Cyclisation of 2-chloro-*N*-(2-pyridinyl)nicotinamides to 5-oxo-5, 6-dihydrodipyrido[1,2-*a*:3',2'-*e*]pyrimidin-11-ium chlorides

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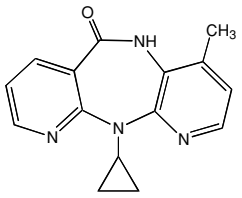
The ease of thermal cyclisation of 2-chloro-*N*-(R-2-pyridinyl)nicotinamides, (**5**: X = NH) to 5-oxo-5,6-dihydrodipyrido-[1,2-*a*:3',2'-*e*]pyrimidin-11-ium chlorides in solution has been found to be in the order: (**5**: X = NH; R = 4-Me) > (**5**: X = NH; R = 5-Me) > (**5**: X = H; R = 6-Me) > (**5**: X =NH; R = 3-Me). This order reflects both steric and electronic effects of the methyl groups. The products of the cyclisations, which were monitored by NMR spectroscopy in DMSO-d_6, were generally characterised by NMR spectroscopy and, specifically for 9-Me-5-oxo-5,6-dihydrodipyrido[1,2-*a*:3',2'-*e*]pyrimidin-11-ium chloride, by X-ray crystallography. The crystal structure of 2-chloro-*N*-(6-methyl-2-pyridinyl)nicotinamide is also reported. The ester and thioester analogues, 2-pyridinyl 2-chloronicotinate and *S*-(2-pyridinyl) 2-chloro-3-pyridinecarbothioate, do not undergo cyclisation under the same conditions used for the amides.

Keywords: cyclisation, nicotinamides, fused pyridines, fused pyrimidines, 1,2-dipyridinium salts

Various 3-pyridinecarboxylic acid (nicotinic acid) derivatives have been found to have significant biological activity, an example being Nevirapine (Viramune, **1**),[1-5] a valuable anti-aids drug.



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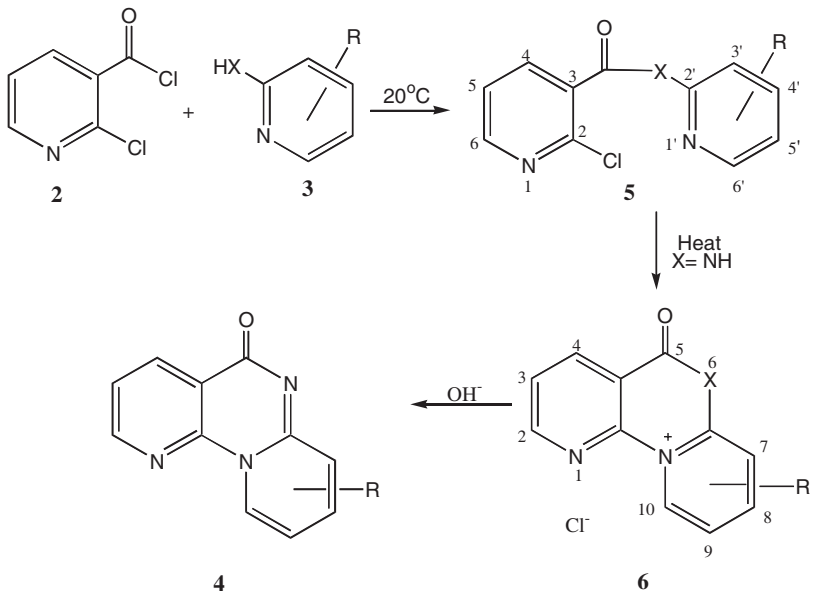
2-Chloronicotinoyl chloride, 2-chloro-3-pyridinecarbonyl chloride (**2**), is a particularly useful precursor to active and more elaborate pyridine-containing compounds. For example, **2** has been reported to undergo cyclisations, either in one- or two-step reactions, with various di-nucleophilic reagents.[6-12] Included among the reported reactions are those with 2-aminopyridines (**3**), which provide dipyrido[2,3-*d*]pyrimidinone derivatives, **4**, *via* the intermediacies of 2-chloro-*N*-(2-pyridinyl)nicotinamides, (**5**: X = NH), and the HCl salts of **4**, *i.e.* **6**, see Scheme 1.[6, 7] Monge *et al.* obtained **4** (R = H, 3-Me or R = 5-Me) by the addition of the appropriate compound **3** to a solution of **2** in toluene, followed by refluxing for 90 min and subsequent treatment with NaOH.[6] The intermediate compounds **5** (X = NH) and **6** were assumed but not characterised, while characterisation of **4** (R = H; R = 3-Me or R = 5-Me) was limited to ^{1}H NMR at 90MHz, and IR spectra.

Our interest in these cyclisation reactions was fed by the realisation that the products of these cyclisations can be considered as analogues of Nevirapine. We have conducted a ^{1}H, at 400 and 500 MHz, and ^{13}C NMR, and IR spectroscopic and X-ray crystallographic study of the ease of cyclisation of 2-chloro-*N*-(2-pyridinyl)nicotinamides (**5**: X = NH) obtained from **2** and **3** (R = 3-, 4-, 5- or 6-Me). In contrast



2 **3** **5** **4** **6**

Scheme 1

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to the study by Monge *et al.*[6], characterisation of both the intermediate amides **5** (X = NH) and the initial products of the cyclisation reactions, the HCl salts of **4**, methyl 5-oxo-5,6-dihydrodipyrido[1,2-*a*:3′,2′-*e*]pyrimidin-11-ium chlorides (**6**), have been carried out in our study. Crystal structures of **6** (R = 9-Me), as a mono-hydrate, as well as of 6-methyl-pyridin-2-amine (**3**: R = 6-Me) are reported. In addition, we have attempted the cyclisation of the ester and thioester analogues, 2-pyridinyl 2-chloronicotinate (**5**: X = O; R = Me), and *S*-(2-pyridinyl) 2-chloro-3-pyridinecarbothioate (**5**: X =S; R = H) under the same conditions used for the amides.

Results and discussion

The reactions of 2-chloronicotinoyl chloride and the methylpyridin-2-amines proceeded readily in the presence of triethylamine at room temperature. While the simple amido compounds (**5**: X = NH) were obtained from **3** (R = 3-, 5- or 6-Me) in high yields, the reaction with **3** (R = 4-Me) under the same reaction conditions proceeded almost completely to the cyclised product (**6**: R = 8-Me). With shorter reaction times and with minimum work-up procedures and, in particular, omitting a recrystallisation step, the presence of **5** (X = NH; R = 4-Me) could be detected by NMR spectroscopy. However, using normal purification procedures, including recrystallisation, only the cyclised material was obtained.

Cyclisation of the other amides **5** (X = NH; R = 3-, 5- or 6-Me), to **6** (R = 7-, 8- or 10-Me) was achieved on a preparative scale by heating EtOH solutions until TLC indicated complete reaction. In addition, the cyclisations of **5** (X = NH; R = 3-, 5- or 6-Me) were readily followed by ^{1}H NMR spectroscopy in DMSO-d_6 solution. The reactions of **5** (X = NH) were monitored by following changes, particularly in the aromatic hydrogen region of the proton NMR spectra, over time and at different temperatures.

The sequence of ease of cyclisation was established as **5** (X = NH; R = 4-Me) > **5** (X = NH; R = 5-Me) > **5** (X = NH; R = 6-Me) > **5** (X = NH; R = 3-Me). Such a sequence is based on both electronic and steric effects. A methyl group *ortho* to the pyridine nitrogen, as in **5** (X = NH; R = 6-Me) hinders the cyclisation from steric effects, while **5** (X = NH; R = 4-Me), having the methyl group in the position for most favourable electron release to the pyridine centre, is the most readily cyclised. Characterisation of compounds **5** and **6** was generally achieved by ^{1}H and ^{13}C NMR spectroscopy in DMSO-d_6 solution, including the use of HMBQ experiments, on 400 and 500 MHz instruments. Thus, hydrogens and carbons have been assigned. While in general the amido hydrogen signals could be detected in the ^{1}H NMR spectra for **5** (X = NH) (in the region 11.06–11.25 ppm), they were not observed in those of the cyclised products **6**. Clearly the NH protons in the cations of the latter compounds are more acidic and more readily exchanged with the deuterons in the DMSO-d_6 solvent.

The cyclisations are essentially intramolecular arylations of pyridine derivatives and the products are 1,2-dipyridinium salts. In contrast to alkylpyridinium salts, arylpyridinium salts are not generally available by direct arylation of the nitrogen centre, except if such activated compounds as 1-chloro-2,4-dinitrobenzene, are used as the arylating reagent.[13] Two useful methods of preparing non-activated-aryl-pyridinium salts are reaction of anilines with either the chlorodinitrobenzene[13] or via pyrylium salts.[14-17] 1,2-Dipyridinium salts, in particular, have been obtained via reaction of halo-*N*-alkoxypyridinium salts with pyridines[18] or via hindered pyrylium salts with 2-aminopyridines.[14] In the cases of **5** (R = 6-Me), and **6** (R = 9-Me), X-ray crystallographic structure determinations at 120 K provided further confirmation of the molecular structures.

Compound **5** (X = NH; R = H) was readily cyclised in EtOH solution. However, even after heating the ester and thioester derivatives (**5**: X = O; R = H and **5**: X = S; R = H) in EtOH solution for long periods, no cyclised products were indicated. It thus appears that either the pyridine nitrogen is much less nucleophilic in **5** (X = O or S; R = H) than in **5** (X = NH; R = H) or that the molecules do not have the correct conformations for cyclisation. We intend to carry out a theroretical study to establish the reason(s) for this inactivity.

Crystal structure determinations

Crystal structure of **5** (X = NH; R = 6-Me): Crystals of **5** (X = NH; R = 6-Me) suitable for X-ray crystallography were grown from EtOH solution. The atom arrangements and the crystallographic numbering system are shown in Fig. 1. All bond lengths and angles are in the normal ranges: geometric parameters are listed in Table 2. The angle between the planes of the two pyridine rings is 63.39(6)°, with a Cl1–N3 separation of 4.906 Å. Such geometric parameters preclude cyclisation occurring in the solid state.

Table 1 also lists the hydrogen bonding parameters, including both strong, N2–H2^{---}N1^{i}, and weak, C4–H4^{---}O1^{ii} and C10–H10^{---}O1^{iii}, intermolecular H-bonds [symmetry operations: i: ½–*x*, ½–*y*, 1–*z*; ii: *x*, –*y*, ½+*z*; iii; 1–*x*, –*y*, 1–*z*]. While a complete hydrogen-bonding analysis of the structure is not performed here, we do wish to point out the interesting net-arrangement of the molecules brought about by the combination of the N2–H2---N1^{i}, and C10–H10---O1 hydrogen bonds, see Fig. 2. In addition, to these hydrogen bonding interactions, PLATON[19] also indicated several π–π stacking interactions.

Crystal structure of the cyclised product **6** (R = 9-Me).H_2O: A solution of **6** (R = 9-Me) in EtOH on slow evaporation produced hydrated crystals (**6**: R = 9-Me.H_2O), suitable for X-ray crystallography. The crystallography numbering scheme for **6** (R = 9-Me).H_2O is shown in Fig. 3.

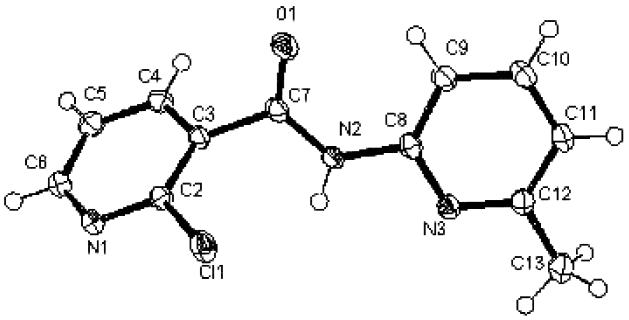


Fig. 1 Atom arrangements and numbering scheme for **5** (X = NH; R = 6-Me). Probability ellipsoids are drawn at the 50% level.

Table 1 Selected geometric parameters, (Å,°) for **5** (X = NH; R = 6-Me)

(a) Bond lengths and angles			
C3–C7	1.513(2)	O1–C7	1.217(2)
N2–C7	1.353(2)	N2–C8	1.411(2)
O1–C7–C3	119.42(15)	N2–C7–C3	114.81(14)
O1–C7–N2	125.75(16)	C7–N2–C8	127.85(15)

(b) Hydrogen bonding parameters

	D–H	H^{---}A	D^{---}A	D–H^{---}A
N2–H2N1^{i}	0.91(2)	2.22(3)	3.108(2)	165.0(18)
C4–H4^{---}O1^{ii}	0.93	2.39	3.312(2)	171
C9–H9^{---}O1	0.93	2.30	2.884(2)	121
C10–H10^{---}O1^{iii}	0.93	2.55	3.242(2)	131

[a]½–*x*, ½–*y*, 1–*z*; [b]*x*, –*y*, ½+*z*; [c]1–*x*, –*y*, 1–*z*.

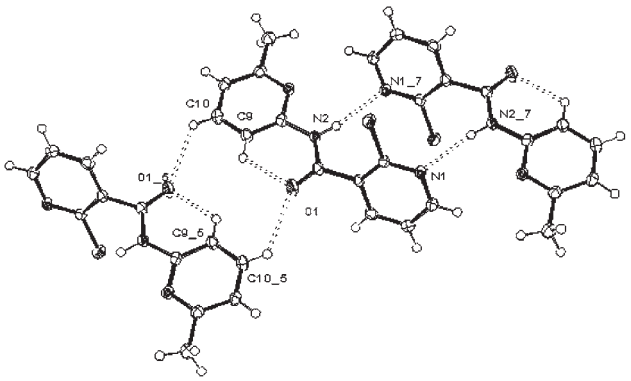


Fig. 2 Network of molecules of (**5**: X = NH; R = 6-Me), formed by N2–H2···N1^{i} and C10–H10···O1 hydrogen bonds: intramolecular C9–H9···O1 also shown.

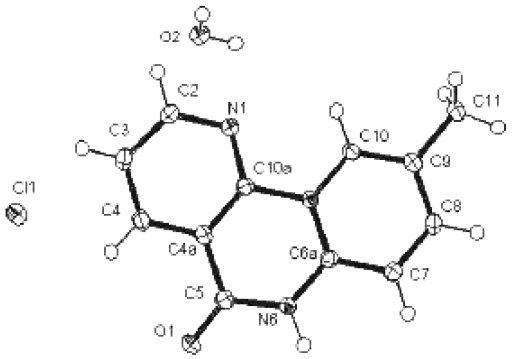
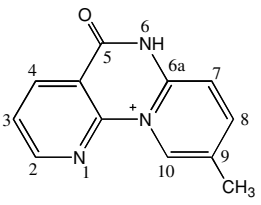
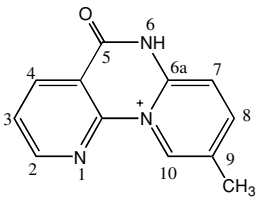


Fig. 3 Atom arrangements and numbering scheme for **6** (R = 9-Me).H_2O. Probability ellipsoids are drawn at the 50% level.

The compound is ionic, with 9-methyl-oxo-5,6-dihydrodipyrido[1,2-*a*:3',2'-*e*]pyrimidin-11-ium cations, chloride anions and water of hydration, linked to varying extents by hydrogen bonds. Geometric parameters are listed in Table 3. The cation, with the exception of the C-9 methyl hydrogens, is near planar. The best plane through the terminal ring, N2–C6A–C7–C8–C9–C10, makes angles to the best planes through the central and other terminal rings of 4.29(13) and 5.51(14)°, respectively.



6A



6B

Table 2 Geometric parameters, [Å, °] for **6** (R = 9-Me).H_2O

(a) Bond lengths and angles

N2–C10A	1.433(3)	C4A–C10A	1.390(3)
N2–C6A	1.355(3)	C4A–C5	1.468(3)
N6–C5	1.378(3)	N6–C6A	1.360(3)
O1–C5	1.217(3)	C6A–C7	1.402(3)
C8–C9	1.409(3)	C7–C8	1.368(3)
C9–C10	1.364(3)	N2–C10	1.384(3)
C10A–C4A–C5	121.24(18)	N6–C5–C4A	113.76(18)
C6A–N6–C5	125.81(19)	N2–C6A–N6	120.09(18)
C6A–N2–C10A	119.62(17)		

(b) Hydrogen bonding parameters

D–H···A	D–H	H···A	D···A	Angle D–H···A
O2–H(1W)···Cl1[a]	0.81(3)	2.34(3)	3.128(2)	167(3)
O2–H(2W)···Cl1[b]	0.78(3)	2.34(3)	3.0997(18)	166(3)
N6–H6···O2[c]	0.91(3)	1.85(3)	2.745(3)	166(3)
C2–H2···O2	0.95	2.45	3.237(3)	140
C3–H3···Cl1	0.95	2.79	3.518(2)	134
C8–H8···O1[d]	0.95	2.54	3.396(3)	150
C10–H10···N1	0.95	2.36	2.695(3)	100
C11–H11A···O1[d]	0.98	2.44	3.376(3)	160

[a] ½+*x*,½−*y*,−½+*z*; [b] 3/2−*x*,−½+*y*,−½−*z*; [c] *x*,1+*y*,*z*; [d] ½+*x*,3/2−*y*,−½+*z*.

The C4–C3–C2–N1–C10A–C4A pyridine ring, in the cation, exhibits bond lengths and angles as expected for a delocalised pyridine ring: in contrast the C7–C8–C9–C10–N2–C6A ring exhibits marked bond fixation with the C6A–C7 and C8–C9 distances significant longer than those for C7–C8 and C9–C10, and N2–C6A shorter than the N2–C10 bond. Thus form **6A** is a more important contributor than **6B** to the overall molecular structure.

The carbonyl bond length is as expected for the amido, –NHC(=O)-, fragment and is essentially the same as that in the open chain amide (**5**: X = NH; R = 6-Me). While, as with **5** (X = NH; R = 6-Me), a complete analysis of the inter-species interactions is not attempted here, we point out that the cations are linked via an aqua molecule, by C2–H2···O2 and N6–H6···O2 hydrogen bonds, (Fig. 4). In addition, to these hydrogen bonding interactions, PLATON[19] also indicated several π–π stacking, C–H···π and C–Cl···π interactions.

Experimental

Melting points were determined on a Büchi apparatus. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer in potassium bromide disks and frequencies are expressed in cm^{-1}. Mass spectra (CG/MS) were recorded on a Agilent Tecnologies 61530A / 5792A mass spectrometer. NMR spectra were recorded on a Bruker Avance 500 spectrometer operating at 500 MHz (^{1}H) and 125 MHz (^{13}C), in DMSO-d_6. Silica gel coated TLC plates were used with ethyl acetate/methanol mixtures as eluents. Column grade silica gel 60 (0.063–0.200 mm mesh size) was employed for column chromatography.

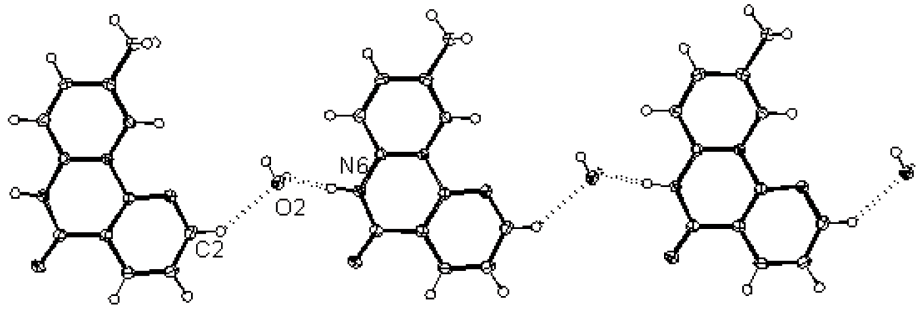


Fig. 4 Chain of cations of (**6**: R = 9-Me).H_2O, linked by C2–H2···O2 and N6–H6···O2 hydrogen bonds.

Table 3 Crystal data and structure refinement

	5 (X = NH; R = 6-Me)	**6** (X = NH; R = 9-Me).H_2O
Empirical formula	$C_{12}H_{10}ClN_3O$	$C_{12}H_{12}ClN_3O_2$
Formula weight	247.68	265.70
Temperature, K	120(2) K	120(2) K
Wavelength, Å	0.71073	0.71073
Crystal system, space group	Monoclinic, C2/*c*	Monoclinic, $P2_1/n$
Unit cell dimensions:		
a, Å	20.6673(7)	10.5221(3)
b, Å	15.6067(6)	10.1509(3)
c, Å	7.0355(3)	11.7952(4)
β, °	97.102(3)	110.6320(17)
Volume, Å^3	2251.88(15)	1179.03(6)
Z, Calculated density, Mg/m^3	8, 1.461	4, 1.497
Absorption coefficient, mm^{-1}	0.325	0.321
F(000)	1024	552
Crystal size, mm	0.25 × 0.25 × 0.25	0.40 × 0.25 × 0.10
θ range for data collection,°	3.25 to 27.49	3.00 to 27.52
Index ranges	–26<=*h*<=26, –20<=*k*<=19, – 8<=*l*<=9	–13<=*h*<=13; –12<=*k*<=13; –15<=*l*<=15
Reflections observed (>2σ)	2205	2143
Reflections collected/unique	13149, 2575 [R(int) = 0.0446]	12186, 2706 [R(int) = 0.0413]
Completeness to 2θ	0.995	0.996
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2575/0/159	2706/0/167
Goodness-of-fit on F^2	1.091	1.032
Final R indices [*I*>2σ(*I*)]	R1 = 0.0438 wR2 = 0.1145	R1 = 0.0449 wR2 = 0.1191
R indices (all data)	R1 = 0.0522 wR2 = 0.1205	R1 = 0.0617 wR2 = 0.1301
Largest diff. peak and hole, e/ Å^3	0.639 and -0.589	0.679 and -0.642

Reactions between 2-chloronicotinoyl chloride (**2**) *and pyridin-2-amines* (**3**): To a solution of 2-chloronicotinoyl chloride, **2**, (1.0 g, 5.68 mmol) in anhydrous THF (30 ml) was successively added with stirring a pyridin-2-amine (**3**) (1.1 ml, 5.68 mmol) and triethylamine (1.63 ml, 11.36 mmol) at room temperature. The reaction mixture was stirred for 8 h at room temperature, then quenched with water (20 ml), and ethyl acetate (15 ml) was added. The organic layer was collected, washed with saturated aqueous sodium bicarbonate (2 × 20 ml), dried over sodium sulfate, and rotary-evaporated. The residue was purified by chromatography, with hexane/ethyl acetate (7 : 3) as eluent.

From each of the reactions of **3** (R = 3-, 5- or 6-Me), the product isolated, after chromatography, was the uncyclised compound, 2-chloro-*N*-(3-, 5- or 6-methyl-2-pyridinyl)nicotinamide (**5**; X = NH; R = 3-, 5- or 6-Me), while from reaction of 4-methylpyridin-2-amine, the product isolated was the cyclised compound, 8-methyl-5-oxo-5,6-dihydrodipyrido[1,2-*a*:3′,2′-*e*]pyrimidin-11-ium chloride (**6**: R = 8-Me). However, with shorter reaction times and without recourse to chromatography and recrystallisation, the presence of the uncyclised compound, 2-chloro-*N*-(4-methyl-2-pyridinyl)nicotinamide (**5**: R = 4-Me) could be detected by NMR spectroscopy in the reaction with **3** (R = 4-Me).

2-Chloro-N-(6-methyl-2-pyridinyl)nicotinamide: (**5**: X = NH: R = 6-Me): yield 1.46g (83%), m.p. 126–127 °C. CG/MS: *m/z* [M]$^+$ 247 [based on ^{35}Cl]. IR: ν_{max} 3271 (NH), 1689 (CO). ^{1}H NMR [400.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6]: δ 11.21 (1H, s, N<u>H</u>), 8.50 (1H, dd, *J* = 2.0 and 5.2 Hz, H_6), 8.03 (1H, dd, *J* = 2.0 and 7.6 Hz, H_4), 8.00 (1H, d, *J* = 8.2 Hz (353 K), $H_{3'}$), 7.74 (1H, dd, *J* = 7.6 and 8.0 Hz, $H_{4'}$), 7.52 (1H, dd, *J* = 4.8 and 7.6 Hz, H_5), 7.05 (1H, d, *J* = 7.6 Hz, $H_{5'}$), 2.43 (3H, s, C<u>H</u>$_3$) ppm. ^{13}C NMR (100.0 MHz, DMSO-d_6) δ: 164.3 (<u>C</u>=O), 156.7 ($C_{6'}$), 150.8 ($C_{2'}$), 150.2 (C_6), 146.3 (C_2), 138.5 ($C_{4'}$), 138.0 (C_4), 132.8 (C_3), 122.8 (C_5), 119.3 ($C_{5'}$), 110.9 ($C_{3'}$), 23.5 (<u>C</u>H$_3$) ppm.

2-Chloro-N-(5-methyl-2-pyridinyl)nicotinamide: (**5**: X = NH; R = 5-Me): yield 1.50g (85%). IR: ν_{max} 3219 (NH), 1711 (CO) cm^{-1}. CG/MS: *m/z* [M]$^{+\cdot}$: 247 [based on ^{35}Cl]. ^{1}H NMR [400.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 11.06 (1H, s, N<u>H</u>), 8.50 (1H, dd, *J* = 1.6 and 4.8 Hz, H_6), 8.20 (1H, s, $H_{6'}$), 8.08 (1H, d, *J* = 7.6 Hz, $H_{3'}$), 8.04 (1H, dd, *J* = 1.2 and 7.6 Hz, H_4), 7.68 (1H, dd, *J* = 1.6 and 8.4 Hz, $H_{4'}$), 7.52 (1H, dd, *J* = 4.8 and 7.6 Hz, H_5), 2.28 (3H, s, C<u>H</u>$_3$) ppm. ^{13}C NMR (100.0 MHz, DMSO-d_6) δ: 164.7 (<u>C</u>=O), 150.8 (C_6), 149.9 ($C_{2'}$), 148.4 ($C_{6'}$), 146.9 (C_2), 139.1 ($C_{4'}$), 138.6 (C_4), 133.4 (C_3), 129.7 ($C_{5'}$), 123.4 (C_5), 114.2 ($C_{3'}$), 17.8 (<u>C</u>H$_3$) ppm.

2-Chloro-N-(4-methyl-2-pyridinyl)nicotinamide: (**5**: X = NH; R = 4-Me). IR: ν_{max} 3151 (NH), 1725 (CO) cm^{-1}. ^{1}H NMR [400.00 MHz (FIDRES ± 0.15 Hz), DMSO-D_6]: δ 11.25 (1H, s, N<u>H</u>), 8.45 (1H, dd, *J* = 2.0 and 4.8 Hz, H_6), 8.23 (1H, d, *J* = 4.8 Hz, $H_{6'}$), 8.19 (1H, dd, *J* = 2.0 and 8.0 Hz, H_4), 7.60 (1H, s, $H_{3'}$), 7.48 (1H, d, *J* = 5.2 and 8.0 Hz, H_5), 7.20 (1H, d, *J* = 5.0 Hz, $H_{5'}$), 2.35 (3H, s, C<u>H</u>$_3$) ppm.^{13}C NMR (100.0 MHz, DMSO-d_6) δ: 167.2 (<u>C</u>=O), 151.1 (C_6), 148.7 ($C_{6'}$), 147.1 ($C_{2'}$), 146.1 (C_2), 137.9 (C_4), 131.2 (C_3), 125.2 ($C_{5'}$), 123.9 ($C_{3'}$), 122.8 (C_5), 116.7 ($C_{4'}$), 20.8 (<u>C</u>H$_3$) ppm.

2-Chloro-N-(3-methyl-2-pyridinyl)nicotinamide: (**5**: X = NH; R = 3-Me): m.p. 121–123 °C. CG/MS: *m/z* [M]$^{+\cdot}$ 247 [based on ^{35}Cl]. IR: ν_{max} 3079 (NH), 1724 (CO) cm^{-1}. ^{1}H NMR [400.00 MHz (FIDRES ± 0.15 Hz), DMSO-D_6] δ: 8.47 (1H, dd, *J* = 1.6 and 4.8 Hz, H_6), 8.24 (1H, d, *J* = 4.8 Hz, $H_{6'}$), 8.16 (1H, dd, *J* = 1.6 and 7.6 Hz, H_4), 7.48 (1H, d, *J* = 4.8 and 7.6 Hz, H_5), 7.32 (1H, dd, *J* = 4.8 and 7.6 Hz, $H_{5'}$), 7.82 (1H, d, *J* = 7.6 Hz, $H_{4'}$), 2.43 (3H, s, C<u>H</u>$_3$) ppm.^{13}C NMR (100.0 MHz, DMSO-d_6): δ 167.0 (<u>C</u>=O), 151.2 (C_6), 148.8 ($C_{2'}$), 146.9 ($C_{4'}$), 146.3 (C_3), 140.7 ($C_{6'}$), 137.7 (C_4), 131.8 (C_3), 131.0 ($C_{3'}$), 124.8 ($C_{5'}$), 122.8 (C_5), 17.0 (<u>C</u>H$_3$) ppm.

8-Methyl-5-oxo-5,6-dihydrodipyrido[1,2-a:3′,2′-e]pyrimidin-11-ium chloride: (**6**: X = NH; R = 8-Me), m.p. 262–263 °C. IR: ν_{max} 3080 (NH), 1712 (CO) cm^{-1}. ^{1}H NMR [400.00 MHz (FIDRES ± 0.15 Hz), DMSO-D_6]: δ 9.80 (1H, d, *J* = 7.3 Hz, H_{10}), 9.15 (1H, dd, *J*= 2.0 and 4.8 Hz, H_2), 8.80 (1H, dd, *J*= 2.0 and 8.0 Hz, H_4), 8.03 (1H, dd, *J*= 4.8 and 8.0 Hz, H_3), 7.71 (1H, s, H_7), 7.64 (1H, dd, *J*= 2.0 and7.2 Hz, H_9), 2.65 (3H, s, C<u>H</u>$_3$) ppm, ^{13}C NMR (100.0 MHz, DMSO-d_6): δ 159.4 (C_5), 157.9 (C_{10}), 154.3 (C_2), 147.0 (C_{6a}), 146.1 (C_{10a}), 137.9 (C_4), 129.9 (C_9), 126.7 (C_3), 120.7 (C_{4a}), 116.7 (C_8), 114.8 (C_7), 21.8 (<u>C</u>H$_3$) ppm.

Cyclisation of **5** (X = NH; R = 3-, 5- or 6-Me) *to 7-, 9- or 10-methyl-5-oxo-5,6-dihydrodipyrido[1,2-a:3′,2′-e]pyrimidin-11-ium chloride*: (**6**: R = 7-, 9-, or 10-Me)

A solution of **5** (X = NH; R = 3-, 5- or 6-Me) (*ca* 1.5 mmol) in ethanol (15 ml) was refluxed until TLC indicated complete reaction. Solvent was removed on a rotary evaporator and the residue was recrystallised from EtOH to give **6** (R = 7-, 9- or 10-Me).

10-Methyl-5-oxo-5,6-dihydrodipyrido[1,2-a:3′,2′-e]pyrimidin-11-ium chloride (**6**: R = 10-Me), m.p. 251–253 °C. ^{1}H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6]: δ 9.03 (1H, dd, *J*= 1.5 and

4.5 Hz, H_2), 8.72 (1H, dd, *J* = 1.5 and 7.5 Hz, H_4), 8.20 (1H, dd, *J* = 8.0 and 8.0 Hz, H_8), 7.95 (1H, dd, *J* = 4.5 and 8.0 Hz, H_3), 7.68 (1H, d, *J* = 8.5 Hz, H_7), 7.41 (1H, d, *J* = 7.0 Hz, H_9), 2.42 (3H, s, C<u>H</u>$_3$) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6): δ 161.5 (C_5), 152.9 (C_2), 151.3 (C_{10}), 149.5 (C_{6a}), 147.1 (C_{10a}), 141.2 (C_4), 137.1 (C_9), 125.4 (C_3), 119.8 (C_{4a}), 118.8 (C_7), 118.1 (C_8), 26.1 (<u>C</u>H$_3$) ppm.

9-Methyl-5-oxo-5,6-dihydrodipyrido[1,2-a:3',2'-e]pyrimidin-11-ium chloride: (**6**: R = 9-Me), m.p. 251–253 °C.IR: ν_{max} 3060 (NH); 1707 (CO) cm^{-1}. ^{1}H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6]: δ 9.78 (1H, s, H_{10}), 9.18 (1H, dd, *J* = 1.2 and 3.6 Hz, H_2), 8.82 (1H, dd, *J* = 1.6 and 6.4 Hz, H_4), 8.46 (1H, dd, *J* = 1.6 and 7.2 Hz, H_8), 8.07 (1H, d, *J* = 7.2 Hz, H_7), 8.06 (1H, dd, *J* = 4.0 and 6.4 Hz, H_3), 2.51 (3H, s, C<u>H</u>$_3$) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6): δ 158.1 (C_5), 154.8 (C_2), 148.6 (C_{10}), 146.8 (C_{6a}), 146.6 (C_{10a}), 138.5 (C_4), 129.6 (C_9), 128.7 (C_8), 127.5 (C_3), 117.7 (C_{4a}), 116.5 (C_7), 17.8 (<u>C</u>H$_3$) ppm.

7-Methyl-5-oxo-5,6-dihydrodipyrido[1,2-a:3',2'-e]pyrimidin-11-ium chloride: (**6**: R = 7-Me). ^{1}H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6]: δ 9.32 (1H, d, *J* = 7.0 Hz, H_{10}), 8.98 (1H, dd, *J* = 2.0 and 4.5 Hz, H_2), 8.63 (1H, dd, *J* = 2.0 and 8.0 Hz, H_4), 7.84 (1H, dd, *J* = 5.0 and 8.0 Hz, H_3), 7.79 (1H, d, *J* = 7.0 Hz,, H_8), 7.05 (1H, dd, *J* = 7.0 and 7.0 Hz, H_9), 2.40 (3H, s, C<u>H</u>$_3$) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6): δ 165.4 (C_5), 165.0 (C_{10}), 152.7 (C_2), 152.6 (C_{6a}), 147.4 (C_{10a}), 137.6 (C_4), 131.9 (C_9),, 126.1 (C_3), 125.0 (C_{4a}), 116.2 (C_8), 112.3 (C_7), 17.7 (<u>C</u>H$_3$) ppm.

5-Oxo-5,6-dihydrodipyrido[1,2-a:3',2'-e]pyrimidin-11-ium chloride: (**6**: R = H), m.p. 343–344 °C. IR: ν_{max} 3080 (NH), 1715 (CO) cm^{-1}. ^{1}H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6]: δ 9.94 (1H, d, *J* = 7.0 Hz, H_{10}), 9.18 (1H, dd, *J* = 1.5 and 5.0 Hz, H_2), 8.83 (1H, dd, *J* = 1.5 and 8.0 Hz, H_4), 8.55 (1H, dd, *J* = 7.5 and 8.5 Hz, H_8), 8.06 (1H, dd, *J* = 5.0 and 8.0 Hz, H_3), 8.00 (1H, d, *J* = 9.0 Hz, H_7), 7.78 (1H, dd, *J* = 7.0 and 7.0 Hz, H_9) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6): δ 158.4 (C_5), 155.0 (C_2), 148.4 (C_{6a}), 146.7 (C_8), 138.5 (C_4), 131.2 (C_{10}), 127.6 (C_3), 119.4 (C_9), 117.6 (C_{4a}), 117.1 (C_7) ppm.

2-Pyridinyl 2-chloronicotinate (**5**: X = O; R = H), *and S-(2-pyridinyl) 2-chloro-3-pyridinecarbothioate* (**5**: X = S; R = H)

These compounds were prepared analogously to the amide derivatives (**5**: X = NH), using pyridin-2-one and pyridine-2-thione respectively, with **2**.

2-Pyridinyl 2-chloro-3-pyridinecarboxylate: (**5**: X = O; R = H), m.p. 171–172 °C. IR: ν_{max} 1750 cm^1 (CO). ^{1}H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6]: δ 8.71 (1H, dd, *J* = 1.0 and 4.5 Hz, H_6), 8.57 (1H, d, *J* = 8.0 Hz, H_4), 8.48 (1H, d, *J* = 4.0 Hz, $H_{6'}$), 8.06 (1H, dd, *J* = 7.0 and 7.0 Hz, $H_{4'}$), 7.68 (1H, dd, *J* = 5.0 and 8.0 Hz, H_5), 7.47 (1H, dd, *J* = 5.5 and 7.0 Hz, $H_{5'}$), 7.44 (1H, d, *J* = 8.0 Hz, $H_{3'}$) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6): δ 166.2, 157.1, 153.5, 152.3, 149.3, 141.8, 141.0, 140.5, 123.5, 123, 117.1 ppm.

S-(2-pyridinyl) 2-chloro-3-pyridinecarbothioate: (**5**: X = S; R = H), m.p. 186–187 °C. IR: ν_{max} 1699 cm^1 (CO). ^{1}H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6]: δ 8.77 (1H, d, *J* = 4.0 Hz, H_6), 8.56 (1H, d, *J* = 4.5 Hz, $H_{6'}$), 8.32 (1H, d, *J* = 7.5 Hz, H_4), 8.23 (1H, d, *J* = 7.5 Hz, $H_{4'}$), 7.95 (1H, d, *J* = 7.5 Hz, $H_{3'}$), 7.67 (1H, dd, *J* = 4.5 and 7.5 Hz, H_5), 7.55 (1H, dd, *J* = 4.5 and 7.0 Hz, $H_{5'}$) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6): δ 166.3, 158.6, 152.2, 151.6, 149.6, 140.0, 139.2, 137.4, 123.7, 123.0, 119.4 ppm.

Attempts to cyclise **5** (X = O or S; R = H): A solution of **5** (X = O or S; R = H) (*ca*. 1.5 mmol) in ethanol (15 ml) was refluxed for 18 h. Chromatography indicated that no cyclisation had occurred.

X-ray crystallography

The crystals of **5** (R = 6-Me; X = NH) and **6** (R = 9-Me; X = NH).H_2O were grown from ethanol solutions. The intensity data were collected at 120K on a Nonius KappaCCD area detector system by the EPSRC X-ray crystallographic service at the University of Southampton, UK. The entire process of data collection, cell refinement and data reduction was accomplished by means of the programs DENZO[20] and COLLECT.[21] Correction for absorption was achieved in each case by a semi-empirical method based upon the variation of equivalent reflections with the program SORTAV.[22] The structures were solved by direct methods in SHELXS-97[23] within the OSCAIL suite of programs[24] and refined in SHELXL-97.[25] Approximate positions for H atoms were obtained from difference maps and were refined with a riding model. PLATON was used for the data analysis.[19] The program ORTEP-3 for Windows was used to obtain the Figures.[26] Conformational and H-bonding analysis was performed using PLATON.[19] Crystal data and structure refinement details are listed in Table 3. CCDC numbers 268198 and 268199 contain the supplementary crystallographic data for **5** (X = NH; R = 6-Me) and **6** (X = NH; R = 9-Me).H_2O. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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