THE SYNTHESIS OF PYRIDO[3,2-*a*]ACRIDINES

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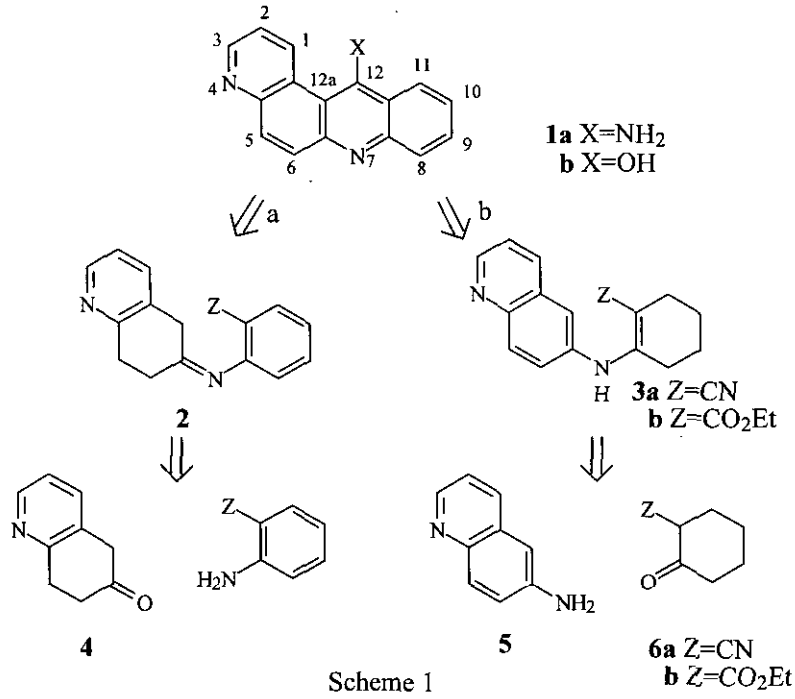
Abstract— 6-Aminoquinoline (**5**) reacts with 2-cyanocyclohexanone (**6a**) or ethyl 2-oxocyclohexanecarboxylate (**6b**) to give enamines which can be cyclised, under Lewis acid catalysed conditions, to tetrahydropyrido[3,2-*a*]acridines (**9**, **13**). Dehydrogenation of these tetrahydropyrido[3,2-*a*]acridines, with palladium-on-charcoal, gives the fully aromatic pyrido[3,2-*a*]acridines (**1a,b**).

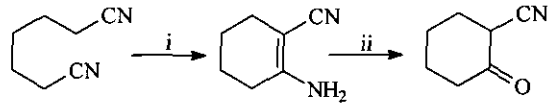
We have recently reported the synthesis of pyrano[2,3-*a*]acridines[1] and pyrido[2,3-*c*]acridines[2] *via* the cyclisation of imines under acid- or base-catalysed conditions, onto a pendant cyano or ester group. We wish to describe here the extension of this methodology to the synthesis of pyrido[3,2-*a*]acridines. Despite the biological activity exhibited by these, and other heterocycle-fused acridines,[3] relatively few syntheses have been reported.

In the retrosynthetic analysis of pyrido[3,2-*a*]acridines (**1**), a number of bond disconnections are possible, one of which is shown in Scheme 1. Disconnection of the 12,12a-bond would require the preparation of either; the imine (**2**) from 7,8-dihydroquinolin-6(5*H*)-one (**4**), Scheme 1a; or enamine (**3**), from 6-aminoquinoline (**5**) and the substituted cyclohexanone (**6**), Scheme 1b. Two syntheses of ketone (**4**) have been reported in the literature,[4,5] both of which were unsuccessful in our hands, so the second route was chosen.



Scheme 1

2-Cyanocyclohexanone (**6a**) was prepared by a modification of the method of Kulp,[6] Scheme 2. Dicyanopentane (**7**) was cyclised to 1-amino-2-cyanocyclohex-1-ene (**8**) in 62.5% yield under base-catalysed conditions. The 1-amino-2-cyanocyclohexene (**8**) was then hydrolysed to 2-cyanocyclohexanone (**6a**) in concentrated HCl/ethanol.

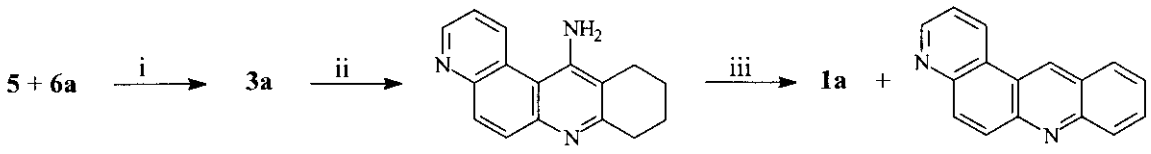


Scheme 2

Reagents and conditions; i, KOBu^t, PhMe, reflux, 2 h, 62.5%; ii, conc. HCl/EtOH, reflux, 1 h, 78%.

Condensation of 2-cyanocyclohexanone (**6a**) with 6-aminoquinoline (**5**) gave the enamine (**3a**) in 67% isolated yield, Scheme 3. Analysis of the ^{1}H NMR spectrum of enamine (**3a**) suggests this is the predominant tautomer, due to the presence of a singlet at δ8.40, exchangeable with D_2O, which can only be assigned to the NH proton. Enamine (**3a**) was cyclised using the method of Lamant *et al.*,[7] in which an equimolar mixture of the enamine (**3a**) and anhydrous aluminium chloride was heated at 190°C for 5 min, to give the tetrahydropyrido[3,2-*a*]acridine (**9**) in 48% yield after work-up. The structure of this

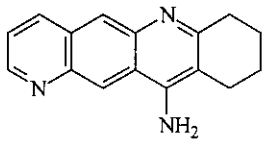
compound was established by analytical and spectroscopic data. The presence of two doublets, at δ7.79 and 7.87, corresponding to the 5-H and 6-H, excludes the linear, pyrido[2,3-*b*]acridine, structure (**11**).



9 **12**

Scheme 3

Reagents and conditions; i, PhMe, pTSA, reflux, 8 h, 67%; ii, $AlCl_3$, 190°C, 5 min, 48%; iii, 10% Pd-on-C, 270-280°C, 30 min.



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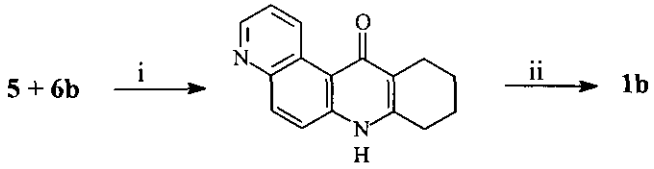
Dehydrogenation of the tetrahydropyrido[3,2-*a*]acridine (**9**) was achieved by heating at 270-300°C, under nitrogen, with palladium-on-charcoal. 12-Aminopyrido[3,2-*a*]acridine (**1a**) was obtained in 75% yield after heating for 30 min, along with pyrido[3,2-*a*]acridine (**12**) (6%). Increasing the reaction time decreased the yield of the aminopyrido[3,2-*a*]acridine (**1a**) and increased the amount of the deaminated product (**12**). For example, on heating for 3 h, the deaminated product (**12**) was obtained in 48% yield and the amino product (**1a**) in 20% yield.

Finally, 8,9,10,11-tetrahydropyrido[3,2-*a*]acridin-12(7*H*)-one (**13**) was obtained in 28% yield by heating an equimolar mixture of 6-aminoquinoline (**5**) and ethyl 2-oxocyclohexanecarboxylate (**6b**) in polyphosphoric acid at 130-150°C for 5 h, Scheme 4. The acridone nature of **13** was established by the presence of a carbonyl signal at δ177.95 in the ^{13}C NMR spectrum,[8] and an absorption at 1637 cm^{-1} in the IR spectrum for the C=O. Once again, the presence of two doublets, at δ7.72 and 8.00, excludes the possibility of the linear system. The tetrahydroacridin-12(7*H*)-one (**13**) was dehydrogenated with palladium-on-charcoal at 300°C for 9 h, under nitrogen, to give the fully aromatic pyrido[3,2-*a*]acridin-12(7*H*)-one (**1b**) in 57% yield.



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Scheme 4

Reagents and conditions; i, polyphosphoric acid, 130-150 °C, 5 h, 28%; ii, 10% Pd-on-C, 300°C, 9 h, 57%.

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. ^{1}H 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 TMS. Low resolution MS 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 perfomed on Perkin-Elmer 240B Elemental Analyzer. TLC 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. Toluene was distilled and stored over sodium wire.

1-Amino-2-cyanocyclohex-1-ene (8)

1,2-Dicyanopentane (7) (15.25 g, 125 mmol) was added dropwise to a suspension of potassium *tert*-butoxide (14 g, 125 mmol) in toluene (150 mL) at reflux, with continuous stirring, over a period of 1 h. After addition was complete, the reaction contents were refluxed for a further 1 h and the stirring was continued overnight. Water (50 mL) was added, the toluene layer was separated and the water layer was extracted with chloroform (3×50 mL). The toluene layer and the chloroform extracts were combined, dried ($MgSO_4$) and evaporated. The residue was recrystallized from chloroform to give the title compound (**8**) (9.54 g, 62.5%) as colourless needles, mp 98-99°C (lit.,[6] 93-94.5°C).

2-Cyanocyclohexanone (6a)

A mixture of 1-amino-2-cyanocylohex-1-ene (**8**) (8.0 g, 65.57 mmol), concn. HCl (74 mL) and ethanol (250 mL) was refluxed for 1 h. On cooling, the solid (NH_4Cl) was filtered off. The filtrate was concentrated, extracted with dichloromethane (3×50 mL), and dried (Na_2SO_4). The solvent was evaporated and the residue was distilled to give the title compound (**6a**) (6.17 g, 78%), bp 88-94 °C at 0.03-0.05 mmHg (lit.,[9] 87°C at 0.5 mmHg).

12-Amino-8,9,10,11-tetrahydropyrido[3,2-*a*]acridine (9)

(i) 6-(2'-Cyanocyclohex-1'-en-1'-ylamino)quinoline (3a). A mixture of 2-cyanocyclohexanone (**6a**) (2.2 g, 17.87 mmol), 6-aminoquinoline (**5**) (2.57 g, 17.87 mmol) and *p*-toluenesulfonic acid (0.34g, 1.79 mmol) in toluene (60 mL) was refluxed for 8 h with azeotropic removal of water. The toluene was evaporated under reduced pressure, the residue was dissolved in dichloromethane (50 mL) and treated with 10% aq. sodium hydrogen carbonate (50 mL). The dichloromethane layer was washed with water (50 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was recrystallized from ethyl acetate to give needles of the title compound (**3a**) (2.84 g, 67%), mp 123-124°C (Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.1; H, 6.0, N, 16.9. Found: C, 76.8; H, 6.1; N, 16.6); ν_{max} (Nujol/cm^{-1}) 3314 (NH), 2176 (CN), 1616, 1594, and 1520 (aromatic); δ_H (DMSO-d_6) 1.53 (4H, m, H-4' and H-5'), 2.17 (2H, m, H-3' or H-6'), 2.26 (2H, m, H-3' or H-6'), 7.26 (1H, d, *J* 2.5, H-5), 7.32 (1H, dd, *J* 8.3, 4.2, H-3), 7.39 (1H, dd, *J* 9.0, 2.5, H-7), 7.78 (1H, d, *J* 9, H-8), 8.10 (1H, d, *J* 8.3, 1.5, H-4), 8.40 (1H, s, exchangeable with D_2O, N*H*), 8.60 (1H, dd, *J* 4.5, 1.5, H-2); m/z (EI) 249 (M^+, 32%), 220 (37), 181 (54), 169 (84), 143 (38), 128 (97), 116 (64), 102 (67), 101 (98), 89 (69), 77 (91), 75 (69), 63 (72), 52 (78), 51 (100), and 41 (99).

(ii) 12-Amino-8,9,10,11-tetrahydropyrido[3,2-*a*]acridine (9). A mixture of 6-(2'-cyanocyclohex-1'-en-1'-ylamino)quinoline (**3a**) (0.5 g, 2 mmol) and aluminium chloride (0.8 g, 2 mmol) was heated to 190° C and kept at this temperature for 5 min. The reaction mixture was then dissolved in 2% aq. HCl (200 mL) and the aluminium complex was destroyed by the addition of sodium hydroxide until the solution was strongly basic. The precipitate was filtered and recrystallized from ethyl acetate to give the title compound (**9**) (0.25 g, 48%), mp 186-187°C (Found: M^+, 249.127. Calcd for $C_{16}H_{15}N_3$: *M*, 249.127) ; ν_{max} (Nujol/cm^{-1}) 3341, 3198 (NH_2), 1661, and 1564 (aromatic); δ_H (DMSO-d_6) 1.95 (4H, m, H-9 and H-10), 2.63 (2H, t, *J* 6, H-11), 2.85 (2H, t, *J* 6, H-8), 6.21 (2H, s, exchangeable with D_2O, NH_2), 7.55 (1H, dd, *J* 8.5, 4.3, H-2), 7.79 (1H, d, *J* 9.2, H-5 or H-6), 7.87 (1H, d, *J* 9.2, H-5 or H-6), 8.78 (1H, d, *J* 4.3, H-3), 9.32 (1H, d, *J* 8.5, H-1); m/z (EI) 250 (M^++1, 20%), 249 (M^+, 100), 248 (M^+-1, 54), 232(14), 231

(16), 221 (17), 220.(17.5), 206 (7), 192 (5), 179 (8), 153 (7), 127 (7), 117 (7), 77 (7.5), 63 (7.5), 51 (10), and 41 (16).

12-Aminopyrido[3,2-*a*]acridine (1a)

(i) A mixture of 12-amino-8,9,10,11-tetrahydropyrido[3,2-*a*]acridine (**9**) (0.1 g, 0.4 mmol) and palladium on activated charcoal (10%) (20 mg) was heated at 270-280 °C, under nitrogen with stirring for 3 h. On cooling, methanol (20 mL) was added and the reaction mixture was filtered through Celite®. The solvent was evaporated and the residue was purified by wet column chromatography using ethyl acetate-methanol as eluent. Pyrido[3,2-*a*]acridine (**12**) (R_F = 0.63 in ethyl acetate) was obtained as the major product (0.045 g, 48%), mp 165-167°C (Anal. Calcd for $C_{16}H_{10}N_2 \cdot H_2O$: C, 77.4; H, 4.9; N, 11.3. Found: C, 77.3, H, 5.05, N, 11.2.); ν_{max} (Nujol/cm^{-1}) 1605, 1584, and 1551 (aromatic); δ_H (DMSO-d_6) 7.73 (1H, t, *J* 7.1, H-10), 7.80 (1H, dd, *J* 8.3, 4.4, H-2), 7.92 (1H, t, *J* 7.1, H-9), 8.15 (1H, d, *J* 9.4, H-5 or H-6), 8.20 (1H, d, *J* 9.4, H-5 or H-6), 8.23 (1H, d, *J* 8.3, H-8 or H-11), 8.27 (1H, d, *J* 8.3, H-8 or H-11), 8.99 (1H, dd, *J* 1.4, 4.4, H-3), 9.38 (1H, dd, *J* 1.4 ,8.3, H-1), 9.97 (1H, s, 1H-2); $^m/_z$ (EI) 231 (M^++1, 23%), 230 (M^+, 97), 229 (20), 203 (11), 202 (12), 176 (17), 150 (15), 111 (18), 99 (25), 87 (48), 75 (75), 74 (78), 63 (93), 52 (85), 51 (100). The title compound (**1a**) (R_F = 0.27 in ethyl acetate) was obtained as the minor product (0.02 g, 20%), mp 158-160°C (Found: M^+, 245.059. Calcd for $C_{16}H_{11}N_3$: *M*, 245.059); ν_{max} (Nujol/cm^{-1}) 3341, 3170 (NH_2) 1632 , 1605, and 1551 (aromatic); δ_H (DMSO-d_6) 7.48 (1H, t, *J* 7.6, H-10), 7.59 (1H, dd, *J* 8.4, 4.4, H-2), 7.65 (2H, br s, exchangeable with D_2O, N*H*$_2$), 7.73 (1H, t, *J* 7.6, H-9), 7.85-7.93 (3H, m, H-5, H-6 and H-8 or H-11), 8.52 (1H, d, *J*8.5, H-8 or H-11), 8.76 (1H, d, *J* 4.4, H-3), 9.3 (1H, d, *J*8.3, H-1); $^m/_z$ (EI) 246 (M^++1, 23%), 245 (M^+, 68), 244 (14), 218 (13), 191 (13), 190 (16), 164 (15.5), 163 (15), 137 (10), 111 (17). 102 (26), 87 (32), 77 (37), 76 (67), 75 (52), 74 (55.5), 69 (43), 63 (100), 57 (88), and 52 (95).

(ii) The title compound (**1a**) (0.037 g, 75%) was obtained, along with the pyrido[3,2-*a*]acridine (**12**) (0.003 g, 6%) from 12-amino-8,9,10,11-tetrahydropyrido[3,2-*a*]acridine (**9**) (0.05 g, 0.2 mmol), when the reaction time was decreased to 30 min.

8,9,10,11-Tetrahydropyrido[3,2-*a*]acridin-12(7*H*)-one (13). A mixture of 6-aminoquinoline (**5**) (0.72 g, 5 mmol), ethyl 2-oxocyclohexanecarboxylate (**6b**) (0.85 g, 5 mmol) and polyphosphoric acid (8.0 g), was heated at 130-150 °C for 5 h. The reaction mixture was poured into ice-cold water (100 mL) and neutralized with 10% ammonium hydroxide. The precipitate was filtered and recrystallized from methanol to give needles of the title compound (**13**) (0.355 g, 28%), mp > 300°C. (Anal Calcd for

$C_{16}H_{14}N_2O \cdot CH_3OH$: C, 72.3; H, 6.4; N, 9.9. Found: C, 72.2; H, 6.6; N, 9.8%); ν_{max} (Nujol/cm^{-1}) 1637 (C=O), 1581, 1544, and 1504 (aromatic); δ_H (DMSO-d_6) 1.63-1.69 (4H, m, H-9 and H-10), 2.42 (2H, t, *J* 6, H-8), 2.66 (2H, t, *J* 6, H-11), 7.53 (1H, dd, *J* 8.5, 4.3, H-2), 7.72 (1H, d, *J* 9.2, H-5 or H-6), 8.00 (1H, d, *J* 9.2, H-5 or H-6), 8.74 (1H, d, *J* 4.3, H-3), 10.53 (1H, d, *J* 8.5, H-1), 11.75 (1H, s, exchangeable with D_2O, N*H*); δ_C (DMSO-d_6) 21.6 (CH_2), 22.0 (CH_2), 22.1 (CH_2), 26.8 (CH_2), 114.4 (quat), 120.3 (quat), 122.0 (CH), 122.6 (CH), 126.8 (quat), 133.4 (CH), 134.0 (CH), 139.2 (quat), 144.5 (quat), 144.9 (quat), 148.2 (CH), 177.95 (quat); $^m/_z$ (EI) 251 (M^++1, 19%), 250 (M^+, 100), 249 (M^+-1, 84), 235 (43), 221 (6) ,and 125 (10).

Pyrido[3,2-*a*]acridin-12(7*H*)-one (1b). A solid mixture of 8,9,10,11-tetrahydropyrido[3,2-*a*]acridin-12(7*H*)-one (**13**) (0.05 g, 0.2 mmol) and palladium on activated charcoal (10%) (0.02 g) was stirred at 300 °C for 9 h under nitrogen. On cooling, methanol (20 mL) was added and then the reaction mixture was filtered through Celite®. The solvent was evaporated and the residue was purified by wet column chromatography using methanol as eluent (R_F = 0.35 in methanol), followed by recrystallization from methanol to give the title compound (**1b**) (0.028 g, 57%), mp >300°C (lit.,[10] 360°C).

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