons (*c* 10.1 for **1g**, **2g**; 11.5 for **1b**, **2b**). The lowfield value for the latter may be due to a preferred conformation in which the carbonyl group is oriented away from the adjacent nitrogen lone pair; the aldehydic proton would thus be close to this lone pair. In the oxo analogs, hydrogen bonding between NH and carbonyl oxygen would favor the opposite conformation.

Of the various mild oxidation conditions available for conversion of aldehydes to acids, we initially used aqueous sodium chlorite [9] which we have successfully used in other situations. Oxidation of the aldehyde function in **1b** was successful, but oxidation also occurred at position 5 to give the oxo acid **1h**. The 5-position is in fact the more reactive; some oxo-aldehyde **1g** was isolated from reaction with less oxidant and a shorter reaction time. This ready conversion of an "acridine" to an "acridone" was potentially of interest but it turns out to require the activation of the extra ring nitrogen. Thus, while **1a** was smoothly changed to **1f**, acridine itself was recovered unchanged. The same **1h** was also prepared from **1g** with this reagent, which also served as a proof of structure of **1h**. In the isomeric series, this reaction was used to prepare **2h**.



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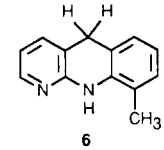

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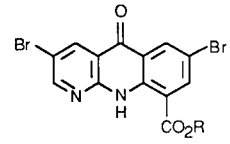
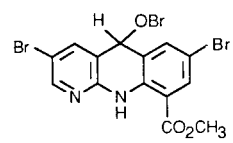


7

a: R = CH_3
b: R = H



8

Oxidation with aqueous alcoholic bromine, reported for facile conversion of aldehydes to esters [10], was even more complicated. Both the aldehyde function and 5-position were again oxidised and, in addition, bromination occurred to give **7a**, though satisfactory microanalytical figures were not obtained for this compound. When *tert*-butyl alcohol replaced methanol, the corresponding acid **7b** was formed. Acridone is known to brominate readily in the equivalent positions [11]. The chlorite and bromine oxidants are probably similar in that they involve nucleophilic oxyhalo species which can add to the activated 5-position. In the bromine case, there was some indirect evidence for such a reaction. The crude product which separated from the reaction mixture in methanol/water solvent was in fact a mixture of **7a** and a species, evidently rather stable in these conditions, but which slowly gave **7a** in chloroform solution or just on standing in the solid form. The ^{1}H nmr spectrum of this compound contained a different set of four aromatic proton signals to **7a** and a characteristic one proton singlet at δ 5.65. A species such as **8** is consistent with such a spectrum and instability.

D-4

Careful control of conditions using alkaline silver oxide [12] successfully achieved the desired conversion of **1b** to **1c** with very little concomitant 5-oxidation. The Ag^+ oxidant acts as an electrophile with the carbonyl group and so there is less chance of reaction at the electrophilic 5-position. When applied to the isomeric **2b**, more vigorous conditions were required for reaction and oxidation at the 10-position did not occur.

Nitration of the methyl compounds **1a** and **2a** under standard electrophilic conditions each gave single products, **1d** and **2d**, readily isolated in high yields. The directing effect of the methyl group has a marked effect as nitration of acridine occurs mainly at the equivalent of the 7-position (of **1**) [13]. These compounds were unreactive to selenium dioxide, but chromic acid gave direct conversion to the acids **1e** and **2e**, the latter requiring more vigorous conditions and giving a poorer yield. Chlorite oxidation of **1e** by the standard route gave the oxo derivative **1j**.

EXPERIMENTAL

^{1}H nmr spectra were recorded in deuteriochloroform, at 90 MHz, unless otherwise specified.

2-Aminopyridine-3-carboxaldehyde (**3a**).

This was prepared by a literature method [3]. Benzoyl peroxide was used as catalyst for *N*-bromosuccinimide bromination of the phthalimido intermediate in refluxing carbon tetrachloride. Progress of the reaction from -CH_3 (δ 2.3 ppm) to -CH_2Br (4.4) to -$CHBr_2$ (6.7) was conveniently monitored by ^{1}H nmr. Additional 0.1 g portions of catalyst were added every 4 hours and the total reaction was *c* 13 hours. The aldehyde had mp 99-100° [from light petroleum (bp 90-110°)] (lit [14] 98-100°); ^{1}H nmr: δ 6.5-7.0 (br s, 2, NH_2), 6.7 (dd, 1, J = 7,4 Hz, H-5), 7.8 (dd, 1, J = 7,1.5 Hz, H-4), 8.75 (dd, 1, J = 4,1.5 Hz, H-6), 9.85 (s, 1, CHO).

3-Aminopyridine-2-carboxaldehyde (**3b**).

3-Aminopyridine-2-carboxylic acid [15] was converted to the ethyl ester according to the liteature method [15]; heating at 100° for 24 hours gave a 71% yield. This (10 g) in dry tetrahydrofuran (600 ml) was treated at <5° with lithium aluminium hydride (3 g). After 1 hour, 50% aqueous tetrahydrofuran (50 ml) was added, the mixture was filtered and the filtrate evaporated to give the intermediate alcohol (7.2 g) as an oil. This was dissolved in chloroform (700 ml), manganese dioxide (23 g) (from manganese sulfate and potassium permanganate [16], and washed with 10% nitric acid before drying) was added, and the mixture was stirred at room temperature for 24 hours. The manganese dioxide was filtered and washed with chloroform, and the filtrate was evaporated to give the yellow aldehyde (5.6 g, 82%), mp 125-127° [from light petroleum (bp 90-110°)] (lit [4] 134°); ^{1}H nmr: δ 6.9-7.3 (m, 2, H-4,5), 8.15 (dd, 1, J = 4,1.5 Hz, H-6), 10.1 (s, 1, CHO).

9-Methyl-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (**4a**).

To a solution of **3a** (0.75 g, 6 mmoles) and 2-methylcyclohexanone (0.81 g, 7.2 mmoles) in warm *tert*-butyl alcohol (30 ml) was added potassium *tert*-butoxide solution (3 ml, 2.5%) and the mixture was refluxed for 1.5 hours. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane, washed with water, dried, the solvent removed, and the residue recrystallized from light petroleum (bp 60-90°) to give the product (1.0 g, 84%), mp 111-112°; ^{1}H nmr: δ 1.55 (d, 3, J = 8 Hz, CH_3), 1.6-2.3 (m, 4, H-7,8), 2.95 (br t, 2, J = 6 Hz, H-6), 3.1-3.4 (m, 1, H-9), 7.3 (dd, 1, J = 8,4 Hz, H-3), 7.75 (s, 1, H-5), 8.0 (dd, 1, J = 8,2 Hz, H-4), 9.0 (dd, 1, J = 4,2 Hz, H-2).

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.8; H, 7.1; N, 14.1. Found: C, 78.6; H, 6.9; N, 14.2.

6-Methyl-6,7,8,9-tetrahydrobenzo[*b*][1,5]naphthyridine (**4b**).

This was obtained in 98% yield as an oil, as for **4a**, and used in further reaction; ^{1}H nmr: δ 1.5 (d, 3, J = 8 Hz, CH_3), 1.8-2.3 (m, 4, H-7,8), 2.9-3.3 (m, 2, H-6,9), 7.5 (dd, 1, J = 8,4 Hz, H-3), 8.0 (s, 1, H-10), 8.3 (d, 1, J = 8 Hz, H-4), 8.85 (d, 1, J = 4 Hz, H-2).

A perchlorate salt was formed in ether/2-propanol and had mp 185-187°.

Anal. Calcd. for $C_{13}H_{14}N_2 \cdot HClO_4$: C, 52.3; H, 5.0; N, 9.4. Found: C, 52.5; H, 5.4; N, 9.5.

9-Methylbenzo[*b*][1,8]naphthyridine (**1a**).

A mixture of **4a** (0.5 g) and 10% palladium on charcoal (0.2 g) in diphenyl ether (10 ml) was heated under reflux, with stirring, for *ca* 4.5 hours, while monitoring the change in the ^{1}H nmr signal for the methyl group. Eight of these reactions were combined, the catalyst was filtered and washed with chloroform and the filtrate was extracted with 10% hydrochloric acid. This extract was washed with chloroform, then basified with 50% sodium hydroxide and extracted five times with ether. The organic extracts were washed with water, dried, and the solvent evaporated to give a yellow powder (3.0 g, 76%), sufficiently pure for further reaction. For microanalysis, a sample was recrystallized from water and had mp 152-153°; ^{1}H nmr: δ 3.0 (s, 3, CH_3), 7.4-7.95 (m, 4, H-3,6,7,8), 8.35 (dd, 1, J = 9,2 Hz, H-4), 8.8 (s, 1, H-5), 9.25 (m, 1, H-2).

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4. Found: C, 80.2; H, 5.1; N, 14.4.

6-Methylbenzo[*b*][1,5]naphthyridine (**2a**).

This was prepared as for **1a**, in 54% yield, mp 123-124° (from water); ^{1}H nmr: δ 2.95 (s, 3, CH_3), 7.5-7.95 (m, 4, H-3,7,8,9), 8.6 (d, 1, J = 9 Hz, H-4), 9.0 (s, 1, H-10), 9.1 (dd, 1, J = 4,2 Hz, H-2).

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4. Found: C, 80.4; H, 5.5; N, 14.8.

Benzo[*b*][1,8]naphthyridine-9-carboxaldehyde (**1b**) and 5-Oxo-5,10-dihydrobenzo[*b*][1,8]naphthyridine-9-carboxaldehyde (**1g**).

A mixture of **1a** (0.5 g) and selenium dioxide (0.57 g) in *o*-dichlorobenzene (25 ml) was heated under reflux until reaction was complete according to ^{1}H nmr analysis (disappearance of methyl signal and appearance of aldehyde signals at 10.1 and 11.7 ppm) (*ca* 9 hours). The mixture was filtered, the solid washed thoroughly with chloroform, and the filtrate extracted with 1:3 hydrochloric acid/water. The acid extract was washed with chloroform, then taken to *p*H 9 with 50% sodium hydroxide solution and extracted with chloroform. This extract was washed with brine, water, dried and the solvent evaporated to give **1b** (0.29 g, 55%), mp 242-244° (from acetonitrile–some solvent was retained even after vacuum drying); ^{1}H nmr: δ 7.4-7.9 (m, 2, H-3,7), 8.3-8.6 (m, 3, H-4,6,8), 9.05 (s, 1, H-5), 9.4 (br s, 1, H-2), 11.7 (s, 1, CHO).

Anal. Calcd. for $C_{13}H_8N_2O \cdot 0.25CH_3CN$: C, 74.2; H, 4.0; N, 14.4. Found: C, 74.1; H, 3.9; N, 14.3.

The dichlorobenzene/chloroform filtrate was then extracted with concentrated hydrochloric acid which was worked up as above to give **1g** (0.07 g, 12%), mp 226-228° (from benzene); ^{1}H nmr: δ 7.2-7.55 (m, 2, H-3,7), 8.1 (dd, 1, J = 7,1.5 Hz, H-4), 8.65-8.8 (m, 3, H-2,6,8), 10.15 (s, 1, CHO), 12.05 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.6; H, 3.6; N, 12.5. Found: C, C, 69.7; H, 3.6; N, 12.3.

Benzo[*b*][1,5]naphthyridine-6-carboxaldehyde (**2b**).

Reaction of **2a** with 3.5 moles of selenium dioxide, as for **1b**, gave the product in 69% yield, mp 193-194° [from light petroleum (bp 90-110°)]; ^{1}H nmr: δ 7.6-7.85 (m, 2, H-3,8), 8.2-8.7 (m, 3, H-4,7,9), 9.0-9.2 (m, 2, H-2,10), 11.55 (s, 1, CHO).

Anal. Calcd. for $C_{13}H_8N_2O$: C, 75.0; H, 3.8; N, 13.5. Found: C, 75.0; H, 4.1; N, 13.5.

10-Oxo-5,10-dihydrobenzo[*b*][1,5]naphthyridine-6-carboxaldehyde (**2g**).

Reaction of **2a** with 7 moles of selenium dioxide, as for **1b**, gave the product in 60% yield, mp 291-293° (from ethanol); ^{1}H nmr: δ 7.25-7.9 (m, 3, H-3,7(9),8), 8.05 (dd, 1, J = 8,2 Hz, H-4), 8.7-8.9 (m, 2, H-2,9(7)), 10.1 (s, 1, CHO), 11.7 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.6; H, 3.6; N, 12.5. Found: C, 69.2; H, 4.2; N, 12.4.

Benzo[*b*][1,8]naphthyridine-9-carboxylic Acid (**1c**).

To an ice-cold solution of silver nitrate (0.97 g) in water (12 ml) was added, dropwise and with vigorous stirring, a solution of sodium hydroxide (0.45 g) in water (12 ml). A solution of **1b** (0.55 g) in ethanol (50 ml) was slowly added to the cold, stirred, silver oxide suspension. After 10 minutes at $<5°$, and a further 30 minutes at room temperature, the mixture was filtered, the solid washed with water, and the filtrate taken to *p*H 1-2 with dilute hydrochloric acid. The yellow solid was filtered, washed with water, dried, and recrystallized from DMSO to give the acid (0.37 g, 62%), mp $>310°$; ^{1}H nmr (DMSO-d_6): δ 7.75-8.05 (m, 2, H-3,7), 8.5-8.9 (m, 3, H-4,6,8), 9.45 (br s, 1, H-2), 9.6 (s, 1, H-5).

Anal. Calcd. for $C_{13}H_8N_2O_2 \cdot 0.25H_2O$: C, 68.3; H, 3.7; N, 12.3. Found: C, 68.2; H, 3.8; N, 12.2.

Benzo[*b*][1,5]naphthyridine-6-carboxylic Acid (**2c**).

This was prepared as for **1c**. After the initial addition at $<5°$, the temperature was raised to 60° for 0.5 hour. In workup, the filtrate was evaporated to a small volume, acidified to *p*H 1-2 and extracted with chloroform to give the acid in 70% yield, mp 263-265° (from 50% aqueous ethanol); ^{1}H nmr: δ 7.75-7.9 (m, 2, H-3,8), 8.35 (d, 1, J = 9 Hz), 8.55 (d, 1, J = 9 Hz), 8.95 (d, 1, J = 9 Hz, H-4), 9.15 (dd, 1, J = 4,2 Hz, H-2), 9.25 (s, 1, H-10).

Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.6; H, 3.6; N, 12.5. Found: C, 70.0; H, 4.2; N, 12.2.

5-Oxo-5,10-dihydrobenzo[*b*][1,8]naphthyridine-9-carboxylic Acid (**1h**).

To a suspension of **1b** (0.2 g) in *tert*-butyl alcohol (22 ml) and 2-methyl-2-butene (5 ml) was added, dropwise over 20 minutes, a solution of 80% sodium chlorite (1.08 g) and sodium dihydrogen phosphate (1.08 g) in water (11 ml). The mixture was stirred overnight and the volatile components were then evaporated under reduced pressure, and the residue was dissolved in water and washed with chloroform. The aqueous layer was taken to *p*H 2 with dilute hydrochloric acid and the solid was filtered, washed with water and recrystallized from ethanol to give the product (0.2 g, 87%), mp 315-317°; ^{1}H nmr (DMSO-d_6): δ 7.0-7.3 (m, 2, H-3,7), 8.2-8.45 (m, 3, H-4,6,8), 8.6 (dd, 1, J = 5,2 Hz, H-2), 11.95 (s, 1, NH).

Anal. Calcd. for $C_{13}H_8N_2O_3 \cdot 0.5H_2O$: C, 62.7; H, 3.6; N, 11.2. Found: C, 62.4; H, 3.1; N, 11.1.

This compound was also prepared, in 90% yield, by analogous oxidation of **1g**.

10-Oxo-5,10-dihydrobenzo[*b*][1,5]naphthyridine-6-carboxylic Acid (**2h**).

This was prepared from **2b**, as for **1h**, in 87% yield, mp $>320°$ (from dimethyl sulfoxide/50% ethanol).

Anal. Calcd. for $C_{13}H_8N_2O_3$: C, 65.0; H, 3.4; N, 11.7. Found: C, 64.8; H, 3.6; N, 11.8.

Methyl 5-Oxo-5,10-dihydrobenzo[*b*[1,8]naphthyridine-9-carboxylate (**1i**).

A mixture of **1h** (0.3 g), concentrated sulfuric acid (3 ml) and methanol (27 ml) was heated under reflux for 6 hours. Unreacted acid (0.2 g) was filtered from the cooled mixture and the filtrate was concentrated, water was added and the whole made basic with ammonium hydroxide and extracted with chloroform. The extract was washed with brine, dried, decolorized with charcoal, and the solvent evaporated to give the ester (0.03 g), mp 204-206° after recrystallization from ethanol; ^{1}H nmr: δ 4.1 (s, 3, OCH_3), 7.2-7.45 (m, 2, H-3,7), 8.5 (dd, 1, J = 8,2 Hz, H-4), 8.6-8.8 (m, 3, H-2,6,8), 12.0 (br s, 1, NH).

Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.1; H, 3.9; N, 11.0. Found: C, 65.8; H, 3.9; N, 10.9.

9-Methyl-6-nitrobenzo[*b*][1,8]naphthyridine (**1d**).

To a solution of **1a** (0.3 g) in concentrated sulfuric acid (6 ml) was added potassium nitrate (0.9 g), with stirring. After being kept at room temperature overnight, the solution was poured onto ice, taken to *p*H 4 with ammonium hydroxide, and extracted with chloroform. The extract was washed with brine, water, dried and the solvent removed to give the product (0.3 g, 81%), mp 207-209° (from ethanol); ^{1}H nmr: δ 3.2 (s, 3, CH_3), 7.6-7.75 (dd, 1, J = 8,4 Hz, H-3), 7.85 (d, 1, J = 8 Hz, H-8), 8.45-8.65 (m, 2, H-4,7), 9.4 (dd, 1, J = 4,2 Hz, H-2), 9.9 (s, 1, H-5).

Anal. Calcd. for $C_{13}H_9N_3O_2 \cdot 0.25H_2O$: C, 64.1; H, 3.9; N, 17.2. Found: C, 64.1; H, 3.8; N, 17.4.

6-Methyl-9-nitrobenzo[*b*][1,5]naphthyridine (**2d**).

This was prepared as for **1d**, in 77% yield, mp 250-252° (from ethanol); ^{1}H nmr: δ 3.0 (s, 3, CH_3), 7.6-7.8 (m, 2, H-3,7), 8.35 (d, 1, J = 8 Hz, H-4), 8.5 (d, 1, J = 9 Hz, H-8), 9.1 (br s, 1, H-2), 9.9 (s, 1, H-10).

Anal. Calcd. for $C_{13}H_9N_3O_2$: C, 65.3; H, 3.8; N, 17.6. Found: C, 65.0; H, 4.2; N, 17.2.

6-Nitrobenzo[*b*][1,8]naphthyridine-9-carboxylic Acid (**1e**).

To a solution of **1d** (0.24 g) in concentrated sulfuric acid (5 ml), potassium dichromate (0.6 g) was added, with stirring, during 30 minutes while maintaining the temperature $<40°$. After 30 minutes at room temperature, the mixture was stirred at 40-50° for 4 hours, then cooled, diluted to 200 ml with ice-water and allowed to stand at 5° for 2 days. The precipitated solid was collected by filtration, washed with water, and dried to give the product (0.14 g, 52%), mp $>320°$ (from DMSO/50% ethanol); ^{1}H nmr (DMSO-d_6): δ 7.8-8.0 (dd, 1, J = 8,4 Hz, H-3), 8.55-8.8 (d + d, 2, J = 8 Hz, H-7,8), 8.9 (d, 1, J = 8 Hz, H-4), 9.45 (br s, 1, H-2), 9.9 (s, 1, H-5).

Anal. Calcd. for $C_{13}H_7N_3O_4 \cdot 1.5H_2O$: C, 52.7; H, 3.4; N, 14.2. Found: C, 53.1; H, 2.8; N, 14.5 [17].

9-Nitrobenzo[*b*][1,5]naphthyridine-6-carboxylic Acid (**2e**).

To a solution of **2d** (0.62 g) in concentrated sulfuric acid (12 ml), potassium dichromate (3.0 g) was added, with stirring, during 30 minutes. The viscous liquid was heated at 70° for 8 hours, then stored at $<5°$ overnight, poured onto ice (to give 200 ml volume) and kept at $<5°$ for 24 hours. The yellow product (0.19 g) was filtered off. Extraction of the filtrate with chloroform gave a second crop (0.02 g, total 30%), mp 280° dec (from ethanol/chloroform); ^{1}H nmr: δ 7.9 (dd, 1, J = 9,4 Hz, H-3), 8.45-8.65 (m, 2, H-4,7(8)), 9.05 (d, 1, J = 9 Hz, H-8(7)), 9.25 (d, 1, J = 4 Hz, H-2), 10.05 (s, 1, H-10).

Anal. Calcd. for $C_{13}H_7N_3O_4$: C, 58.0; H, 2.6; N, 15.6. Found: C, 57.7; H, 2.7; N, 15.3.

Methyl 3,7-Dibromo-5-oxo-5,10-dihydrobenzo[*b*][1,8]naphthyridine-9-carboxylate (**7a**).

To solution of **1b** (0.1 g) and sodium hydrogen carbonate (0.84

g) in methanol/water (15 ml, 9:1) was added bromine (0.32 g) in methanol/water (2 ml). The mixture was stirred at room temperature for 5 hours, during which time the solid separated. Water (15 ml) was added, the mixture was refluxed for 0.5 hour (to react any **8**), cooled, and the solid filtered off and recrystallized from ethanol to give the ester (0.14 g, 71%), mp 225-227°; ^{1}H nmr: δ 4.05 (s, 3, CH_3), 8.5 (d, 1, J = 2 Hz), 8.7-8.8 (m, 3), 11.9 (br s, 1, NH).

3,7-Dibromo-5-oxo-5,10-dihydrobenzo[*b*][1,8]naphthyridine-9-carboxylic Acid (**7b**).

Compound **1b** was reacted as above, but in *tert*-butyl alcohol/water and the orange mixture was stirred at room temperature for 24 hours. The solvent was removed at reduced pressure and the residue was dissolved in water and extracted with chloroform. The aqueous layer was taken to *p*H 1-2 with hydrochloric acid to give the acid (52%), mp >320° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 3.2 (br s, H_2O), 8.1, 8.25, 8.45, 8.65 (4 x br s, 4).

Anal. Calcd. for $C_{13}H_6Br_2N_2O_3 \cdot 3H_2O$: C, 34.5; H, 2.6; N, 6.2. Found: C, 34.5; H, 1.9; N, 6.2 [17].

9-Methyl-5-oxo-5,10-dihydrobenzo[*b*][1,8]naphthyridine (**1f**).

This compound was prepared in 92% yield by chlorite oxidation of **1a**, as for **1b** to **1h**, mp 226-228° (from ethanol/water); ^{1}H nmr: δ 2.55 (s, 3, CH_3), 7.1-7.3 (m, 2, H-3,7), 7.5 (d, 1, J = 7 Hz, H-8), 8.3 (d, 1, J = 8 Hz, H-6), 8.6-8.8 (m, 3, H-2,4 + NH).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.3; H, 4.8; N, 13.3. Found: C, 73.8; H, 4.7; N, 13.2.

6-Nitro-5-oxo-5,10-dihydrobenzo[*b*][1,8]naphthyridine-9-carboxylic Acid (**1j**).

To a suspension of finely ground **1e** (0.6 g) in *tert*-butyl alcohol (60 ml) and 2-methyl-2-butene (15 ml) was slowly added a solution of 80% sodium chlorite (1.2 g) and sodium dihydrogen phosphate (1.2 g) in water (33 ml) and the mixture was then stirred at room temperature for 3 days. The solvents were then evaporated under reduced pressure, the residue was suspended in water, taken to *p*H 1 with dilute hydrochloric acid. The bright yellow solid was filtered off and washed with water and ethanol to give the acid (0.55 g, 87%), mp >320° (from DMSO/ethanol); ^{1}H nmr (DMSO-d_6): δ 7.4-7.7 (m, 2, H-3,8), 8.45-8.7 (m, 2, H-4,7), 8.9 (br s, 1, H-2), 12.6 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_7N_3O_5 \cdot 0.5H_2O$: C, 53.1; H, 2.7; N, 14.3. Found: C, 53.3; H, 2.9; N, 14.6.

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