Synthesis of pyrido[2,3-*c*]acridines

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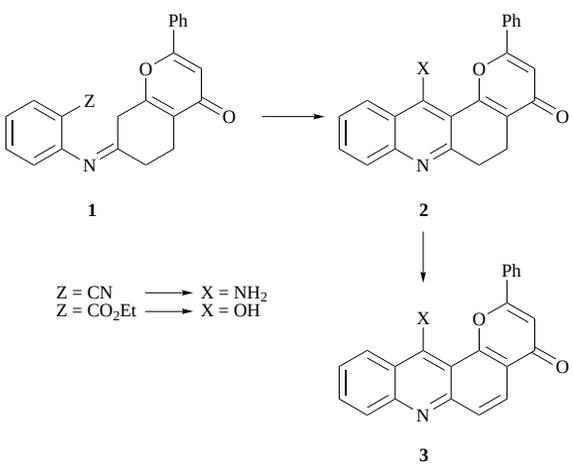
1 PERKIN

The synthesis of a range of pyrido[2,3-*c*]acridines 10, 11, 18 and 20, *via* imine formation from pyrido-fused cyclohexanones 6, 14 and 16 and anthranilonitrile or anthranilic acid esters, followed by base-catalysed cyclisation and aromatisation, is described.

Pyrido-fused acridines, *e.g.* pyrido[2,3-*c*]acridines, exhibit a broad spectrum of biological activities, including anti-cancer and anti-malarial.[1] We have recently reported the synthesis of the pyranoacridines **3**, *via* the base-catalysed cyclisation of the imines **1** followed by the aromatisation of the dihydro inter-

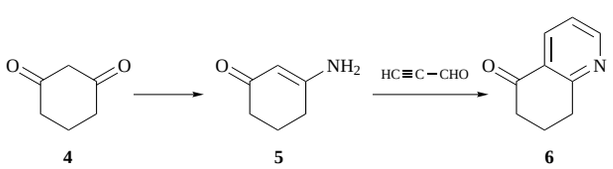


Scheme 1

mediate **2** (Scheme 1);[2] the biological testing of these compounds was also described. We describe here the extension of this imine anion cyclisation methodology to the synthesis of pyrido[2,3-*c*]acridines, and the initial biological testing of some of these compounds.

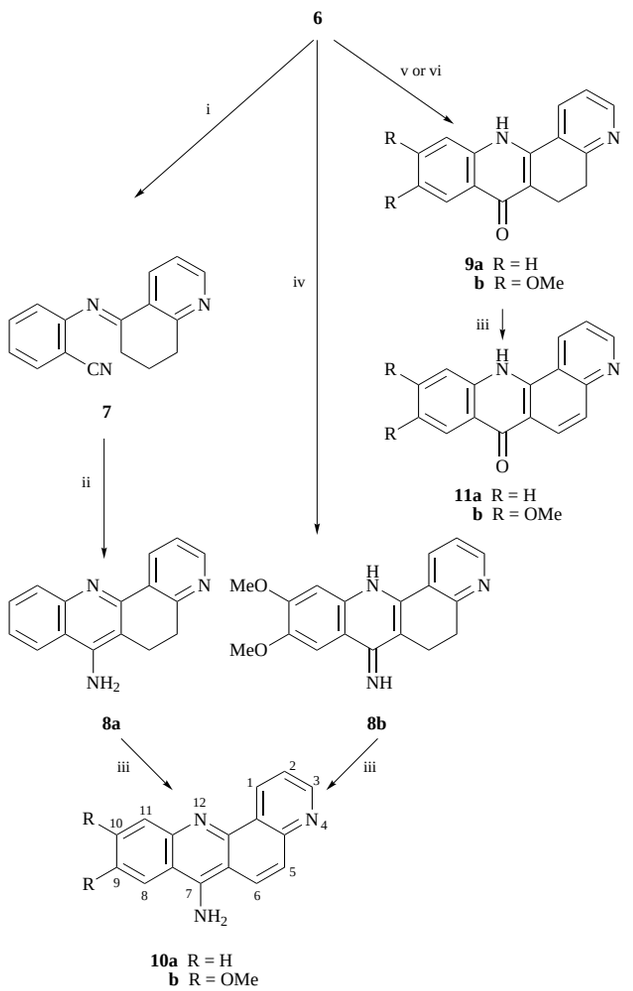
Results and discussion

7-Aminopyrido[2,3-*c*]acridines **10** and pyrido[2,3-*c*]acridin-7(12*H*)-ones **11** were each prepared in four steps, starting from cyclohexane-1,3-dione **4**. Formation of 3-aminocyclohex-2-enone **5**, by the method of Dubas-Sluyter *et al.*,[3] followed by reaction with propynal gave 5,6,7,8-tetrahydroquinolin-5-one **6**[4] (Scheme 2). The condensation of the quinoline **6** with



Scheme 2

anthranilonitrile was then investigated under three different sets of conditions (Scheme 3). Method A involved the formation of the imine **7** under the standard conditions for the azeotropic removal of water. Isolation of the imine **7**, followed by base-



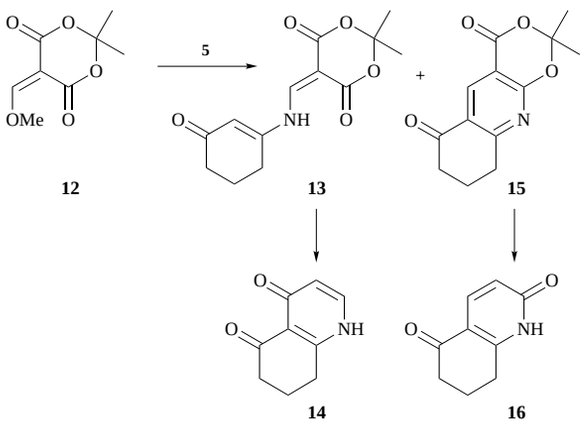
Scheme 3 *Reagents and conditions:* i, 2-$H_2NC_6H_4CN$, $PhCH_3$, PTSA, reflux, 90 h, 35.5%; ii, $NaNH_2$, DME, reflux, 2.5 h, 93%; iii, MnO_2, DMF, reflux; iv, 4,5-dimethoxyanthranilonitrile, $PhCH_3$, PTSA, 16 h reflux, then $NaNH_2$, DME, 15-crown-5, reflux, 65%; v, 2-$H_2NC_6H_4CO_2Et$, $PhCH_3$, PTSA, reflux, then $NaNH_2$, DME, reflux, 63.5%; vi, methyl 4,5-dimethoxyanthranilate, $PhCH_3$, PTSA, reflux, then $NaNH_2$, DME, reflux, 46%.

catalysed cyclisation gave the dihydropyrido[2,3-*c*]pyridine **8a** in 33% yield over the two steps. In method B, the imine **7** was not isolated and the crude product of the initial condensation was used in the cyclisation step to give **8a** (66.5%). Finally, in method C, the quinolone **6** and anthranilonitrile were heated together in polyphosphoric acid to give the pyridoacridine **8a** (30%). In all subsequent cyclisations method B, the one-pot generation/cyclisation of the imine, was thus employed.

7-Imino-9,10-dimethoxy-5,6,7,12-tetrahydropyrido[2,3-*c*]-

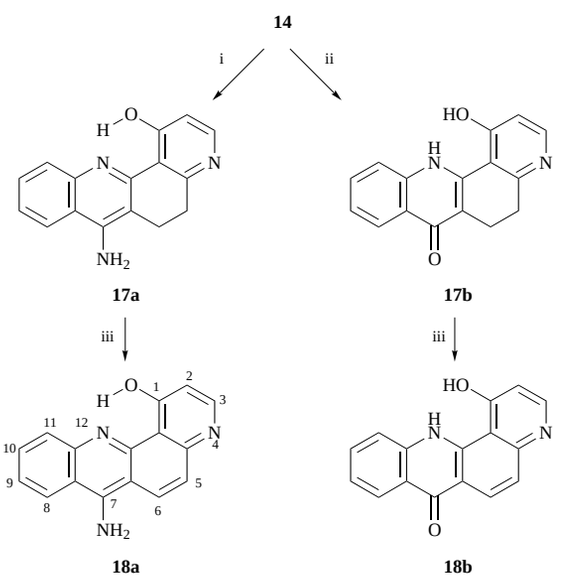
acridine **8b**, 5,6-dihydro- **9a**, and 9,10-dimethoxy-5,6,7,12-tetrapyrido[2,3-*c*]acridin-7-one **9b** were prepared from the quinoline **6** using this methodology (Scheme 3). In one case, the formation of **8b**, it was found that the addition of 15-crown-5 and the use of a longer refluxing time gave an improved yield. Compounds **9a,b** were prepared from the initial condensation of quinoline **6** with the appropriate anthranilate ester.

1,4,5,6,7,8-Hexahydroquinoline-4,5-dione **14** was prepared from the oxocyclohexenylaminomethylene-1,3-dioxane-4,6-dione **13**, itself prepared from methoxymethylene-1,3-dioxane-4,6-dione **12** and the enamine **5**, whilst the 1,2,5,6,7,8-hexahydroquinoline-2,5-dione **16** was prepared from the 6,7,8,9-tetrahydro-4*H*-1,3-dioxino[4,5-*b*]quinoline-4,6-dione **15** (Scheme 4).[5] More substituted dihydropyrido[2,3-*c*]acridines **17**



Scheme 4

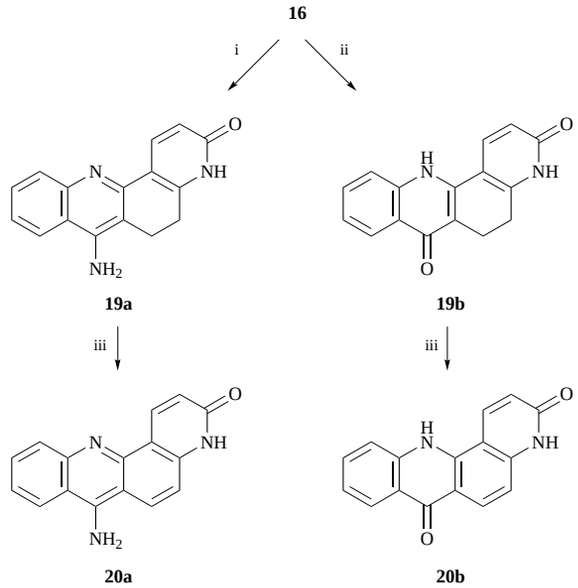
and **19** were then prepared by the condensation of either quinoline-4,5-dione **14** (Scheme 5), or the 2,5-dione **16** (Scheme



Scheme 5 *Reagents and conditions*: i, 2-$H_2NC_6H_4CN$, $PhCH_3$, PTSA, reflux, 24 h, then $NaNH_2$, DME, 16%; ii, 2-$H_2NC_6H_4CO_2Et$, polyphosphoric acid, 240–260 °C, 5 h, 60%; iii, MnO_2, DMF.

6), with the appropriate anthranilonitrile or anthranilate ester.

The IR and ^{1}H NMR spectra of compound **8a** indicates that the compound exists as the amino tautomer on the basis of the following evidence: the presence of symmetrical and asymmetrical stretching absorptions for the primary amine (ν_{max} 3340 and 3223 cm^{-1}) and a signal at δ_H 6.70 (s, exchangeable with D_2O, NH_2). The doublets of doublets corresponding to the 1-H (δ 8.66, J 7.8 and 1.6 Hz) and 3-H (δ 8.50, J 4.8 and 1.6 Hz) can



Scheme 6 *Reagents and conditions*: i, 2-$H_2NC_6H_4CN$, $PhCH_3$, PTSA, reflux, 24 h, then $NaNH_2$, DME, 11%; ii, 2-$H_2NC_6H_4CO_2Et$, polyphosphoric acid, 240–260 °C, 3 h, 33%; iii, MnO_2, DMF.

be clearly identified as they are the most deshielded signals. The 1-H is significantly deshielded with respect to the 3-H, probably due to the combination of *para* and *peri*[6] deshielding effects operating on the 1-H, in contrast to the sole *ortho* deshielding effect operating on the 3-H. In contrast, the compound **8b** appears to exist as the imine tautomer: two signals at δ_H 8.24 and 13.67 (both br s), each integrating to one proton and exchangeable with D_2O, indicate that the NH protons are non-identical and favour the imine structure **8b**. Interestingly, significant upfield shifts were observed for the 1-H ($\Delta\delta$ 0.37), 8-H ($\Delta\delta$ 0.48) and 11-H ($\Delta\delta$ 0.24) signals upon shaking with D_2O, whereas no significant change in the H-3 signal was observed.

The spectra of compounds **9a,b** indicate that these compounds exist in the keto form with a key feature being the presence of a signal at δ 170.6 in the spectrum of **9a** which is consistent with literature values for acridones.[7]

Similarly, the spectra of the more highly substituted derivatives **17** and **19** suggests the structures shown. For example, the ^{1}H NMR spectrum of **17a** suggests that this is the structure adopted, primarily because of a one-proton singlet at δ 17.34, presumably the result of the OH hydrogen being strongly H-bonded to the acridine nitrogen. Compound **19a** appears to exist as the 2-pyridone tautomer, primarily on the basis of the magnitude of the coupling constant between 1-H and 2-H (J 9.4 Hz) which is in good agreement with the reported value for 2-pyridones;[8] also absorption at 1667 cm^{-1} in the IR spectrum is in good agreement with the carbonyl stretching frequencies in 2-quinolones.[9] Compound **19b** also exhibits a coupling constant between the 1- and 2-H characteristic of 2-pyridones, whilst IR absorption at 1675 and 1629 cm^{-1} is in good agreement with the reported frequencies for 2-quinolones and acridones respectively.[8]

All the dihydropyrido[2,3-*c*]acridines were oxidized to the corresponding fully aromatic systems with activated manganese(IV) oxide[10] (10:1, w/w, ratio of MnO_2 to substrate) in refluxing DMF (15–24 h). Once again, the possibility of tautomerism exists, with pyrido[2,3-*c*]acridines **10a,b** existing as the amine tautomers [**10a** ν_{max} 3406 and 3298 cm^{-1} and δ 7.85 (2H, br s, exchangeable with D_2O); **10b** ν_{max} 3463 and 3320 cm^{-1} and δ 7.55–7.71 (4H, m, 2H exchangeable with D_2O, H-2, H-5 or H-6, NH_2)].

The acridone nature of compounds **11a,b** can be justified by the signal at δ 174.3 in the ^{13}C NMR spectrum, which can only be attributed to the carbonyl carbon, and the IR absorption at

Table 1 Inhibition of the spontaneous proliferation of MKN 45 cells by the pyrido[2,3-*c*]acridines **8a** and **10a**

Compound (μM)	Inhibition (%)	Cell viability (%)
8a (1)	12	—
8a (10)	59	>90
10a (1)	80	—
10a (10)	95	>90

ca. 1630 cm^{-1}, which is also reminiscent of the acridone nucleus. A unique feature of the ^1H NMR spectrum of **18a** is the singlet at δ 18.42, exchangeable with D_2O, which can only be attributed to the hydroxy group strongly hydrogen-bonded to the acridine nitrogen. The IR spectrum of **18b** contains only one carbonyl stretch, at 1616 cm^{-1}, and this taken with the two signals at δ 11.44 and 14.61 (both br s) suggests the structure shown.

The magnitude of the coupling constant between the 1-H (δ 9.06, J 9.3 Hz) and 2-H (δ 6.61, J 9.3 Hz) in the ^1H NMR spectrum of **20a** confirms the 2-pyridone nature of this fused pyridine ring, in agreement with the structure of its dihydro precursor. Finally, the magnitude of the coupling constant ($J_{1,2}$ 9.5 Hz) between the 1-H and 2-H signals favours the dione structure for **20b**, as do the two IR carbonyl stretching frequencies, at 1659 and 1625 cm^{-1}, corresponding to carbonyl groups in the pyridones and acridones.

7-Aminopyrido[2,3-*c*]acridine **10a** and its dihydro derivative **8a** were tested as inhibitors of the spontaneous proliferation of a human-derived gastric carcinoma cell line, MKN 45 (Table 1). Both compounds were shown to be reasonably potent inhibitors, with the aromatic and planar **10a** being more active than the dihydro derivative **8a**. This result is in agreement with our previous findings, in which the pyrano[2,3-*a*]acridones exhibited greater biological activity than their dihydro derivatives.[2] Interestingly, cell viability studies showed that neither compound **10a** nor **8a** was cytotoxic at the concentrations employed.

Experimental

Melting points were determined on either a Gallenkamp melting-point apparatus or a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrophotometer. Liquid samples were examined as thin films and solid samples as Nujol mulls on sodium chloride plates. ^1H and ^{13}C NMR spectra were obtained on a Bruker WM360 at 360 and 90 MHz, respectively. Coupling constants are reported in Hz and chemical shifts are reported with respect to $SiMe_4$. Low resolution mass spectra were recorded on a Fisons Instruments VG Platform II and high-resolution spectra were recorded on a VG ZAB-E spectrometer (EPSRC Mass Spectrometry Service Centre, Swansea). Microanalyses for carbon, hydrogen and nitrogen were performed on a Perkin-Elmer 240B Elemental Analyzer. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ plates. Dry column flash and wet column chromatography were carried out using Merck silica gel 60. 1,2-Dimethoxyethane (DME) and tetrahydrofuran (THF) were dried over sodium wire with benzophenone. Toluene was distilled and stored over sodium wire. Dimethyl sulfoxide was dried over calcium hydride and distilled under reduced pressure. Propynal was prepared by the method of Sauer,[11] 3-aminocyclohex-2-enone **5** by the method of Dubas-Sluyter *et al.*,[3] 5,6,7,8-tetrahydroquinolin-5-one **6** by the method of Rimek and Zymalkowski,[4] and 2,2-dimethyl-5-(3′-oxocyclohex-1′-enyl)aminomethylene-1,3-dioxane-4,6-dione **13** 1,4,5,6,7,8-hexahydroquinoline-4,5-dione **14**, 2,2-dimethyl-6,7,8,9,-tetrahydro-4*H*-1,3-dioxino[4,5-*b*]quinoline-4,6-dione **15**, and 1,2,5,6,7,8-tetrahydroquinoline-2,5-dione **16** by the method of Gatta *et al.*[5]

7-Amino-5,6-dihydropyrido[2,3-*c*]acridines

7-Amino-5,6-dihydropyrido[2,3-*c*]acridine 8a. *Method A.*—This involves two steps. (i) 5-(2′-Cyanophenylimino)-5,6,7,8-tetrahydroquinoline **7** was prepared as follows. A mixture of 7,8-dihydroquinoline-5(6*H*)-one **6** (1.34 g, 9.11 mmol), anthranilonitrile (1.08 g, 9.15 mmol), and toluene-*p*-sulfonic acid (0.2 g, 1 mmol) in toluene (50 cm^3) was refluxed for 90 h with azeotropic removal of water. After this, the mixture was concentrated by evaporation of the toluene and the resulting solid was recrystallized from ethyl acetate to give the title compound **7** (0.8 g, 35.5%), mp 161–162 °C (Found: C, 77.6; H, 5.4; N, 16.8. $C_{16}H_{13}N_3$ requires C, 77.7; H, 5.3, N, 17.0%); ν_{max}(Nujol/cm^{-1}) 2217 (C≡N), 1629 (C=N) and 1563; δ_H($CDCl_3$) 2.0 (2H, m, 7-H), 2.5 (2H, t, J 7, H-6), 3.14 (2H, t, J 7, H-8), 6.9 (1H, d, J 8, 3′ or 6′-H), 7.15 (1H, t, J 8, 4′-H), 7.27 (1H, dd, J 8, 4, H-3), 7.55 (1H, t, J 8, 5′-H), 7.63 (1H, d, J 8, 3′ or 6′-H), 8.57 (1H, d, J 8, 4-H) and 8.64 (1H, d, J 4, H-2); δ_C($CDCl_3$) 21.8 (CH_2), 29.8 (CH_2), 32.7 (CH_2), 103.2 (quat), 117.2 (quat), 120.1 (CH), 122.1 (CH), 123.6 (CH), 128.85 (quat), 133.0 (CH), 133.5 (CH), 134.8 (CH), 152.0 (CH), 154.4 (quat), 160.9 (quat) and 167.0 (quat); *m*/*z* (EI) 247 (M^+, 100%), 246 (29), 219 (46), 145 (35), 130 (15), and 118 (11.5).

(ii) Compound **7** (1.05 g, 4.25 mmol) was added to a suspension of sodium amide (0.41 g, 10.62 mmol) in DME (35 cm^3) under nitrogen and refluxed for 2.5 h. The reaction mixture was quenched with 10% aqueous ammonium chloride (60 cm^3) and kept for 30 min at room temperature. After this, the resulting yellow precipitate was filtered off and recrystallized from methanol to give the title compound **8a** (1.0 g, 93%), mp 166–168 °C (Found: C, 72.2; H, 6.1; N, 15.6. $C_{16}H_{13}N_3 \cdot H_2O$ requires C, 72.45; H, 5.7; N, 15.85%); ν_{max}(Nujol/cm^{-1}) 3340, 3223 (NH_2 stretching) 1661, 1613 and 1573 (aromatic); δ_H([$^2H_6$]-DMSO) 3.0 (2H, t, J 7, H-5 or H-6), 3.08 (2H, t, J 7, H-5 or H-6), 6.70 (2H, s, exchangeable with D_2O, NH_2), 7.37–7.41 (2H, m, H-2 and H-9), 7.59 (1H, t, J 7.8, H-10), 7.83 (1H, d, J 8.3, H-8 or H-11), 8.22 (1H, d, J 8.3, H-8 or H-11), 8.50 (1H, dd, J 4.8, 1.6, H-3) and 8.66 (1H, dd, J 7.8, 1.6, H-1); δ_C ([$^2H_6$]-DMSO) 21.0 (CH_2), 30.25 (CH_2), 108.1 (quat), 118.3 (quat), 122.4 (CH), 122.45 (CH), 123.9 (CH), 128.7 (CH), 129.2 (CH), 130.5 (quat), 132.8 (CH), 147.4 (CH), 148.2 (quat), 149.3 (quat), 150.4 (quat) and 158.45 (quat); *m*/*z* (EI) 247 (M^+, 100%), 246 (65), 230 (9), 124 (15), 123 (8), 110 (9.5), 96 (5.5) and 77 (2).

Method B.—A mixture of compound **6** (1.34 g, 9.11 mmol), anthranilonitrile (1.07 g, 9.11 mmol), and toluene-*p*-sulfonic acid (0.17 g, 0.911 mmol) in toluene (50 cm^3) was refluxed for 100 h with azeotropic removal of water. After this, the water was concentrated by removal of the toluene under reduced pressure and the resulting residue was dissolved in dry 1,2-dimethoxyethane (50 cm^3), to which sodium amide (0.89 g, 22.77 mmol) was then added. The reaction mixture was refluxed for 3 h under nitrogen after which it was concentrated by evaporation of the dimethoxyethane. The residue was treated with 10% aqueous ammonium chloride (50 cm^3) and the resulting precipitate was filtered off and recrystallized from methanol to give the title compound **8a** (1.5 g, 66.5%), mp 166–168 °C.

Method C.—A mixture of compound **7** (0.3 g, 2.04 mmol), anthranilonitrile (0.42 g, 2.04 mmol), and polyphosphoric acid (5 g) was heated under nitrogen at 150–160 °C for 3 h after which it was poured into cold water and neutralized with ammonium hydroxide. The precipitate was filtered off and recrystallized from methanol to give the title compound **8a** (0.153 g, 30%) mp 166–168 °C.

Method B was employed for the following syntheses.

7-Imino-9,10-dimethoxy-5,6,7,12-tetrahydropyrido[2,3-*c*]-acridine 8b. (i) The title compound **8b** (0.204 g, 22%) was prepared from compound **6** (0.441 g, 3 mmol) and 4,5-dimethoxyanthranilonitrile (0.534 g, 3 mmol), using method B, and recrystallized from ethyl acetate; it had mp 239–241 °C (Found: M^+, 307.132. Calc. for $C_{18}H_{17}N_3O_2$: *M*, 307.132); ν_{max}(Nujol)/cm^{-1} 3327 (NH), 3177 (NH), 1645 (C=N), 1606, 1569 and 1537

(aromatic); $\delta_H([^2H_6]$-DMSO) 2.98 (2H, t, *J* 7.5, H-5 or H-6), 3.14 (2H, t, *J* 7.5, H-5 or H-6), 3.94 (6H, s, 2, OCH_3), 7.53 (1H, dd, *J* 7.9, 4.9, H-2), 7.81 (1H, s, H-8 or H-11), 7.83 (1H, s, H-8 or H-11), 8.24 (1H, br s, exchangeable with D_2O, NH), 8.62 (1H, d, *J* 4.9, H-3), 8,79 (1H, d, *J* 7.9, H-1), 13.67 (1H, br s, exchangeable with D_2O, NH); *m/z* (EI) 308 (M^+ + 1, 21%), 307 (M^+, 100), 292 (26), 264 (11), 154 (14) and 131 (10).

(ii) The title compound **8b** (0.61 g, 65%) was prepared from compound **6** (0.441 g, 3 mmol) and 4,5-dimethoxyanthranilonitrile (0.534 g, 3 mmol), by method B but with the addition of 15-crown-5 ether (4-drops) to the reaction mixture which was subsequently refluxed overnight (16 h).

5,6,7,12-Tetrahydropyrido[2,3-*c*]acridin-7-one 9a. The title compound **9a** (1.34 g, 63.5%) was prepared from compound **6** (1.25 g, 8.5 mmol) and ethyl anthranilate (1.4 g, 8.5 mmol), using method B. The product, recrystallized from ethanol, had mp >300 °C (Found: C, 77.6; H, 4.9; N, 11.25. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.8; N, 11.3%); ν_{max}(Nujol)/cm^{-1} 3206 (NH), 1630 (C=O) and 1610 (aromatic); $\delta_H([^2H_6]$-DMSO) 2.89 (2H, t, *J* 7, H-5), 3.08 (2H, t, *J* 7, H-6), 7.33 (1H, t, *J* 8, H-9), 7.52 (1H, dd, *J* 8, 5, H-2), 7.67 (1H, t, *J* 8, H-10), 7.81 (1H, d, *J* 8, H-8 or H-11), 8.13 (1H, d, *J* 8, H-8 or H-11), 8.44 (1H, d, *J* 8, H-1), 8.58 (1H, d, *J* 5, H-3) and 11.58 (1H, br s, exchangeable with D_2O, NH); $\delta_C([^2H_6]$-DMSO) 19.2 (CH_2), 30.6 (CH_2), 115.7 (quat), 118.6 (CH), 122.15 (CH), 123.1 (CH), 124.1 (quat), 124.4 (quat), 125.1 (CH), 131.6 (CH), 131.7 (CH), 140.05 (quat), 140.9 (quat), 150.2 (CH), 159.45 (quat) and 170.6 (quat); *m/z* (EI) 248 (M^+, 82%), 247 (100), 219 (12), 124 (11.5), 110 (13) and 96 (9).

9,10-Dimethoxy-5,6,7,12-tetrapyrido[2,3-*c*]acridin-7-one 9b. The title compound **9b** (0.77 g, 46%) was prepared from compound **6** (0.735 g, 5 mmol) and methyl 4,5-dimethoxyanthranilate (1.055 g, 5 mmol), using method B, and recrystallized from methanol; it had mp >285 °C (Found: C, 66.5; H, 5.55; N, 8.5. $C_{18}H_{16}N_2O_3 \cdot H_2O$ requires C, 66.3; H, 5.5; N, 8.6%); ν_{max}(Nujol)/cm^{-1} 3219 (NH), 1635 (C=O), 1604 and 1566 (aromatic); $\delta_H([^2H_6]$-DMSO) 2.85 (2H, t, *J* 7, H-5 or H-6), 3.0 (2H, t, *J* 7, H-5 or H-6), 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 7.25 (1H, s, H-11), 7.46 (1H, s, H-8), 7.5 (1H, dd, *J* 7.9, 4.9, H-2), 8.36 (1H, d, *J* 7.9, H-1), 8.54 (1H, d, *J* 4.9, H-3), 11.41 (1H, br s, exchangeable with D_2O, NH); *m/z* (EI) 309 (M^+ + 1, 20%), 308 (M^+, 100), 307 (50) 293 (12.5), 291 (8), 265 (9), 263 (8) and 154 (8).

7-Amino-1-hydroxy-5,6,-dihydropyrido[2,3-*c*]acridine 17a. (i) The title compound **17a** (0.025 g, 8%) was prepared from compound **14** (0.2 g, 1.2 mmol) and anthranilonitrile (0.14 g, 1.2 mmol), using method B, and recrystallized from methanol; it had mp 272–275 °C (decomp.) (Found: M^+, 263.106. Calc. for $C_{16}H_{13}N_3O$: *M*, 263.106); ν_{max}(Nujol)/cm^{-1} 3363 br (NH and OH), 1688, 1638 and 1581; $\delta_H([^2H_6]$-DMSO) 3.0 (4H, m, H-5 and H-6), 6.69 (1H, d, *J* 6, H-2), 7.23 (2H, s, exchangeable with D_2O, NH_2), 7.49 (1H, t, *J* 8, H-9), 7.69 (1H, t, *J* 8, H-10), 7.79 (1H, d, *J* 8, H-8), 8.12 (1H, d, *J* 6, H-3), 8.32 (1H, d, *J* 8, H-11) and 17.34 (1H, s, exchangeable with D_2O, OH); *m/z* (EI) 264 (M^+ + 1, 19%), 263 (M^+, 100), 262 (37), 235 (15), 234 (27), 118 (11) and 117 (15).

(ii) The title compound **17a** (0.105 g, 16%) was prepared from compound **14** (0.4 g, 2.4 mmol) and anthranilonitrile (0.28 g, 2.4 mmol) by the same method as described above but with an increased period under reflux (24 h) subsequent to the addition of sodium amide.

1-Hydroxy-5,6,7,12-tetrahydropyrido[2,3-*c*]acridin-7-one 17b. A mixture of compound **14** (0.3, 1.84 mmol), ethyl anthranilate (0.31 g, 1.88 mmol) and polyphosphoric acid (5 g) was heated at 240–260 °C under nitrogen for 5 h after which it was poured into ice-cooled water (100 ml) and neutralized with ammonium hydroxide. The precipitate was filtered off and recrystallized from methanol to give the title compound **17b** (0.29 g, 60%), mp >285 °C (Found: C, 61.6; H, 5.3; N, 9.1. $C_{16}H_{12}N_2O_2 \cdot 2.5H_2O$ requires C, 62.1; H, 5.5; N, 9.05%); ν_{max}(Nujol)/cm^{-1} 3370 (OH), 1623 (C=O), 1545 and 1523 (aromatic); $\delta_H([^2H_6]$-DMSO) 2.92 (2H, t, *J* 7.5, H-5 or H-6), 3.02 (2H, t, *J* 7.5, H-5 or H-6), 6.49 (1H, d, *J* 7.1, H-2), 7.37 (1H, t, *J* 7.5, H-9), 7.61–7.71 (2H, m, H-10 and H-3), 7.88 (1H, d, *J* 8.1, H-11), 8.2 (1H, d, *J* 8.1, H-8), 11.4 (1H, br s, exchangeable with D_2O, NH) and 14.21 (1H, s, exchangeable with D_2O, OH); *m/z* (ES) 264 (M^+, 14%), 263 (75), 256 (40), 219 (22), 168 (29), 113 (55), 97 (64), 88 (69), 62 (39) and 58 (100).

7-Amino-3,4,5,6-tetrahydropyrido[2,3-*c*]acridin-3-one 19a. (i) The title compound **19a** (0.178 g, 11%) was prepared from compound **16** (0.61 g, 3.74 mmol) and anthranilonitrile (0.45 g, 3.81 mmol), using method B and refluxing for 24 h in the initial condensation; it was purified by dry flash column chromatography using ethyl acetate–methanol as eluent to give the title compound **19a**; R_F 0.5 (methanol), mp 278–280 °C (decomp.) (Found: M^+, 263.106. Calc. for $C_{16}H_{13}N_3O$: *M*, 263.106); ν_{max}(Nujol)/cm^{-1} 3356 (NH), 1667 (C=O), 1638 (NH_2 bending), 1564 and 1537 (aromatic); $\delta_H([^2H_6]$-DMSO) 2.85–2.93 (4H, m, H-5 and H-6), 6.34 (1H, d, *J* 9.4, H-2), 6.69 (2H, br s, exchangeable with D_2O, NH_2), 7.35 (1H, t, *J* 7.5, H-9), 7.56 (1H, t, *J* 7.5, H-10), 8.18 (1H, d, *J* 8.3, H-8), 8.3 (1H, d, *J* 8.3, H-11), 8.39 (1H, d, *J* 9.4, H-1), 11.96 (1H, br s, exchangeable with D_2O, NH); *m/z* (EI) 264 (M^+ + 1, 23%), 263 (M^+, 100%), 262 (30), 235 (20), 234 (53), 218 (10), 207 (5), 117 (11), 103 (9), 77 (15), 63 (10), 51 (17), 44 (50) and 43 (29).

(ii) The title compound **19a** (0.39 g, 7%) was obtained from compound **16** (0.36 g, 2.2 mmol) and anthranilonitrile (0.26 g, 2.2 mmol) when 15-crown-5 ether was used along with sodium amide and the period under reflux was increased to 20 h.

3,4,5,6,7,12-Hexahydropyrido[2,3-*c*]acridine-3,7-dione 19b. A mixture of compound **16** (0.3, 1.84 mmol), ethyl anthranilate (0.31 g, 1.88 mmol) and polyphosphoric acid (5 g) was heated at 250–260 °C under nitrogen for 3 h after which it was poured into ice-cooled water (100 ml) and neutralized with ammonium hydroxide. The resulting precipitate was filtered off and recrystallized from methanol to give the title compound **19b** (0.160 g, 33%), mp 280–284 °C (decomp.) (Found: C, 69.7; H, 4.8; N, 10.1. $C_{16}H_{12}N_2O_2 \cdot \frac{2}{3}H_2O$ requires C, 69.55; H, 48; N, 10.1%); ν_{max}(Nujol)/cm^{-1} 1675 (C=O), 1629, 1588 and 1551 (aromatic); $\delta_H([^2H_6]$-DMSO) 2.78 (4H, m, H-5 and H-6), 6.44 (1H, d, *J* 9.5, H-2), 7.28 (1H, t, *J* 7.5, H-9), 7.60 (1H, t, *J* 7.5, H-10), 7.74 (1H, d, *J* 8.3, H-11), 8.08 (1H, d, *J* 8.3, H-8), 8.15 (1H, d, *J* 9.5, H-1), 11.27 (1H, s, exchangeable with D_2O, NH) and 12.22 (1H, br s, exchangeable with D_2O, NH).

Pyrido[2,3-*c*]acridines

7-Aminopyrido[2,3-*c*]acridine 10a. Compound **8a** (0.25 g, 0.94 mmol) and activated MnO_2 (2.5 g) in DMF (25 ml) was heated under reflux, with stirring, overnight (15 h), after which the reaction mixture was cooled and filtered through Celite®. The filtrate was evaporated under reduced pressure and the residue was purified by dry flash column chromatography, using methanol as the eluent (R_F 0.73), and then recrystallized from ethanol to give the title compound **10a** (0.09 g, 36%), mp 246–248 °C (Found: C, 78.4; H, 4.6; N, 16.95. $C_{16}H_{11}N_3$ requires C, 78.35; H, 4.5; N, 17.1%); ν_{max}(Nujol)/cm^{-1} 3406, 3298 (NH_2), 1656, 1603 and 1568 (aromatic); $\delta_H([^2H_6]$-DMSO) 7.48 (1H, m, H-9), 7.68–7.7 (2H, m, H-2 and H-5), 7.77 (1H, m, H-10), 7.85 (2H, br s, exchangeable with D_2O, NH_2), 8.03 (1H, d, *J* 8, H-11), 8.48 (1H, d, *J* 8, H-8), 8.53 (1H, d, *J* 9.5, H-6), 8.98 (1H, dd, *J* 4, 2, H-3) and 9.57 (1H, dd, *J* 8, 2, H-1); $\delta_C([^2H_6]$-DMSO) 108.6 (quat), 115.1 (quat), 121.7 (CH), 123.1 (CH), 123.2 (quat and CH), 125.2 (CH), 126.8 (quat), 129.3 (CH), 130.2 (CH), 133.0 (CH), 146.65 (quat), 147.0 (quat), 150.0 (CH), 150.3 (CH) and 151.15 (quat); *m/z* (EI) 246 (M^+ + 1, 17%), 245 (M^+, 100), 218 (8.5), 217 (8), 123 (12) and 96 (13).

The same procedure for dehydrogenation was employed for the following conversions.

7-Amino-9,10-dimethoxypyrido[2,3-*c*]acridine 10b. The title compound **10b** (0.89 g, 36%), prepared from compound **8b** and

then purified by dry flash column chromatography using methanol as the eluent (R_F 0.45) and recrystallization from methanol, had mp 268–270 °C (Found: MH^+, 306.124. Calc. for $C_{18}H_{15}N_3O_2$: MH, 306.124); ν_{max}(Nujol)/cm^{-1} 3463, 3320 (NH_2), 1650, 1590, 1574 and 1558 (aromatic); δ_H([$^2H_6$]-DMSO) 3.99 (3H, s, OCH_3), 4.0 (3H, s, OCH_3), 7.27 (1H, s, H-11), 7.55–7.71 (4H, m, 2H exchangeable with D_2O, H-2, H-5 or H-6, NH_2), 7.76 (1H, s, H-8), 8.53 (1H, d, *J* 9.7, H-5 or H-6), 8.95 (1H, d, *J* 4, H-3) and 9.57 (1H, d, *J* 7.5, H-1); δ_C([$^2H_6$]-DMSO) 55.75 (CH_3), 56.30 (CH_3), 101.91 (CH), 107.13 (quat), 108.31 (CH), 109.47 (quat), 121.37 (CH), 122.48 (CH), 125.26 (CH), 126.3 (quat), 132.59 (CH), 144.46 (quat), 144.90 (quat), 147.8 (CH), 148.60 (quat), 149.76 (quat), 150.71 (quat) and 153.28 (quat); *m*/*z* (CI) 306 (MH^+, 5%), 123 (5), 111 (6), 85 (10), 73 (12), 71 (20), 57 (64) and 41 (100).

7,12-Dihydropyrido[2,3-*c*]acridin-7-one 11a. A mixture of compound **9a** (0.25 g, 1.02 mmol) and activated MnO_2 (1.25 g) in DMF (25 ml) was heated under reflux with stirring for 24 h after which it was cooled and filtered through Celite®. The filtrate was evaporated under reduced pressure and the residue was recrystallized from methanol to give the title compound **11a** (0.123 g, 50%), mp >300 °C (Found: C, 73.9; H, 4.4; N, 10.6. $C_{16}H_{10}N_2O\cdot{}^3/_4H_2O$ requires C, 74.0; H, 4.4; N, 10.8%); ν_{max}(Nujol)/cm^{-1} 3260 (NH), 1634 (C=O), 1609, 1580 and 1559 (aromatic); δ_H([$^2H_6$]-DMSO) 7.41 (1H, t, *J* 8, H-9), 7.73 (1H, d, *J* 9, H-5), 7.80–7.86 (2H, m, H-2 and H-10), 8.0 (1H, d, *J* 8, H-11), 8.31 (1H, d, *J* 8, H-8), 8.48 (1H, d, *J* 9, H-6), 9.1 (1H, dd, *J* 1.5, 4, H-3), 9.41 (1H, d, *J* 8, H-1) and 12.0 (1H, br s, exchangeable with D_2O, NH).

9,10-Dimethoxy-7,12-dihydropyrido[2,3-*c*]acridin-7-one 11b. The title compound **11b** (0.214 g, 86%), prepared from compound **9b** (0.25 g, 0.82 mmol) and recrystallized from methanol, had mp >300 °C (Found: C, 63.5; H, 4.9; N, 8.2. $C_{18}H_{14}N_2O_3\cdot 2H_2O$ requires C, 63.2; H, 5.3; N, 8.2%); ν_{max}(Nujol)/cm^{-1} 3234 (NH), 1631 (C=O), 1582, 1523 and 1503 (aromatic); δ_H([$^2H_6$]-DMSO) 3.90 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 7.41 (1H, s, H-11), 7.60 (1H, s, H-8), 7.70 (1H, d, *J* 9, H-5), 7.78 (1H, dd, *J* 8.3, 4, H-2), 8.46 (1H, d, *J* 9, H-6), 9.06 (1H, d, *J* 4, H-3), 9.29 (1H, d, *J* 8.3, H-1) and 11.86 (1H, br s, exchangeable with D_2O, NH); δ_C([$^2H_6$]-DMSO) 55.7 (CH_3), 55.9 (CH_3), 99.8 (CH), 104.7 (CH), 115.9 (quat), 116.0 (quat), 119.0 (quat), 121.1 (CH), 121.9 (CH), 126.5 (CH), 131.25 (CH), 137.1 (quat), 138.0 (quat), 146.2 (quat), 149.9 (quat), 151.8 (CH), 154.1 (quat) and 174.3 (quat, C=O).

7-Amino-1-hydroxypyrido[2,3-*c*]acridine 18a. The title compound **18a** (0.049 g, 49%), prepared from compound **17a** (0.1 g, 0.38 mmol) and recrystallized from ethanol, had mp 222–225 °C (decomp.) (Found: M^+, 261.090. Calc. for $C_{16}H_{11}N_3O$: *M*, 261.090); ν_{max}(Nujol)/cm^{-1} 3392 (NH_2), 1681, and 1588; δ_H([$^2H_6$]-DMSO) 6.58 (1H, d, *J* 6, H-2), 7.55 (2H, m), 7.85 (1H, m), 7.95 (1H, d, *J* 9.1, H-5 or H-6), 8.41–8.58 (5H, m), 18.42 (1H, s, exchangeable with D_2O, OH); *m*/*z* (EI) 261 (M^+, 3%), 233 (22), 205 (6), 178 (5), 152 (10), 129 (10), 102 (23), 87 (20), 77 (70), 76 (60), 63 (50) and 52 (100).

1-Hydroxy-7,12-dihydropyrido[2,3-*c*]acridin-7-one 18b. The title compound **18b** (0.017 g, 17%), prepared from compound **17b** (0.1 g, 0.38 mmol) and recrystallized from methanol, had mp 205 –208 °C (decomp.) (Found: M^+, 262.074. Calc. for $C_{16}H_{10}N_2O_2$: *M*, 262.074); ν_{max}(Nujol)/cm^{-1} 3362 (OH), 1616, 1545, and 1530 (aromatic); δ_H([$^2H_6$]-DMSO) 6.34 (1H, d, *J* 7.3, H-2), 7.29 (1H, d, *J* 8.9, H-5), 7.33 (1H, t, *J* 7.5, H-9), 7.68 (1H, d, *J* 8, H-11), 7.74 (1H, t, *J* 7.5, H-10), 8.07 (1H, d, *J* 7.3, H-3), 8.26 (1H, d, *J* 8.0, H-8), 8.37 (1H, d, *J* 8.9, H-6), 11.44 (1H, br, s, exchangeable with D_2O, NH) and 14.61 (1H, s, exchangeable with D_2O, OH); *m*/*z* (EI) 263 (M^+ + 1, 27%), 262 (M^+, 76), 234 (31), 206 (24), 205 (30), 178 (18), 151 (17), 131 (17), 103 (50), 89 (60), 77 (35.5), 76 (72), 73 (65), 69 (35), 57 (45), 55 (52) and 44 (100).

7-Amino-3,4-dihydropyrido[2,3-*c*]acridin-3-one 20a. The title compound **20a** (0.51 g, 50%), prepared from compound **19a** (0.1 g, 0.38 mmol) and recrystallized from methanol, had mp >285 °C (Found: M^+, 261.090. Calc. for $C_{16}H_{11}N_3O$: *M*, 261.090); ν_{max}(Nujol)/cm^{-1} 3356 and 3250 (NH_2), 1667 (C=O), 1638 (NH_2 bending) and 1564 and 1538 (aromatic); δ_H([$^2H_6$]-DMSO) 6.61 (1H, d, *J* 9.3, H-2), 7.25 (1H, d, *J* 9.2, H-6), 7.40 (1H, t, *J* 8.4, H-9), 7.75 (1H, t, *J* 8.4, H-10), 7.93 (1H, d, *J* 8.4, H-8), 8.13 (2H, br s, exchangeable with D_2O, NH_2), 8.44 (1H, d, *J* 8.4, H-11), 8.48 (1H, d, *J* 9.2, H-5), 9.06 (1H, d, *J* 9.3, H-1) and 12.18 (1H, br s, exchangeable with D_2O, NH); *m*/*z* (EI) 262 (18%), 261 (M^+, 100), 246 (19) and 233 (36).

3,4,7,12-Tetrahydropyrido[2,3-*c*]acridine-3,7-dione 20b. The title compound **20b** (0.016 g, 16%), prepared from compound **19b** (0.1 g, 0.38 mmol), had mp >285 °C (Found: MH^+, 263.082. Calc. for $C_{16}H_{11}N_2O_2$: *M*, 263.082); ν_{max}(Nujol)/cm^{-1} 1659 (C=O) and 1626, 1594 and 1559 (aromatic); δ_H([$^2H_6$]-DMSO) 6.72 (1H, d, *J* 9.5, H-2), 7.17 (1H, d, *J* 9, H-5), 7.33 (1H, t, *J* 7.5, H-9), 7.77 (1H, t, *J* 7.5, H-10), 7.85 (1H, d, *J* 8, H-11), 8.23 (1H, d, *J* 8, H-8), 8.31 (1H, d, *J* 9, H-6), 8.85 (1H, d, *J* 9.5, H-1), 11.5 (1H, br s, exchangeable with D_2O, NH) and 12.3 (1H, br s, exchangeable with D_2O, NH); *m*/*z* (CI) 263 (MH^+, 100%), 91 (33), 77 (39) and 73 (43).

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