The Reaction of 1-Aryl- and 1-Pyridyl-1,2,3,4-tetrahydroisoquinolin-3-ones with Dimethylcarbamoyl Chloride: The Preparation of Amidines, Isoquinolines and *N*-Carbamoylated Products

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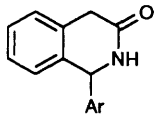
1-(Halogenophenyl)-1,2,3,4-tetrahydroisoquinolin-3-ones, such as **3**, react with neat dimethylcarbamoyl chloride at 95–165 °C to give high yields of the corresponding *N,N*-dimethylamidines; higher temperatures favoured *N*-carbamoylation. At 155 °C the related 1-(3-pyridyl)-1,2,3,4-tetrahydroisoquinolin-3-ones **6–8**, **10** and **11** gave lower yields of amidine, with those lactams not bearing an electron-releasing substituent on the benzo ring (**6–8**) giving medium to good yields of 1-(3-pyridyl)isoquinolines. In contrast, treatment of the corresponding 1-(4-pyridyl)-1,2,3,4-tetrahydroisoquinolin-3-one **12** with neat dimethylcarbamoyl chloride at temperatures between 125 °C and reflux gave none of the corresponding amidine. At high temperature the *N*-carbamoylated product **30** predominated, whereas at 125 °C, 3-(*N,N*-dimethylcarbamoyloxy)-1-(4-pyridyl)isoquinoline **37** was the major product.

As part of a programme involving the design of new anti-arthritic drugs,[1] we wished to convert the lactams **1** into the corresponding dimethylamidines **2**. Several groups have shown dimethylcarbamoyl chloride (either neat[2,3] or diluted with toluene[4]) to effect similar transformations in reasonable to good yields, in 'one pot'. We now report the results of our investigations using this reagent.



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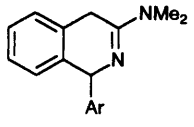

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Results and Discussion

The initial substrate for these studies, 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-3-one **3**, was prepared from phenylacetonitrile and 4-chlorobenzaldehyde in polyphosphoric acid.[5,6] The products from the treatment of this lactam with neat dimethylcarbamoyl chloride at various temperatures, or with 1 equiv. of dimethylcarbamoyl chloride in toluene at reflux, were the amidine **13** and the *N*-substituted structure **22**.

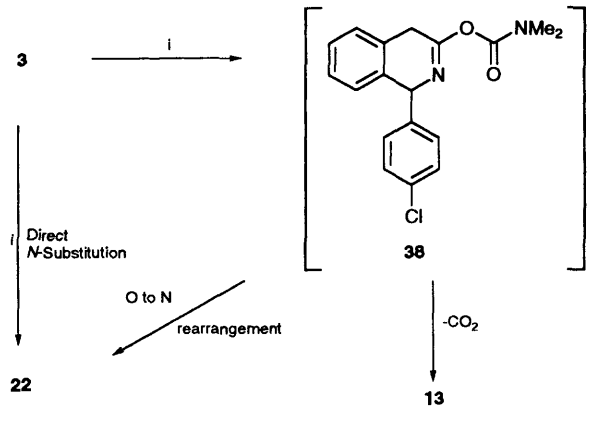
The variation in both product yield and composition on altering the reaction conditions is shown in Table 1. It is clear that the conditions (dimethylcarbamoyl chloride/toluene) reported[4] to give high yields of a wide range of acyclic amidines from the corresponding secondary amides, proved to be of less value in this instance than did the neat reagent when used at temperatures in the range 95–165 °C. Furthermore, at even higher temperatures the *N*-substituted product predominates (to an extent that may indicate a synthetically useful method for the preparation of *N*-carbamoylated amides such as **22**). None of the previous publications covering this reaction describe the formation of an *N*-carbamoylated product, although secondary *N*-carbamoylation has been reported from the treatment of a number of related lactams with isocyanates.[7]

We are not aware of a published mechanism for this type of transformation and propose the following scheme to explain our results (Scheme 1). The kinetic product, by analogy with the acylation of amides,[8] is **38**. At lower temperatures, loss of carbon dioxide occurs to give **13** whereas towards the reflux temperature, O to N rearrangement is faster than the decarboxylative process.

Table 1 The effect of temperature on the reaction of compound **3** with dimethylcarbamoyl chloride

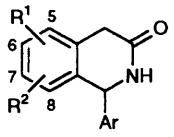
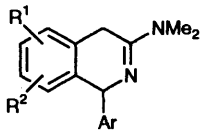
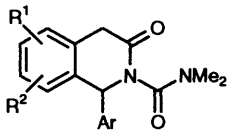
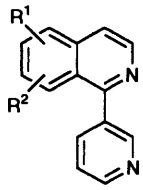
Dimethylcarbamoyl chloride	Oil bath (°C)	Time (h)	Product yield (%) **13**[a]	**22**[a]
Mixture with toluene	Reflux temp.	6	32	26
Neat	95	52	63[b]	*c*
Neat	125	18	80	*c*
Neat	165	3	59	8
Neat	195	2	6	54

[a] Both **13** and **22** were recovered unchanged on treatment with dimethylcarbamoyl chloride at reflux temperature. [b] 4–5% Of starting material remaining, all other cases were allowed to proceed to complete consumption of **3**. [c] Not detected.



Scheme 1 *Reagents:* i, Me_2NCOCl

As a result of the data generated in Table 1 we chose to perform subsequent reactions in neat dimethylcarbamoyl chloride at 155 °C. This temperature was chosen as a compromise between maximum yield and the convenience of a

R^1	R^2	Ar				
H	H	4-Chlorophenyl	**3**	**13**[a]	**22**	
H	H	2-Fluorophenyl	**4**	**14**[a]	**23**	
6-F	H	2-Fluorophenyl	**5**	**15**[a]	**24**	
6-F	H	3-Pyridyl	**6**	**16**[b]	**25**	**31**
5-Cl	H	3-Pyridyl	**7**	**17**[b]	**26**	**32**
H	H	3-Pyridyl	**8**	**18**[b]	**27**	**33**[b]
8-OMe	5-Br	3-Pyridyl	**9**			
8-OMe	H	3-Pyridyl	**10**	**19**[b]	**28**	**34**[b]
5,6-Benzo		3-Pyridyl	**11**	**20**[b]	**29**	**35**
H	H	4-Pyridyl	**12**	**21**	**30**[a]	**36**

[a] Isolated as the hydrochloride salt. [b] Isolated as the dihydrochloride salt.

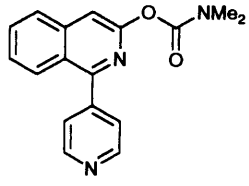


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Table 2 The products obtained from the reaction of the lactams **4–8**, **10** and **11** with dimethylcarbamoyl chloride

Lactam	Amidine	Yield (%)	*N*-Substituted product	Yield (%)	Isoquinoline	Yield (%)
4	**14**	65	**23**	9		
5	**15**	66	**24**	14		
6	**16**	8	**25**	*a*	**31**	57
7	**17**	11	**26**	*a*	**32**	57
8	**18**	14	**27**	*a*	**33**	26
10	**19**	3[b]	**28**	30	**34**	11
11	**20**	27	**29**	30	**35**	*a*

[a] None of this product observed. [b] Amidine unstable–isolated as an air- and heat-sensitive foam.

short reaction time. Under these conditions, two further lactams **4** and **5**, prepared in an analogous fashion to **3**, gave good yields of amidine (Table 2) adding further credence to the generality of our initial results.

In addition to the amidines **13–15**, the preparation of related pyridyl analogues such as **16** was of particular interest. The required intermediate lactams (**6–9** and **11**) were prepared from the correspondingly substituted phenylacetonitrile or phenylacetamide derivatives and pyridine-3-carbaldehyde in polyphosphoric acid under the conditions previously described for **8**.[9] The bromo lactam **9** was converted into **10** by catalytic hydrogenation over palladium in the presence of sodium acetate. Reaction of lactams **6–8** and **10**, **11** with dimethylcarbamoyl chloride gave up to three different products (Table 2).

The most surprising result from these experiments was that all the pyridyl lactams, with the exception of **11**, gave a quantity of the corresponding aromatised isoquinoline. This type of product was not detected in the 1-(halogenophenyl) substituted series; the absence of an electron-rich benzo ring in the isoquinolone nucleus appears to predispose this system to isoquinoline formation.

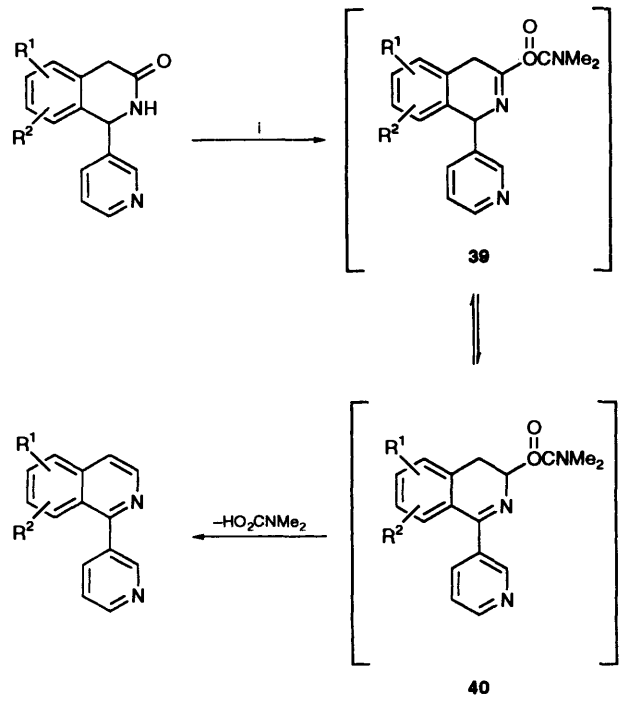
We found that both **18** and **28** were recovered unchanged when treated with dimethylcarbamoyl chloride under the conditions described above and, therefore, propose the following mechanism for the formation of the isoquinoline derivatives (Scheme 2).

For those lactams lacking an electron-rich benzo ring (**6–8**) equilibration to, and elimination from, **40** occurs more rapidly than the rearrangement of **39** to the corresponding amidine or *N*-substituted product. It is likely that the different product ratios described in Table 2 result from the enhanced acidity of the 1- and/or 4-hydrogens in **6–8** when compared with those in **10** and, in particular, **11**. Although it is not clear whether equilibration to **40** or elimination of dimethylcarbamic acid is the rate-limiting step in the formation of the isoquinoline nucleus, the absence of such a product from the 1-(halogenophenyl) series suggests a pivotal role for the pyridyl moiety and thus for the acidity of the 1-hydrogen. Such an acidity would, of course, be inductively enhanced by reaction of the pyridine nitrogen atom with the excess of reagent present during the reaction.

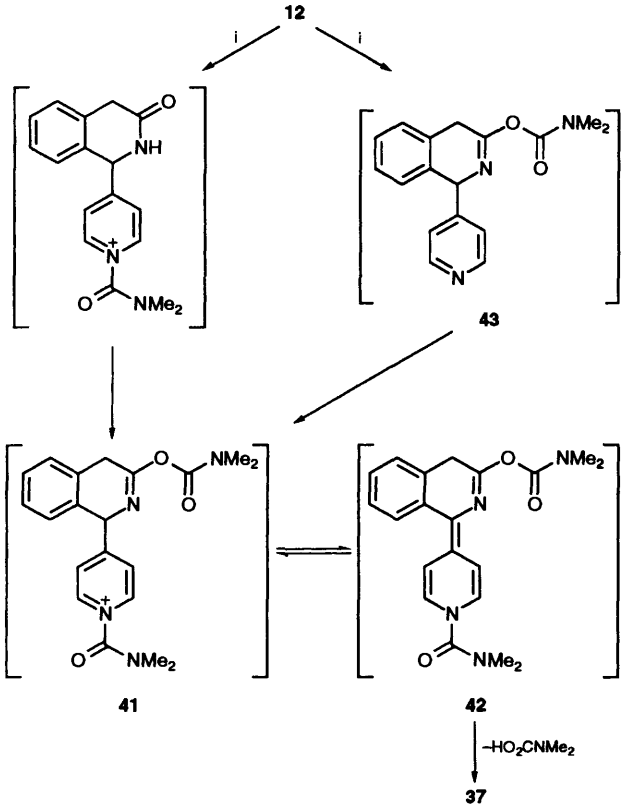
As a result of some interesting biological results found with a number of the amidines **16–20**, we wished to prepare the parent 4-pyridyl derivative **21**. However, treatment of **12**[9] with dimethylcarbamoyl chloride gave none of the desired amidine **21** or even of the isoquinoline **36**. Instead, two products **30** and **37** were obtained, the ratio of which varied with reaction temperature (Table 3).

In this case, the results are somewhat analogous to those described for the halogenophenyl series, although oxidation of the presumed intermediate **41** (Scheme 3) is now more rapid than the rearrangement to the amidine **21**. Also the yield of *N*-substituted product **30** increases with temperature, as does the ratio of **30**:**37**.

The formation of varying amounts of **37** clearly contrasts



Scheme 2 *Reagents:* i, Me_2NCOCl



Scheme 3 *Reagents:* i, Me_2NCOCl

with the products obtained from the 3-pyridyl lactam **8** and suggests the possibility of a reaction pathway not available to the 3-pyridyl derivatives. Reaction of dimethylcarbamoyl chloride with the pyridine nitrogen atom of **12** followed by *O*-carbamoylation (or *vice versa*) would give **41**. Reversible loss of a proton is well known in similar systems[10] and in this case would give **42**. Loss of dimethylformamide would then give **37** directly. Clearly, direct oxidation of an intermediate such as **41** or **43** could lead to **37**. That the same products (**30** and **37**) were obtained in the absence of air, whilst not ruling out such a possibility, argues against it.

Table 3 The effect of temperature on the reaction of **12** with dimethylcarbamoyl chloride

		Product yield (%)	
Oil bath temp. (°C)	Time (h)	**30**	**37**
125	24	4[a]	40[a]
165	3	17	22
195 (reflux temp.)	2	36	23

[a] 15% of starting material remaining. All other cases were allowed to proceed to complete consumption of **12**.

The effect of temperature on the ratio of **30** to **37** (Table 3) is somewhat analogous to that described for the (1-halogenophenyl) series in Table 1 and Scheme 1. The likely effect of increasing temperature in both cases is to allow the rate of O to N rearrangement to compete more effectively with alternative pathways. The major difference is that for the compounds of Table 1 the alternative pathway is towards amidine formation, whereas for **12** it is towards the oxidised isoquinoline **37**.

In conclusion, under suitably chosen conditions dimethylcarbamoyl chloride has been shown to be a useful reagent for the direct conversion of lactams such as **3** into the corresponding dimethylamidines. Under more forcing conditions (reflux temperature) it may also prove a useful reagent for the *N*,*N*-dimethylcarbamoylation of lactams. The reagent appears of less value for the conversion of 3-pyridyl lactams such as **8** into the related amidines, but may prove useful for the dehydration of lactams such as **6** and **7**, bearing electron-withdrawing groups in the benzo ring, into the corresponding isoquinolines. The reaction of dimethylcarbamoyl chloride with the 4-pyridyl lactam **12** gave rapid access to the novel 3-protected-1-(4-pyridyl)hydroxyisoquinoline **37**.

Experimental

^1H NMR spectra (δ_H) were recorded using Bruker AMX 400 (at 400 MHz), JEOL GX 270 (at 270 MHz), Bruker AC 250 (at 250 MHz) and Varian CFT 20 (at 80 MHz) spectrometers. Samples were prepared as solutions in $CDCl_3$ unless otherwise detailed. Tetramethylsilane was used as internal standard. *J*-Values are given in Hz. Mass spectra were recorded on a JEOL DX303 instrument. Analytical TLC was performed on 100 μM silica gel plates (Kodak). Merck Kieselgel 60 was used for column chromatography. M.p.s were recorded with a Reichert m.p. apparatus and are uncorrected. Organic solutions were dried over sodium sulfate. Evaporation of solvents was conducted under reduced pressure.

General Procedure for the Preparation of Lactams **3–9**, **11** *and* **12**.—The method used was similar to that previously described.[5,9,11] Thus, a mixture of benzyl cyanide (2 equiv.) and polyphosphoric acid (0.5 g $mmol^{-1}$ of nitrile) was heated and stirred at 80 °C for 0.75 h. The aldehyde (1 equiv.) was added with very vigorous stirring over 0.5 h to the mixture which was then heated to 135 °C for 3.5 h. After this it was cooled to 100 °C and poured into water (1 cm^3 g^{-1} of polyphosphoric acid). Ammonium hydroxide (*d* 0.880; 1.5 cm^3 g^{-1} of polyphosphoric acid) was added to the mixture which was stored for 16 h and then filtered. The solid thus obtained was heated under reflux in 1.25 mol dm^{-3} aqueous sodium hydroxide (1.5 cm^3 g^{-1} of polyphosphoric acid) for 2 h; the treatment with sodium hydroxide was omitted for those lactams (**6–9**, **11** and **12**) containing a 1-pyridyl substituent. The mixture was filtered

whilst hot, the solid washed with water, chromatographed using chloroform as eluent, and recrystallised to give lactam.

1-(2-*Fluorophenyl*)-1,2,3,4-*tetrahydroisoquinolin*-3-*one* **4**. M.p. 167–170 °C (from EtOH) (Found: C, 74.6; H, 5.1; N, 5.7. $C_{15}H_{12}FNO$ requires C, 74.7; H, 5.0; N, 5.8%); δ_H(400 MHz) 3.67 (1 H, d, J_{AB} 19, 4-H), 3.76 (1 H, d, J_{AB} 19, 4-H), 6.00 (1 H, br s, 1-H), 6.33 (1 H, br s, NH) and 6.95–7.35 (8 H, br m, 8 ArH) (Found: M^+, 241.0915. $C_{15}H_{12}FNO$ requires 241.0903); *m/z* 241 (M^+, 100%), 197 (44), 146 (89) and 118 (46).

6-*Fluoro*-1-(2-*fluorophenyl*)-1,2,3,4-*tetrahydroisoquinolin*-3-*one* **5**. M.p. 143–145 °C [from EtOAc–light petroleum (b.p. 60–80 °C)] (Found: C, 69.5; H, 4.5; N, 5.5. $C_{15}H_{11}F_2NO$ requires C, 69.5; H, 4.3; N, 5.4%); ν_{max}(Nujol)/cm^{-1} 1670; δ_H(400 MHz) 3.59 (1 H, d, J_{AB} 20, 4-H), 3.71 (1 H, d, J_{AB} 20, 4-H), 5.95 (1 H, s, 1-H) and 6.8–7.35 (7 H, br m, 7 ArH) (Found: M^+, 259.0804. $C_{15}H_{11}F_2NO$ requires 259.0809); *m/z* 259 (M^+, 100%) and 164 (100).

6-*Fluoro*-1-(3-*pyridyl*)-1,2,3,4-*tetrahydroisoquinolin*-3-*one* **6**. M.p. 184–185 °C (from EtOH) (Found: C, 69.4; H, 4.5; N, 11.6. $C_{14}H_{11}FN_2O$ requires C, 69.4; H, 4.6; N, 11.6%); δ_H(270 MHz; CD_3OD) 5.80 (1 H, s, 1-H), 6.95–7.20 (3 H, m, 5-H, 7-H and 8-H), 7.45 (1 H, m, py 5-H), 7.72 (1 H, m, py 4-H), 8.48 (1 H, dd, *J* 1, 5, py 6-H) and 8.55 (1 H, d, *J* 1, py 2-H); *m/z* 242 (M^+, 30%) and 164 (100).

5-*Chloro*-1-(3-*pyridyl*)-1,2,3,4-*tetrahydroisoquinolin*-3-*one* **7**. M.p. 182–185 °C (from EtOH) (Found: C, 64.8; H, 4.1; N, 10.7. $C_{14}H_{11}ClN_2O$ requires C, 65.0; H, 4.3; N, 10.8%); δ_H(80 MHz) 3.80 (2 H, s, 2 × 4-H), 5.80 (1 H, br s, 1-H), 6.95–7.75 (6 H, m, NH, 6-H, 7-H and 8-H, py 4-H and py 5-H), 8.70 (2 H, m, py 2-H and 6-H); *m/z* 258 (M^+, 38%), 223 (35), 190 (100), 152 (25) and 117 (40).

5-*Bromo*-8-*methoxy*-1-(3-*pyridyl*)-1,2,3,4-*tetrahydroisoquinolin*-3-*one* **9**. M.p. 242–248 °C (from EtOAc) (Found: C, 53.85; H, 4.1; N, 8.3. $C_{15}H_{13}BrN_2O_2$ requires C, 54.1; H, 3.9; N, 8.4%); δ_H[80 MHz; $(CD_3)_2SO$] 3.6 (2 H, m, 2 × 4-H), 3.8 (3 H, s, OCH_3), 5.8 (1 H, br d, 1-H), 7.0 (1 H, d, *J* 8, 7-H), 7.4 (1 H, ddd, *J* 1, 5 and 8, py 5-H), 7.65 (2 H, d, *J* 8, 6-H and m, py 4-H), 8.5 (2 H, m, py 2-H and 6-H) and 8.75 (1 H, br d, NH) (Found: M^+, 334.0131. $C_{15}H_{13}BrN_2O_2$ requires 334.0140); *m/z* 334 (M^+, 26%), 332 (39) and 252 (100).

8-*Methoxy*-1-(3-*pyridyl*)-1,2,3,4-*tetrahydroisoquinolin*-3-*one* **10**. A solution of the isoquinoline **9** (2.5 g, 7.5 mmol) in glacial acetic acid (80 cm^3) containing 10% palladium-on-carbon (0.2 g) and sodium acetate (2.5 g, 30 mmol, 4 equiv.) was hydrogenated at 70 °C and at atmospheric pressure for 8 h. The cooled solution was evaporated to dryness, partitioned between chloroform and 0.9 mol dm^{-3} aqueous sodium carbonate, dried, and evaporated to give the title compound **10** (1.5 g, 79%), m.p. 195–197 °C (from EtOH) (Found: C, 71.0; H, 5.2; N, 11.0. $C_{15}H_{14}N_2O_2$ requires C, 70.85; H, 5.55; N, 11.0%); δ_H(270 MHz) 3.58 (1 H, d, J_{AB} 21, 4-CH), 3.71 (1 H, d, J_{AB} 21, 4-CH), 3.80 (3 H, s, OCH_3), 5.95 (1 H, d, *J* 5, 1-CH), 6.77 and 6.82 (2 H, 2 × d, *J* 8 and 7, 5-H and 7-H), 7.15–7.33 (3 H, m, NH, 6-H and py 5-H), 7.55 (1 H, m, py 4-H), 8.48 (1 H, dd, *J* 1 and 5, py 6-H) and 8.59 (1 H, d, *J* 1, py 2-H) (Found: M^+, 254.1046. $C_{15}H_{14}N_2O_2$ requires 254.1056); *m/z* 254 (M^+, 18%) and 176 (100).

1-(3-*Pyridyl*)-1,2,3,4-*tetrahydrobenzo*[f]*isoquinolin*-3-*one* **11**. M.p. 209–210 °C (from EtOH) (Found: C, 78.6; H, 5.4; N, 10.3. $C_{18}H_{14}N_2O$ requires C, 78.8; H, 5.1; N, 10.2%); δ_H[80 MHz; $(CD_3)_2SO$] 4.05 (2 H, br d, 2 × 4-H), 6.45 (1 H, br s, 1-H), 7.3–8.15 (8 H, br m, 6 ArH, py 5-H and py 4-H), 8.5 (1 H, dd, *J* 1 and 5, py 6-H), 8.7 (1 H, dd, *J* 1 and 3, py 2-H) and 8.75 (1 H, br s, NH) (Found: M^+, 274.1103. $C_{18}H_{14}N_2O$ requires 274.1106); *m/z* 274 (M^+, 90%), 196 (100) and 168 (44).

General Procedure for the Reaction of the Lactams **3–8** *and* **10–12** *with Dimethylcarbamoyl Chloride.*—A mixture of the appropriate lactam and dimethylcarbamoyl chloride (1.5 cm^3 mmol^{-1} of lactam) was heated in an oil-bath under the conditions described in the text. The cooled solution was evaporated to dryness and the residue partitioned between equal volumes of hydrochloric acid, ethyl acetate and chloroform. The organic layer was separated, extracted with water and the combined aqueous extracts were washed with ethyl acetate. The combined organic layer and extracts were dried and evaporated to give, after chromatography (ether–ethyl acetate or chloroform) compounds **22**, **23** or **24**. The aqueous layers were made basic with saturated aqueous sodium hydrogen carbonate and were extracted with ethyl acetate. The combined extracts were dried, filtered, evaporated and chromatographed (ether–ethyl acetate or chloroform) to give compounds **28–34**. The aqueous layer which remained was brought to pH 14 with 1.25 mol dm^{-3} aqueous sodium hydroxide, and the oil so formed was extracted with ethyl acetate and the extract dried and evaporated. The residue was dissolved in diethyl ether and treated with ethereal hydrogen chloride to precipitate the salt which, upon trituration followed by crystallisation, gave the desired amidine **13–20**.

From 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-3-one **3** the following were formed. 1-(4-*Chlorophenyl*)-3-*dimethylamino*-1,4-*dihydroisoquinoline hydrochloride* **13**. M.p. 141–144 °C (from EtOH–Et_2O) (Found: C, 60.1; H, 5.8; N, 8.4. $C_{17}H_{17}ClN_2{\cdot}HCl{\cdot}H_2O$ requires C, 60.2; H, 5.9; N, 8.3%); ν_{max}(Nujol)/cm^{-1} 3200–3400br, 2250 and 1615; δ_H(80 MHz) 3.3 (3 H, s, NCH_3), 3.45 (3 H, s, NCH_3), 3.65 (1 H, d, J_{AB} 18, 4-H), 4.15 (1 H, d, J_{AB} 18, 4-H), 6.25 (1 H, br s, 1-H) 7.0–7.5 (8 H, br m, 8 ArH) and 12.0 (1 H, br s, NH^+) (Found: M^+, 284.1081. $C_{17}H_{17}ClN_2$ requires 284.1080); *m/z* 284 (M^+, 50%), 256 (10) and 173 (100).

1-(4-*Chlorophenyl*)-N,N-*dimethyl*-3-*oxo*-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxamide* **22**. M.p. 114–115 °C [from EtOAc–light petroleum (b.p. 60–80 °C)] (Found: C, 65.7; H, 5.0; N, 8.4. $C_{18}H_{17}ClN_2O_2$ requires C, 65.75; H, 5.2; N, 8.5%); δ_H(270 MHz) 2.72 (3 H, br s, NCH_3), 2.98 (3 H, br s, NCH_3), 3.7 (2 H, br m, 2 × 4-H), 6.0–6.4 (1 H, br m, 1-H) and 6.9–7.4 (8 H, br m, 8 ArH) (Found: M^+, 330.0959. $C_{18}H_{17}ClN_2O_2$ requires 330.0948); *m/z* 328 (M^+, 25%) and 256 (100).

From 1-(2-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-3-one **4** the following were formed. 3-*Dimethylamino*-1-(2-*fluorophenyl*)-1,4-*dihydroisoquinoline hydrochloride* **14**. M.p. 268–270 °C (from $ClCH_2CH_2Cl$–EtOH–EtOAc) (Found: C, 67.15; H, 5.9; N, 9.2. $C_{17}H_{17}FN_2{\cdot}HCl$ requires C, 67.0; H, 5.95; N, 9.2%); δ_H(400 MHz) 3.40 (3 H, s, NCH_3), 3.55 (3 H, s, NCH_3), 4.04 (1 H, d, J_{AB} 20, 4-H), 4.12 (1 H, d, J_{AB} 20, 4-H), 6.31 (1 H, br s, 1-H), 6.92–7.61 (8 H, br m, 8 ArH) and 11.65 (1 H, br s, NH^+) (Found: M^+, 268.1367. $C_{17}H_{17}FN_2$ requires 268.1376); *m/z* 268 (M^+, 100%), 197 (22) and 173 (100).

1-(2-*Fluorophenyl*)-N,N-*dimethyl*-3-*oxo*-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxamide* **23**. M.p. 153–155 °C [from EtOAc–light petroleum (b.p. 60–80 °C)] (Found: C, 69.2; H, 5.7; N, 8.8. $C_{18}H_{17}FN_2O_2$ requires C, 69.2; H, 5.4; N, 9.0%); δ_H(270 MHz) 2.75 (3 H, br s, NCH_3), 2.93 (3 H, br s, NCH_3), 3.71 (1 H, d, J_{AB} 19, 4-H), 3.93 (1 H, d, J_{AB} 19, 4-H), 6.52 (1 H, br s, 1-H), 6.95–7.40 (8 H, m, 8 ArH) (Found: M^+, 312.1275. $C_{18}H_{17}FN_2O_2$ requires 312.1274); *m/z* 312 (M^+, 26%), 240 (77) and 72 (100).

From 6-fluoro-1-(2-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-3-one **5** the following were formed. 3-*Dimethylamino*-6-*fluoro*-1-(2-*fluorophenyl*)-1,4-*dihydroisoquinoline hydrochloride* **15**. M.p. 280–285 °C (from CH_2Cl_2–EtOAc) (Found: C, 63.0; H, 5.4; N, 8.8. $C_{17}H_{16}F_2N_2{\cdot}HCl$ requires C, 63.3; H, 5.3; N, 8.7%); ν_{max}(Nujol)/cm^{-1} 3100–2500br and 1650; δ_H(80 MHz) [$CDCl_3$/$(CD_3)_2SO$] 3.3 (3 H, s, NCH_3), 3.45 (3 H, s, NCH_3), 4.3 (2 H, br s, 2 × 4-H), 6.3 (1 H, br s, 1-H), 6.9–7.6 (7 H, br m, 7 ArH) and 10.65 (1 H, br s, NH^+) (Found: M^+, 286.1272.

$C_{17}H_{16}F_2N_2$ requires 286.1282); *m/z* 286 (M^+, 65%) and 191 (100).

6-*Fluoro*-1-(2-*fluorophenyl*)-N,N-*dimethyl*-3-*oxo*-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxamide* **24**. M.p. 116–118 °C (from Et_2O–hexane) (Found: C, 65.5; H, 5.0; N, 8.5. $C_{18}H_{16}F_2N_2O_2$ requires C, 65.45; H, 4.9; N, 8.5%); ν_{max}(Nujol)/cm^{-1} 1685br; δ_H(250 MHz) 2.75 (3 H, s, NCH_3), 2.95 (3 H, s, NCH_3), 3.68 (1 H, d, J_{AB} 19, 4-H), 3.92 (1 H, d, J_{AB} 19, 4-H), 6.45 (1 H, s, 1-H) and 6.85–7.4 (7 H, br m, 7 ArH) (Found: M^+, 330.1173. $C_{18}H_{16}F_2N_2O_2$ requires 330.1180); *m/z* 330 (M^+, 8%), 258 (95) and 72 (100).

From 6-fluoro-1-(3-pyridyl)-1,2,3,4-tetrahydroisoquinolin-3-one **6** the following were formed. 3-*Dimethylamino*-6-*fluoro*-1-(3-*pyridyl*)-1,4-*dihydroisoquinoline dihydrochloride* **16**. M.p. 212–220 °C (from $CHCl_3$) (Found: C, 53.4; H, 5.5; N, 11.5. $C_{16}H_{16}FN_3{\cdot}2HCl{\cdot}H_2O$ requires C, 53.3; H, 5.6; N, 11.7%); ν_{max}(Nujol)/cm^{-1} 3480, 3350, 2350–2700br, 2050 and 1655; δ_H[270 MHz; $(CD_3)_2SO$] 3.25 (3 H, s, NCH_3), 3.34 (3 H, s, NCH_3), 4.22 (1 H, d, J_{AB} 19, 4-H), 4.40 (1 H, d, J_{AB} 19, 4-H), 6.35 (1 H, br s, 1-H), 7.15–7.55 (3 H, m, 3 ArH), 7.88 (1 H, m, py 5-H), 8.37 (1 H, m, py 4-H), 8.78 (1 H, d, *J* 4, py 6-H), 9.0 (1 H, s, py 2-H) and 10.70 (1 H, br s, NH^+); *m/z* 269 (M^+, 60%) and 191 (100).

6-*Fluoro*-1-(3-*pyridyl*)*isoquinoline* **31**. M.p. 192–195 °C (from EtOH–Et_2O) (Found: C, 74.75; H, 4.2; N, 12.4. $C_{14}H_9FN_2$ requires C, 75.0; H, 4.05; N, 12.5%); ν_{max}(Nujol)/cm^{-1} no absorption between 1625–1700; δ_H(270 MHz) 7.35 (1 H, m, 7-H), 7.52 (2 H, m, 8-H and py 5-H), 7.66 (1 H, d, *J* 7, 5-H), 8.05 (2 H, m, 4-H and py 4-H), 8.64 (1 H, d, *J* 5, 3-H), 8.76 (1 H, dd, *J* 1 and 5, py 6-H), 8.95 (1 H, d, *J* 1, py 2-H) (Found: M^+, 224.0746. $C_{14}H_9FN_2$ requires 224.0750); *m/z* 224 (M^+, 45%) and 223 (100).

From 5-chloro-1-(3-pyridyl)-1,2,3,4-tetrahydroisoquinolin-3-one **7** the following were formed. 5-*Chloro*-3-*dimethylamino*-1-(3-*pyridyl*)-1,4-*dihydroisoquinoline dihydrochloride* **17**. M.p. 245–252 °C (from $CHCl_3$) (Found: C, 52.2; H, 4.95; N, 11.3. $C_{16}H_{16}ClN_3{\cdot}2HCl{\cdot}0.5H_2O$ requires C, 52.3; H, 5.2; N, 11.4%); ν_{max}(Nujol)/cm^{-1} 3400br, 2350br, 2100, 1995 and 1650; δ_H[80 MHz; $(CD_3)_2SO$] 3.25 (3 H, s, NCH_3), 3.35 (3 H, s, NCH_3), 4.25 (2 H, br s, 2 × 4-H), 6.40 (1 H, br s, 1-H), 7.30–7.90 (4 H, m, py 5-H and 3 ArH), 8.30 (1 H, d, *J* 9, py 4-H), 8.75 (1 H, d, *J* 5, py 6-H), 9.00 (1 H, br s, py 2-H) and 10.65 (1 H, br s, NH^+) (Found: M^+, 285.1017. $C_{16}H_{16}ClN_3$ requires 285.1033); *m/z* 285 (M^+, 70%) and 207 (100).

5-*Chloro*-1-(3-*pyridyl*)*isoquinoline* **32**. M.p. 141–143 °C (from EtOAc) (Found: C, 70.0; H, 3.6; N, 11.9 $C_{14}H_9ClN_2$ requires C, 69.9; H, 3.8; H, 11.6%); ν_{max}(Nujol)/cm^{-1} no absorption 1610–1700; δ_H(270 MHz) 7.52 (2 H, m, py 5-H and 7-H) 7.82, 7.97 and 8.05 (3 H, 2 × d, *J* 6 and 7 and m, 6-H, 8-H and py 4-H), 8.13 (1 H, d, *J* 5, 4-H), 8.76 (2 H, m, py 6-H and 3-H), 8.94 (1 H, br s, py 2-H); *m/z* 239 (M^+, 95%) and 205 (100).

From 1-(3-pyridyl)-1,2,3,4-tetrahydroisoquinolin-3-one **8** the following were formed. 3-*Dimethylamino*-1-(3-*pyridyl*)-1,4-*dihydroisoquinoline dihydrochloride* **18**. M.p. 210–218 °C (from $CHCl_3$–Et_2O) (Found: C, 56.1; H, 6.0; N, 12.5. $C_{16}H_{17}N_3{\cdot}2HCl{\cdot}H_2O$ requires C, 56.15; H, 6.2; N, 12.3%); δ_H[80 MHz; $(CD_3)_2SO$], 3.3 (3 H, br s, NCH_3), 3.4 (3 H, br s, NCH_3), 4.30 (2 H, br s, 2 × 4-H), 6.4 (1 H, br d, 1-H), 7.25 (4 H, br m, 4 ArH), 7.9 (1 H, dd, *J* 5 and 7, py 5-H), 8.4 (1 H, m, py 4-H), 8.8 (1 H, dd, *J* 1 and 5, py 6-H), 9.0 (1 H, d, *J* 1, py 2-H) and 10.7 (1 H, br m, NH^+, exchanges with D_2O) (Found: M^+, 251.1436. $C_{16}H_{17}N_3$ requires 251.1422); *m/z* 251 (M^+, 76%), 173 (100) and 145 (38).

1-(3-*Pyridyl*)*isoquinoline dihydrochloride* **33**. A foam (Found: C, 59.95; H, 4.35; N, 10.0. $C_{14}H_{10}N_2{\cdot}2HCl$ requires C, 60.2; H, 4.3; N, 10.0%); δ_H[80 MHz; $(CD_3)_2SO$], 7.4–8.45 (8 H, br m, 6 ArH and 2 py H), 8.65 (1 H, dd, *J* 1 and 5, py 6-H), 8.8 (1 H, d, *J* 1, py 2-H) (Found: M^+, 206.0837. $C_{14}H_{10}N_2$ requires 206.0844); *m/z* 206 (M^+, 49%) and 205 (100).

From 8-methoxy-1-(3-pyridyl)-1,2,3,4-tetrahydroisoquinolin-3-one **10** the following were formed. 3-*Dimethylamino*-8-*methoxy*-1-(3-*pyridyl*)-1,4-*dihydroisoquinoline dihydrochloride* **19**. δ_H(270 MHz) 3.40 (3 H, s, NCH_3), 3.53 (3 H, s, NCH_3), 3.75 (3 H, s, OCH_3), 4.04 (1 H, d, J_{AB} 19, 4-H), 4.44 (1 H, d, J_{AB} 19, 4-H), 6.60 (1 H, d, *J* 2, 1-H), 6.85 and 6.97 (1 H, d, *J* 8, and 1 H, d, *J* 8, 5-H and 7-H), 7.41 (1 H, t, *J* 8, 6-H), 7.91 (1 H, br m, py 5-H), 8.58 and 9.21 (2 H, br m, and 1 H, br m, py 2-H, py 4-H and py 6-H) and 11.88 (1 H, br s, NH^+) (Found: M^+, 281.1518. $C_{17}H_{19}N_3O$ requires 281.1528); *m/z* 281 (M^+, 49%) and 203 (100).

8-*Methoxy*-N,N-*dimethyl*-3-*oxo*-1-(3-*pyridyl*)-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxamide* **28**. M.p. 178–179 °C (from EtOH) (Found: C, 66.3; H, 5.9; N, 12.8. $C_{18}H_{19}N_3O_3$ requires C, 66.45; H, 5.9; N, 12.9%); δ_H[270 MHz; $(CD_3)_2SO$, spectrum acquired at 110 °C due to considerable broadening at lower temperatures] 2.73 (6 H, s, 2 × NCH_3), 3.57 (1 H, d, *J* 19, 4-H), 3.78 (3 H, s, OCH_3), 3.90 (1 H, d, *J* 19, 4-H), 6.27 (1 H, s, 1-H), 6.89 and 6.94 (2 H, 2 × d, *J* 8 and 8, 5-H and 7-H), 7.30 (2 H, m, 6-H and py 5-H), 7.60 (1 H, br d, *J* 8, py 4-H) and 8.44 (2 H, m, py 2-H and py 6-H) (Found: M^+, 325.1412. $C_{18}H_{19}N_3O_3$ requires 325.1426); *m/z* 325 (M^+, 27%), 253 (54) and 72 (100).

8-*Methoxy*-1-(3-*pyridyl*)*isoquinoline dihydrochloride* **34**. M.p. 205–210 °C (from Et_2O) (Found: C, 58.5; H, 4.6; N, 9.1. $C_{15}H_{12}N_2O{\cdot}2HCl$ requires C, 58.3; H, 4.6; N, 9.1%); δ_H[400 MHz; $(CD_3)_2SO$] 3.72 (3 H, s, OCH_3), 7.21 (1 H, d, *J* 9, 7-H), 7.73 (1 H, d, *J* 9, 5-H), 7.88 (1 H, 2 × d, *J* 9 and 9, 6-H), 8.10 (2 H, d, *J* 5 and m, 4-H and py 5-H), 8.63 (2 H, d, *J* 5 and m, 3-H and py 4-H), 9.01 (1 H, dd, *J* 5 and 1, py 6-H) and 9.10 (1 H, d, *J* 1, py 2-H) (Found: M^+, 236.0957. $C_{15}H_{12}N_2O$ requires 236.0950); *m/z* 236 (M^+, 22%), 221 (100) and 205 (27).

From 1-(3-pyridyl)-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-3-one **11** the following were formed. 3-*Dimethylamino*-1-(3-*pyridyl*)-1,4-*dihydrobenzo*[f]*isoquinoline dihydrochloride* **20**. A foam (Found: C, 61.0; H, 5.7; N, 10.6. $C_{20}H_{19}N_3{\cdot}2HCl{\cdot}H_2O$ requires C, 61.2; H, 5.9; N, 10.7%); δ_H[80 MHz; $(CD_3)_2SO$] 3.3 (3 H, s, NCH_3), 3.55 (3 H, s, NCH_3), 4.7 (2 H, br s, 2 × 4-H), 6.5 (1 H br s, 1-H) and 7.65–9.15 (10 H, br m, 6 ArH and 4 pyH) (Found: M^+, 301.1575. $C_{20}H_{19}N_3$ requires 301.1579); *m/z* 301 (M^+, 75%) and 223 (100).

N,N-*Dimethyl*-3-*oxo*-1-(3-*pyridyl*)-1,2,3,4-*tetrahydrobenzo*-[f]*isoquinoline*-2-*carboxamide* **29**. M.p. 223–224 °C (from EtOH) (Found: C, 73.3; H, 5.5; N, 12.2. $C_{21}H_{19}N_3O_2$ requires C, 73.0; H, 5.5; N, 12.2%); δ_H(80 MHz), 2.7 (3 H, br s, NCH_3), 2.95 (3 H, br s, NCH_3), 4.2 (2 H, br s, 2 × 4-H), 6.45 (1 H, br s, 1-H), 7.0–8.05 (8 H, br m, 6 ArH, py 5-H and py 4-H), 8.5–8.65 (2 H, br m, py 2-H and py 6-H) (Found: M^+, 345.1485. $C_{21}H_{19}N_3O_2$ requires 345.1477); *m/z* 345 (M^+, 51%), 273 (84) and 72 (100).

From 1-(4-pyridyl)-1,2,3,4-tetrahydroisoquinolin-3-one **12** the following were formed. N,N-*Dimethyl*-3-*oxo*-1-(4-*pyridyl*)-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxamide* **30**. M.p. 197–200 °C (from $CHCl_3$–EtOAc) (Found: C, 58.3; H, 5.5; N, 11.75. $C_{17}H_{17}N_3O_2{\cdot}HCl{\cdot}H_2O$ requires C, 58.4; H, 5.8; N, 12.0%); δ_H(270 MHz) 2.83 (3 H, s, NCH_3), 3.07 (3 H, s, NCH_3), 3.38 (1 H, br s, 4-H), 3.73 (1 H, d, *J* 19, 4-H), 6.29 (1 H, br s, 1-H), 7.20–7.75 (4 H, m, 5-H, 6-H, 7-H and 8-H), 7.90 (2 H, d, *J* 6, py 3-H and py 5-H) and 8.68 (2 H, d, *J* 6, py 2-H and py 6-H) (Found: M^+, 295.1335. $C_{17}H_{17}N_3O_2$ requires 295.1320); *m/z* 295 (M^+, 27%), 223 (28) and 72 (100).

3-(N,N-*Dimethylcarbamoyloxy*)-1-(4-*pyridyl*)*isoquinoline hydrochloride* **37**. M.p. 157–160 °C [from EtOAc–light petroleum (b.p. 60–80 °C)] (Found: C, 69.6; H, 5.1; N, 14.6. $C_{17}H_{15}N_3O_2$ requires C, 69.6; H, 5.15; N, 14.3%); δ_H(270 MHz) 3.06 (3 H, s, NCH_3), 3.20 (3 H, s, NCH_3), 7.53 (1 H, s, 4-H), 7.52 and 7.71 (2 H, 2 × dt, *J* 8 and 1, 6-H and 7-H), 7.6 (2 H, 2 × d, *J* 6 and 6, py 3-H and py 5-H), 7.90 and 8.02 (2 H,

2 × d, *J* 8 and 8, 5-H and 8-H), 8.8 (2 H, 2 × d, *J* 6 and 6, py 2-H and py 6-H); *m/z* 293 (M^+, 95%), 220 (17) and 72 (100).

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