Indolizine Studies. Part 3.[1] Synthesis and Dynamic NMR Analysis of Indolizine-2-carboxamides

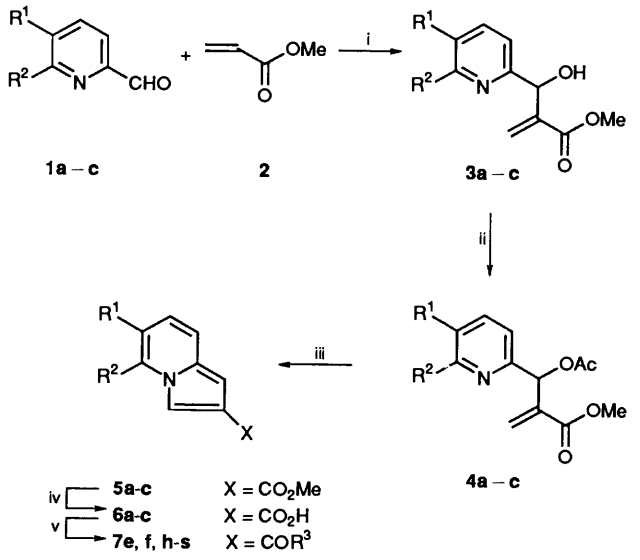
Moira L. Bode, Perry T. Kaye* and, in part, Rosemary George
Department of Chemistry, Rhodes University, PO Box 94, Grahamstown, 6140, South Africa

Reaction of indolizine-2-carboxylic acids with primary and secondary amines in the presence of 1,1′-carbonyldiimidazole provides convenient and efficient access to the corresponding secondary and tertiary amides and offers a significant improvement on previously reported methodology. The N–CO rotational barriers in the symmetrically substituted tertiary amides have also been explored using variable-temperature ^1H and ^{13}C NMR spectroscopy.

Our interest in indolizine chemistry stems from the discovery[2] of a convenient synthesis of 2-substituted indolizines *via* thermal cyclisation of certain 2-pyridyl derivatives.[1] The salient features of the general approach are illustrated in Scheme 1. As part of our ongoing research in this area a series of indolizine-2-carboxamides were required for development as chloroquine analogues and, in this communication, we report the synthesis and dynamic NMR (DNMR) analysis of such compounds.

The most obvious route to the required secondary and tertiary amides, *via* the corresponding indolizine-2-carbonyl chlorides, does not appear to be feasible. In contrast to the ready formation of indolizine-3-carbonyl chloride,[3] our attempted conversion of indolizine-2-carboxylic acid **6a** into indolizine-2-carbonyl chloride using thionyl chloride proved unsuccessful—a result which is consistent with earlier attempts by De and Saha.[4] In fact, the only reported syntheses of indolizinecarboxamides involve heating indolizine-2-carboxylates with ammonia or primary amines in a sealed tube for extended periods. Parrick and co-workers,[5,6] using a slight modification of a method initially developed by De and Saha,[4] obtained indolizine-2-carboxamides in no more than 52% yield. Jones and Stanyer[3] obtained 2-carbamoylindolizine in 46% yield by heating methyl indolizine-2-carboxylate with ammonia in methanol at 155 °C, under pressure, for 65 h. In our hands, heating methyl indolizine-2-carboxylate **6a** in a sealed tube with various primary amines afforded the corresponding indolizine-2-carboxamides in yields in the range 14–60%;† with *tert*-butylamine, however, none of the carboxamide **7g** was obtained, even after heating for 53 h at 100 °C. Treatment of methyl indolizine-2-carboxylate with ethanolic dimethylamine at room temperature for 3 days afforded the required *N,N*-dimethylcarboxamide **7j** in only 2% yield, while heating the reactants in an autoclave at 150 °C and 15 bar‡ for 8 h gave a mixture containing a large number of products (as shown by TLC analysis). The generally low yields, extended reaction times and inapplicability to secondary and sterically hindered primary amines prompted us to explore alternatives to the ester–aminolysis approach. Several methods were examined with little or no success; these included attempted activation of the acyl substrate as the mixed indolizine-2-carboxylic trifluoroacetic anhydride and use of dicyclohexylcarbodiimide as a coupling agent.

Finally, attention was given to use of the coupling agent, 1,1′-carbonyldiimidazole (CDI).[7,8] 3-(Diethylamino)propylamine was added to a complex of indolizine-2-carboxylic acid **6a** and CDI. The reaction was quenched after 15 min and flash chromatography afforded the required amide **7h** in 79% yield (see Table 1). Similarly, reaction of indolizine-2-carboxylic acid **6a** with the branched amine, 5-(diethylamino)pentan-2-ylamine gave the amide **7i** in 45% yield after 15 min and in 71% yield after 2 days. Perhaps even more significantly, use of CDI



	R^1	R^2	R^3
a	H	H	—
b	H	Me	—
c	–[CH]$_4$–		—
d	H	H	$NHCH_2CH_3$
e	H	H	$NH[CH_2]_2CH_3$
f	H	H	$NH[CH_2]_3CH_3$
g	H	H	$NHC(CH_3)_3$
h	H	H	$NH[CH_2]_3NEt_2$
i	H	H	$NHCH(CH_3)[CH_2]_3NEt_2$
j	H	H	NMe_2
k	H	H	NEt_2
l	H	H	$N[CH_2]_3CH_2$
m	H	H	$N[CH_2]_4CH_2$
n	H	Me	NMe_2
o	H	Me	$N[CH_2]_3CH_2$
p	H	Me	$N[CH_2]_4CH_2$
q	–[CH]$_4$–		NEt_2
r	–[CH]$_4$–		$NH[CH_2]_3NEt_2$
s	–[CH]$_4$–		$NHCH(CH_3)[CH_2]_3NEt_2$

Scheme 1 *Reagents and conditions:* i, DABCO; ii, Ac_2O; iii, heat; iv, aq. KOH then H^+; v, CDI, R^3NH_2

† Examples of compounds so obtained (reaction conditions and corresponding yields) are: **7d** (100 °C, 53 h; 37%), **7h** (100 °C, 13 h; 60%) and **7i** (150 °C, 25 h; 14%).
‡ 1 bar = 10^5 Pa.

Table 1 Yields of indolizine-2-carboxamides **7** prepared by treating indolizine-2-carboxylic acids **6** with the amine in the presence of 1,1'-carbonyldiimidazole

Compound 7	Reaction time	Yield[a] (%)
e	15 min	72
f	15 min	63
h	15 min	79
i	2 d	71
j	1 d	87
k	10 min	45
l	30 min	80
m	30 min	70
n	5 min[b]	61
o	5 min	48
p	5 min	48
q	15 min[c]	25
r	2 d	92
s	2 d	57

[a] After column chromatography. [b] Me_2NH_2Cl used instead of Me_2NH. [c] Extending the reaction time, in this case, appeared to increase formation of side-products.

Ar = indolizin-2-yl

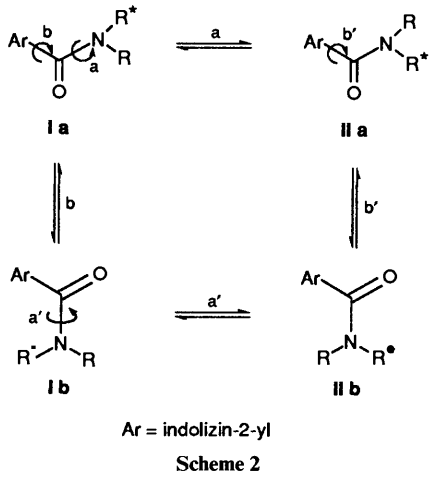
Fig. 1 Lone pair delocalisation in the carboxamide group

permitted the synthesis of the symmetrically substituted tertiary amides listed in Table 1 in good yield. To our knowledge, the synthesis of tertiary indolizine-2-carboxamides has not been reported previously. Use of the low-boiling dimethylamine (b.p. 7 °C) in the preparation of the *N,N*-dimethylcarboxamides **7j** and **n** was successfully obviated by using dimethylammonium hydrochloride. The only unsuccessful reaction encountered was the attempted preparation of *N,N*-diisopropylindolizine-2-carboxamide, the failure in this case being attributed to the prohibitive steric bulk of the nucleophile, diisopropylamine.

The established phenomenon of hindered rotation in carboxamides arises from lone pair delocalisation and the consequent partial double-bond character of the N–CO bond (see Fig. 1). In the symmetrically substituted tertiary indolizine-2-carboxamides **7j–q**, the conformational energy minima associated with simultaneous internal rotation about the C(2)–CO and N–CO bonds are presumed to correspond to two equivalent pairs of quasi-planar conjugated rotamers (**Ia** ≡ **IIa** and **Ib** ≡ **IIb**; Scheme 2). The observed splitting of *N*-alkyl ^1H and ^{13}C NMR signals (see Fig. 2) is attributed to slow rotation about the N–CO bond; however, since rotation types (a) and (a') (Scheme 2) are non-equivalent, the measured rates of site-exchange may be viewed as weighted averages of the individual rates, k_a[**Ia**] and $k_{a'}$[**Ib**].*

Dynamic NMR data for the systems examined are detailed in Table 2. The frequency separation at coalescence ($\Delta\nu_c$) was determined, in each case, by extrapolating a linear plot of $\Delta\nu$ *vs.* T, at temperatures well below coalescence.[10] The coalescence data were obtained using either ^1H or ^{13}C NMR spectroscopy, the latter being necessary when resolution of the ^1H signals was inadequate (compounds **7m** and **p**). In a comparative study of the carboxamide **7q**, the rotational barriers (ΔG^*) obtained using both methods were in close agreement.

From an examination of the DNMR data in Table 2 it may



Ar = indolizin-2-yl

Scheme 2

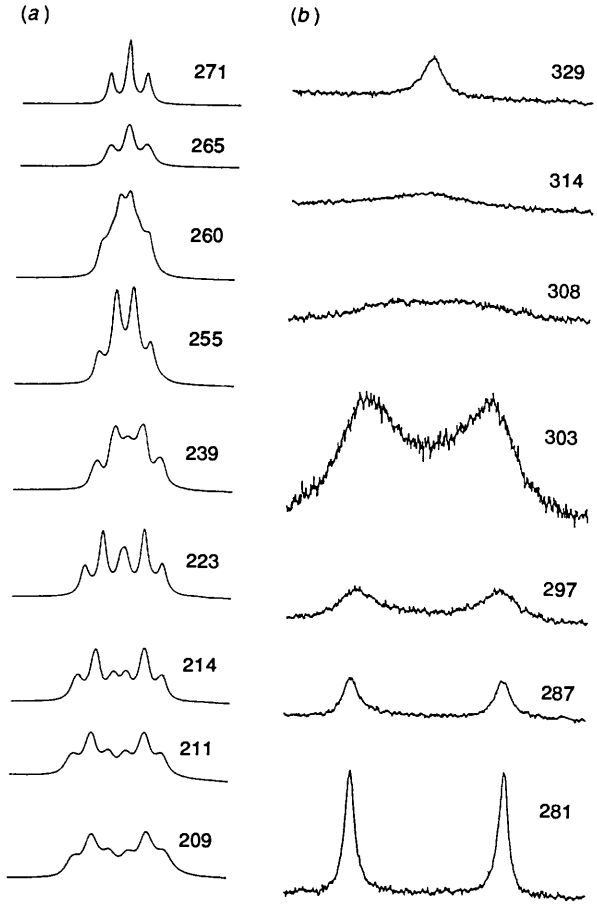


Fig. 2 Variable temperature spectra at the indicated temperature (K) of *N,N*-diethylpyrrolo[1,2-*a*]quinoline-2-carboxamide **7q** in $CDCl_3$. (*a*) ^1H NMR spectra. (*b*) ^{13}C NMR spectra.

be observed that: i, the rotational barriers (ΔG^*) lie within the typical amide range (50–100 kJ mol^{-1}); ii, the magnitude of ΔG^* is insensitive (within the limits of experimental error) to introduction of a 5-methyl substituent or an additional aromatic ring; iii, increasing the steric bulk of the *N*-alkyl substituents [*e.g.* $R^3 = NMe_2$ (**7j**) ⟶ $R^3 = NEt_2$ (**7k**)] decreases ΔG^*, presumably as a result of steric destabilisation of the carboxamide ground state;[11] and iv, the pyrrolidine derivatives **7l** and **o** exhibit significantly higher rotational barriers than their piperidine analogues **7m** and **p**, following the pattern observed in our study of 2-carboxamidochromones.[9]

* For a similar analysis of rotational isomerism in chromone-2-carboxamides see reference 9.

Table 2 Dynamic NMR data for indolizine-2-carboxamides **7j–q**[a]

Compound 7	T/K[b]	$\Delta\nu_c$/Hz[c]	ΔG^*/kJ mol^{-1}[d]	k_{298}/s^{-1}[e]
j	298	48.9	61.4	109
k	265	4.2	59.7	210
l	318	25.6	67.4	10
m	319[f]	538.2	59.5	230
n	298	51.7	61.2	116
o	323	34.3	67.7	9
p	316[f]	540.1	58.9	293
q	260	3.3	59.1	272
	308[f]	302.7	58.8	301

[a] From variable temperature 400 MHz ^{1}H NMR spectra recorded in $CDCl_3$. [b] Coalescence temperature (± 1 K). [c] Frequency separation at coalescence; estimated errors ≤ ± 1 Hz. [d] Free energy of activation for N–CO rotation; $\Delta G^* = RT_c(22.96 + \ln T_c/\Delta\nu_c)$; estimated errors ≤ ± 0.3 kJ mol^{-1}. [e] First-order rate constant at 298 K for N–CO rotation; $\ln k = \ln(k_BT/h) - \Delta G^*/RT$. [f] From 100 MHz ^{13}C NMR spectra.

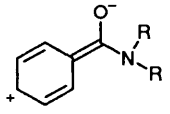


Fig. 3 Competitive delocalisation in arenecarboxamides

An interesting general observation is that rotational barriers reported for corresponding systems follow the trend: indolizine-2-carboxamides < benzamides[12,13] < 2-carboxamidochromones.[9] This trend may be rationalised in terms of competitive delocalisation which decreases the partial double-bond character of the N–CO bond and, hence, the magnitude of ΔG^* (illustrated for benzamides in Fig. 3). Such delocalisation will be enhanced by the electron-rich indolizine nucleus but inhibited by the electron-withdrawing chromone nucleus.

Experimental

NMR spectra were obtained from $CDCl_3$ solutions on a Bruker AMX400 NMR spectrometer and are referenced using the solvent signals (δ_H 7.25 and δ_C 77.0 ppm); proton coupling constants, J_H, are given in Hz. Low-resolution mass spectra were obtained by direct probe analysis on a Hewlett-Packard 5988A mass spectrometer and high-resolution data on a Kratos double-focusing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit).

The indolizine-2-carboxylic acids **6a–c** were prepared by hydrolysis of the corresponding methyl esters, the synthesis of which has been described previously.[1] The carboxamides **7e, f, h–s** were prepared using 1,1′-carbonyldiimidazole (see Table 1); carboxamides **7d, f, h–j** were also obtained *via* aminolysis of methyl indolizine-2-carboxylate.

Indolizine-2-carboxylic Acid **6a**.—*General procedure.* Methyl indolizine-2-carboxylate **5a** (1.0 g, 5.7 mmol) was added to a solution of KOH (2.0 g, 36 mmol) in EtOH (40 cm^3) and the mixture was heated at reflux for 16 h. Sufficient water was added to solubilize the solid material present in the reaction mixture and the pH was adjusted with dilute HCl to pH 2–3. The aqueous layer was extracted with EtOAc (2 × 100 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford indolizine-2-carboxylic acid **6a** as cream-coloured crystals (0.92 g, 100%), m.p. 220–222 °C (from EtOH) (lit.,[14] 240–241 °C); δ_H(400 MHz; $CDCl_3$–[$^2H_6$]DMSO) 2.92 (1 H, br s, OH), 6.13 (1 H, td, $J_{5,6}$ and $J_{6,7}$ 6.8 and $J_{6,8}$ 1.3, 6-H), 6.27 (1 H, ddd, $J_{7,8}$ 9.2, $J_{6,7}$ 6.5 and $J_{5,7}$ 1.0, 7-H), 6.35 (1 H, s, 1-H), 6.94 (1 H, d, $J_{7,8}$ 9.1, 8-H), 7.42 (1 H, d, $J_{1,3}$ 0.9, 3-H) and 7.55 (1 H, dd, $J_{5,6}$ 7.0 and $J_{5,7}$ 1.1, 5-H).

5-Methylindolizine-2-carboxylic acid **6b** (79%); δ_H(400 MHz; $CDCl_3$) 2.51 (3 H, s, CH_3Ar), 6.44 (1 H, d, *J* 7.5, 6-H), 6.71 (1 H, dd, $J_{7,8}$ 8.9 and $J_{6,7}$ 7.5, 7-H), 6.98 (1 H, s, 1-H), 7.33 (1 H, d, *J* 8.9, 8-H), 7.80 (1 H, s, 3-H) and 9.8 (1 H, br s, OH); δ_C 18.5 (CH_3Ar), 101.6 (C-1), 111.7 (C-6), 114.0 (C-3), 118.1 (C-8), 118.7 (C-7), 118.8 (C-2), 133.1 (C-9), 133.8 (C-5) and 171.0 (CO).

Pyrrolo[1,2-a]*quinoline-2-carboxylic acid* **6c** (94%), m.p. 234–236 °C (from EtOH); δ_H(400 MHz; $CDCl_3$–[$^2H_6$]DMSO) 2.75 (1 H, br s, OH), 6.32 (1 H, d, $J_{1,3}$ 1.3, 3-H), 6.52 (1 H, d, $J_{4,5}$ 9.4, 5-H), 6.75 (1 H, d, $J_{4,5}$ 9.4, 4-H), 6.85 (1 H, t, $J_{6,7}$ and $J_{7,8}$ 7.5, 7-H), 7.01 (1 H, td, $J_{7,8}$ and $J_{8,9}$ 7.8 and $J_{6,8}$ 1.2, 8-H), 7.13 (1 H, d, $J_{6,7}$ 6.9, 6-H), 7.49 (1 H, d, $J_{8,9}$ 8.3, 9-H) and 7.93 (1 H, s, 1-H).

N-[3-(*Diethylamino*)*propyl*]*indolizine-2-carboxamide* **7h**.—*General procedure.* Indolizine-2-carboxylic acid **6a** (0.83 g, 5.2 mmol) was dissolved in dry DMF (10 cm^3) in a round-bottomed flask fitted with a condenser and a drying tube. 1,1′-Carbonyldiimidazole (1.35 g, 8.3 mmol) was added to the stirred solution, and the resulting mixture was heated at 40 °C for 5 min, after which time gas evolution had ceased. The reaction mixture was allowed to cool to room temperature, when 3-diethylaminopropylamine (2.46 cm^3, 15.6 mmol) was added to it and stirring was continued for 15 min. After this the reaction was quenched with water (7 cm^3), volatiles were removed under reduced pressure and to the residue was added 1 mol dm^{-3} aq. Na_2CO_3 (50 cm^3). The mixture was extracted with EtOAc (2 × 80 cm^3) and the combined extracts were washed with water (80 cm^3) and brine (80 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The crude material was chromatographed [flash chromatography on silica gel; elution with CH_2Cl_2–MeOH–ammonia (20:4:1)] to afford 4-[3-(*diethylamino*)*propyl*]*indolizine-2-carboxamide* **7h** as a yellow oil (1.12 g, 79%) (Found: M$^+$, 273.184. $C_{16}H_{23}N_3O$ requires *M*, 273.184); δ_H(400 MHz; $CDCl_3$) 0.96 (6 H, t, *J* 7.2, 2 × CH_3), 1.65 (2 H, quintet, *J* 6.2, $CH_2CH_2CH_2$), 2.47 (6 H, m, 2 × CH_3CH_2 and CH_2NEt_2), 3.44 (2 H, q, *J* 5.7, $CONHCH_2$), 6.37 (1 H, td, $J_{5,6}$ and $J_{6,7}$ 6.8 and $J_{6,8}$ 1.0, 6-H), 6.50 (1 H, s, 1-H), 6.55 (1 H, dd, $J_{6,7}$ 6.7 and $J_{7,8}$ 8.7, 7-H), 7.21 (1 H, d, $J_{7,8}$ 8.7, 8-H), 7.66 (1 H, m, 3-H), 7.73 (1 H, d, $J_{5,6}$ 7.0, 5-H) and 8.11 (1 H, br s, NH); δ_C(100 MHz; $CDCl_3$) 11.2 (2 × CH_3), 25.2 ($CH_2CH_2CH_2$), 39.8 and 52.4 (CH_2NH and CH_2NEt_2), 46.7 (2 × CH_3CH_2), 97.2 (C-1), 111.4 (C-6), 113.8 (C-3), 117.8 (C-7), 119.7 (C-8), 124.2 (C-2), 125.3 (C-5), 132.6 (C-9) and 164.7 (CO); *m/z* 273 (M$^+$, 72%) and 86 (100). Further purification of this compound by semi-preparative HPLC (elution with MeOH) was carried out prior to spectral analysis in order to remove a minor impurity, found to be imidazole. An alternative purification procedure employing a cross-linked Sephadex gel was also carried out, but HPLC proved to be the most effective purification procedure.

Alternative procedure. Methyl indolizine-2-carboxylate **5a** (0.50 g, 2.9 mmol) and 3-diethylaminopropylamine (4 cm^3, 25 mmol) were heated in a sealed vial at 100 °C for 13 h and at 150 °C for 25 h. The reaction mixture was poured into water and extracted with EtOAc (2 × 60 cm^3). The combined extracts were washed with water (60 cm^3), dried ($MgSO_4$) and evaporated. The residue was dissolved in 0.1 mol dm^{-3} aq. HCl and extracted with EtOAc to remove any starting material. The aqueous layer was then basified with aq. NaOH and re-extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to yield the crude title compound **7h** (0.48 g, 60%). This product was purified by chromatography [gravity neutral alumina column; elution with $CHCl_3$–MeOH (99:1)].

Compounds **7d**, **7e** [m.p. 100–102 °C (hexane) (lit.,[4] 78–80 °C)] and **7f** [m.p. 75–77 °C (hexane) (lit.,[4] 70–72 °C)]

are known. Analytical data for other compounds are as follows:

N-[5-(*Diethylamino*)*pentan*-2-*yl*]*indolizine*-2-*carboxamide* **7i**, a yellow oil (71%) (Found: M^+, 301.217. $C_{18}H_{27}N_3O$ requires *M*, 301.215); δ_H(400 MHz; $CDCl_3$) 1.00 (6 H, t, *J* 7.2, 2 × CH_3CH_2), 1.23 (3 H, d, *J* 6.6, CH_3CH), 1.55 (4 H, m, $CH[CH_2]_2CH_2N$), 2.46 (2 H, m, CH_2NEt_2), 2.53 (4 H, q, *J* 7.1, 2 × CH_3CH_2), 4.29 (1 H, m, CH_3CH), 6.09 (1 H, d, *J* 7.9, NH), 6.49 (1 H, td, $J_{5,6}$ and $J_{6,7}$ 6.8 and $J_{6,8}$ 0.9, 6-H), 6.56 (1 H, s, 1-H), 6.66 (1 H, dd, $J_{6,7}$ 6.5 and $J_{7,8}$ 8.7, 7-H), 7.30 (1 H, d, $J_{7,8}$ 9.1, 8-H), 7.73 (1 H, m, 3-H) and 7.84 (1 H, d, $J_{5,6}$ 6.7, 5-H); δ_C(100 MHz; $CDCl_3$) 10.4 (2 × CH_3CH_2), 21.3, 22.7 and 34.5 (CH_3CH and $CH[CH_2]_2CH_2$), 44.9 and 52.4 (CHNH and CH_2NEt_2), 46.7 (2 × CH_3CH_2), 97.4 (C-1), 111.7 (C-6), 114.0 (C-3), 118.1 (C-7), 119.8 (C-8), 124.1 (C-2), 125.4 (C-5), 132.8 (C-9) and 164.3 (CO); *m*/*z* 301 (M^+, 48%) and 86 (100).

N,N-*Dimethylindolizine*-2-*carboxamide* **7j** (87%), m.p. 80–83 °C (crude, as attempts at recrystallization resulted in the formation of a black, tarry material) (Found: M^+, 188.093. $C_{11}H_{12}N_2O$ requires *M*, 188.095); δ_H(400 MHz; $CDCl_3$) 3.16 (6 H, br s, 2 × CH_3), 6.47 (1 H, td, $J_{5,6}$ and $J_{6,7}$ 6.8 and $J_{6,8}$ 1.2, 6-H), 6.54 (1 H, s, 1-H), 6.65 (1 H, ddd, $J_{6,7}$ 6.5, $J_{7,8}$ 9.1 and $J_{5,7}$ 1.0, 7-H), 7.31 (1 H, d, $J_{7,8}$ 9.0, 8-H), 7.55 (1 H, m, 3-H) and 7.83 (1 H, dq, $J_{5,6}$ 7.0 and $J_{5,7}$ 1.0, 5-H); δ_C(100 MHz; $CDCl_3$) 35.7 and 39.4 (2 × CH_3), 99.4 (C-1), 111.4 (C-6), 113.9 (C-3), 117.8 (C-7), 119.6 (C-8), 123.3 (C-2), 125.1 (C-5), 132.0 (C-9) and 167.5 (CO); *m*/*z* 188 (M^+, 50%) and 144 (100).

N,N-*Diethylindolizine*-2-*carboxamide* **7k** (45%), m.p. 98–99 °C (from hexane) (Found: M^+, 216.124. $C_{13}H_{16}N_2O$ requires *M*, 216.126); δ_H(400 MHz; $CDCl_3$) 1.23 (6 H, t, *J* 7.1, 2 × CH_3), 3.55 (4 H, q, *J* 7.1, 2 × CH_2), 6.48 (1 H, td, $J_{5,6}$ and $J_{6,7}$ 6.8 and $J_{6,8}$ 1.2, 6-H), 6.51 (1 H, s, 1-H), 6.66 (1 H, ddd, $J_{6,7}$ 6.6, $J_{7,8}$ 9.1 and $J_{5,7}$ 0.9, 7-H), 7.32 (1 H, d, $J_{7,8}$ 9.0, 8-H), 7.54 (1 H, m, 3-H) and 7.85 (1 H, dd, $J_{5,6}$ 7.0 and $J_{5,7}$ 1.0, 5-H); δ_C(100 MHz; $CDCl_3$) 13.8 (2 × CH_3), 40.0 and 42.8 (2 × CH_2), 98.5 (C-1), 111.2 (C-6), 113.2 (C-3), 117.7 (C-7), 119.5 (C-8), 123.9 (C-2), 125.1 (C-5), 132.1 (C-9) and 166.9 (CO); *m*/*z* 216 (M^+, 39%) and 117 (100).

2-(*Pyrrolidin*-1-*ylcarbonyl*)*indolizine* **7l** (80%), m.p. 104–105 °C (crude, as all attempts at recrystallization led to the formation of black, tarry material) (Found: M^+, 214.111. $C_{13}H_{14}N_2O$ requires *M*, 214.111); δ_H(400 MHz; $CDCl_3$) 1.91 (4 H, m, $CH_2[CH_2]_2CH_2$), 3.68 (4 H, m, $N[CH_2]_2$), 6.46 (1 H, td, $J_{5,6}$ and $J_{6,7}$ 6.8 and $J_{6,8}$ 1.1, 6-H), 6.63 (2 H, m, 1-H and 7-H), 7.30 (1 H, d, $J_{7,8}$ 9.1, 8-H), 7.66 (1 H, m, 3-H) and 7.83 (1 H, dd, $J_{5,6}$ 7.0 and $J_{5,7}$ 1.0, 5-H); δ_C(100 MHz; $CDCl_3$) 24.1 and 26.5 ($CH_2[CH_2]_2CH_2$), 46.6 and 48.7 ($N[CH_2]_2$), 99.5 (C-1), 111.5 (C-6), 114.5 (C-3), 117.7 (C-7), 119.7 (C-8), 124.1 (C-2), 125.1 (C-5), 132.1 (C-9) and 164.9 (CO); *m*/*z* 214 (M^+, 32%) and 117 (100%).

2-(*Piperidin*-1-*ylcarbonyl*)*indolizine* **7m** (70%), m.p. 139–141 °C (from hexane) (Found: M^+, 228.126. $C_{14}H_{16}N_2O$ requires *M*, 228.126); δ_H(400 MHz; $CDCl_3$) 1.63 (6 H, m, $CH_2[CH_2]_3CH_2$), 3.68 (4 H, t, *J* 5.3 $N[CH_2]_2$), 6.47 (2 H, m, 1-H and 6-H), 6.66 (1-H, td, $J_{6,7}$ 6.5, $J_{7,8}$ 9.1 and $J_{5,7}$ 1.0, 7-H), 7.31 (1 H, d, $J_{7,8}$ 9.0, 8-H), 7.50 (1 H, m, 3-H) and 7.84 (1 H, dd, $J_{5,6}$ 7.0 and $J_{5,7}$ 1.0, 5-H); δ_C(100 MHz; $CDCl_3$) 24.8 ($CH_2CH_2CH_2,CH_2CH_2$), 26.2 ($CH_2CH_2CH_2CH_2CH_2$), 43.5 and 48.5 ($N[CH_2]_2$), 98.8 (C-1), 111.3 (C-6), 113.3 (C-3), 117.9 (C-7), 119.5 (C-8) 123.5 (C-2), 125.2 (C-5), 132.1 (C-9) and 166.4 (CO); *m*/*z* 228 (M^+, 35%) and 117 (100).

4,4,5-*Trimethylindolizine*-2-*carboxamide* **7n** (61%) (Found: M^+, 202.110. $C_{12}H_{14}N_2O$ requires *M*, 202.111); δ_H(400 MHz; $CDCl_3$) 2.49 (3 H, s, CH_3) 3.18 (6 H, br s, $N[CH_3]_2$), 6.38 (1 H, d, *J* 6.3, 6-H), 6.61 (1 H, s, 1-H), 6.69 (1 H, dd, $J_{7,8}$ 9.4 and $J_{6,7}$ 6.3, 7-H), 7.28 (1 H, d, *J* 9.4, 8-H) and 7.51 (1 H, s, 3-H); δ_C 18.6 (CH_3Ar), 29.7 ($N[CH_3]_2$), 99.9 (C-1), 110.6 (C-6), 111.4 (C-3), 117.3 (C-7), 118.3 (C-8), 123.2 (C-2), 132.8 (C-5), 133.0 (C-9) and 167.9 (CO); *m*/*z* 202 (M^+, 74%) and 131 (100).

5-*Methyl*-2-(*pyrrolidin*-1-*yl*)*indolizine* **7o** (48%) (Found: M^+, 228.128. $C_{14}H_{16}N_2O$ requires *M*, 228.126); δ_H(400 MHz; $CDCl_3$) 1.89 (4 H, br s, $CH_2[CH_2]_2CH_2$), 2.45 (3 H, s, CH_3), 3.70 (4 H, m, $N[CH_2]_2$) and 6.34 (1 H, d, *J* 6.6, 6-H), 6.63 (1 H, m, 7-H), 6.70 (1 H, s, 1-H), 7.25 (1 H, d, *J* 8.5, 8-H) and 7.61 (1 H, s, 3-H); δ_C 18.4 (CH_3Ar), 24.1 and 26.5 ($CH_2[CH_2]_2CH_2$), 46.6 and 48.7 ($N[CH_2]_2$), 99.8 (C-1), 110.6 (C-6), 111.9 (C-3), 117.4 (C-7), 118.1 (C-8), 124.0 (C-2), 132.80 (C-9), 132.83 (C-5) and 165.2 (CO); *m*/*z* 228 (M^+, 31%) and 131 (100).

5-*Methyl*-2-(*piperidin*-1-*ylcarbonyl*)*indolizine* **7p** (48%) (Found: M^+, 242.140. $C_{15}H_{18}N_2O$ requires *M*, 242.142); δ_H(400 MHz; $CDCl_3$) 1.65 (6 H, m, $CH_2[CH_2]_3CH_2$), 2.50 (3 H, s, CH_3Ar), 3.70 (4 H, br s, $N[CH_2]_2$), 6.36 (1 H, d, *J* 6.6, 6-H), 6.52 (1 H, s, 1-H), 6.70 (1 H, dd, $J_{7,8}$ 9.0 and $J_{6,7}$ 6.6, 7-H), 7.27 (1 H, d, *J* 9.0, 8-H) and 7.45 (1 H, s, 3-H); δ_C 18.5 (CH_3Ar), 24.2, 26.6 and 30.9 ($CH_2[CH_2]_3CH_2$), 46.7 and 48.9 ($N[CH_2]_2$), 99.9 (C-1), 110.7 (C-6), 112.1 (C-3), 117.5 (C-7), 118.2 (C-8), 124.1 (C-2), 132.9 (C-5), 133.0 (C-9) and 165.3 (CO); *m*/*z* 242 (M^+, 0.03%) and 131 (100).

N,N-*Diethylpyrrolo*[1,2-a]*quinoline*-2-*carboxamide* **7q** (25%), m.p. 81–83 °C (Found: M^+, 266.140. $C_{17}H_{18}N_2O$ requires *M*, 266.142); δ_H(400 MHz; $CDCl_3$) 1.22 (6 H, t, *J* 7.1, 2 × CH_3), 3.54 (4 H, q, *J* 7.1, 2 × CH_2), 6.57 (1 H, d, $J_{1,3}$ 1.5, 3-H), 6.92 (1 H, d, $J_{4,5}$ 9.4, 5-H), 7.18 (1 H, d, $J_{4,5}$ 9.3, 4-H), 7.24 (1 H, td, $J_{6,7}$ and $J_{7,8}$ 7.5 and $J_{7,9}$ 1.0, 7-H), 7.41 (1 H, td, $J_{7,8}$ and $J_{8,9}$ 7.8 and $J_{6,8}$ 1.4, 8-H), 7.53 (1 H, dd, $J_{6,7}$ 7.8 and $J_{6,8}$ 1.2, 6-H), 7.77 (1 H, d, $J_{8,9}$ 8.3, 9-H) and 8.10 (1 H, d, $J_{1,3}$ 1.2, 1-H); δ_C(100 MHz; $CDCl_3$) 13.5 (2 × CH_3), 40.3 and 42.4 (2 × CH_2), 101.9 (C-3), 113.4 (C-1), 114.0 (C-9), 118.5 (C-4), 119.7 (C-5), 123.0 and 123.7 (C-2 and C-5a), 124.0 (C-7), 127.8 (C-8), 128.4 (C-6), 130.3 (C-3a), 132.7 (C-9a) and 166.5 (CO); *m*/*z* 266 (M^+, 0.1%) and 86 (100).

N-[3-(*Diethylamino*)*propyl*]*pyrrolo*[1,2-a]*quinoline*-2-*carboxamide* **7r**, a viscous yellow oil (92%) (Found: M^+, 323.202. $C_{20}H_{25}N_3O$ requires *M*, 323.200); δ_H(400 MHz; $CDCl_3$) 1.07 (6 H, t, *J* 7.2, 2 × CH_3), 1.76 (2 H, quintet, *J* 6.0, $CH_2CH_2CH_2$), 2.59 (6 H, m, 2 × CH_3CH_2 and CH_2NEt_2), 3.55 (2 H, q, *J* 5.7, $CONHCH_2$), 6.65 (1 H, d, $J_{1,3}$ 1.1, 3-H), 6.97 (1 H, d, $J_{4,5}$ 9.4, 5-H), 7.21 (1 H, d, $J_{4,5}$ 9.4, 4-H), 7.30 (1 H, t, $J_{6,7}$ and $J_{7,8}$ 7.4, 7-H), 7.46 (1 H, td, $J_{7,8}$ and $J_{8,9}$ 7.8 and $J_{6,8}$ 1.0, 8-H), 7.58 (1 H, d, $J_{6,7}$ 7.7, 6-H), 7.83 (1 H, d, $J_{8,9}$ 8.3, 9-H), 8.25 (1 H, br s, NH) and 8.34 (1 H, s, 1-H); δ_C(100 MHz; $CDCl_3$) 11.5 (2 × CH_3), 25.2 ($CH_2CH_2CH_2$), 40.2 and 46.9 (CH_2NEt_2 and CH_3CH_2), 52.8 (CH_2NH), 100.6 (C-3), 113.8 (C-1), 114.3 (C-9), 118.9 (C-4), 120.0 (C-5), 123.6 and 124.0 (C-2 and C-5a), 124.3 (C-7), 128.1 (C-8), 128.6 (C-6), 131.1 (C-3a), 133.1 (C-9a) and 164.5 (CO); *m*/*z* 323 (M^+, 8%) and 86 (100).

N-[5-(*Diethylamino*)*pentan*-2-*yl*]*pyrrolo*[1,2-a]*quinoline*-2-*carboxamide* **7s**, a viscous yellow oil (57%) (Found: M^+, 351.231. $C_{22}H_{29}N_3O$ requires *M*, 351.231); δ_H(400 MHz; $CDCl_3$) 1.00 (6 H, t, *J* 7.2, 2 × CH_3CH_2), 1.25 (3 H, d, *J* 6.6, CH_3CH), 1.57 (4 H, m, $CH[CH_2]_2CH_2N$), 2.46 (2 H, m, CH_2NEt_2), 2.52 (4 H, q, *J* 7.2, 2 × CH_3CH_2), 4.23 (1 H, m, CH_3CH), 6.19 (1 H, d, *J* 8.2, NH), 6.66 (1 H, d, $J_{1,3}$ 1.5, 3-H), 6.99 (1 H, d, $J_{4,5}$ 9.4, 5-H), 7.22 (1 H, d, $J_{4,5}$ 9.4, 4-H), 7.32 (1 H, td, $J_{6,7}$ and $J_{7,8}$ 7.5 and $J_{7,9}$ 1.0, 7-H), 7.48 (1 H, td, $J_{7,8}$ and $J_{8,9}$ 7.8 and $J_{6,8}$ 1.5, 8-H), 7.60 (1 H, dd, $J_{6,7}$ 7.8 and $J_{6,8}$ 1.3, 6-H), 7.86 (1 H, d, $J_{8,9}$, 8.3, 9-H) and 8.34 (1 H, d, $J_{1,3}$ 1.3, 1-H); δ_C(100 MHz; $CDCl_3$) 11.3 (2 × CH_3CH_2), 21.1 (CH_3CH), 23.6 and 35.0 ($CH[CH_2]_2CH_2$), 45.2 (CH_3CH), 46.8 and 52.7 (2 × CH_3CH_2 and CH_2NEt_2), 100.5 (C-3), 113.9 (C-1), 114.4 (C-9), 118.8 (C-4), 120.2 (C-5), 123.4 and 124.0 (C-2 and C-5a), 124.4 (C-7), 128.2 (C-8), 128.7 (C-6), 131.2 (C-3a), 133.0 (C-9a) and 164.1 (CO); *m*/*z* 351 (M^+, 0.1%) and 86 (100).

Dynamic NMR Studies.—Variable temperature ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded for solutions of the carboxamides **7j–q** in $CDCl_3$ on a Bruker AMX400 NMR spectrometer, equipped with a variable temperature unit which has been calibrated using 4% MeOH in CD_3OD and 80% ethylene glycol in $[^2H_6]$DMSO. Temperature stability is judged to be ±0.1 K and the overall error in coalescence temperatures (T_C) is estimated to be ±1.0 K. An equilibration time (≥5 min) was allowed at each new temperature prior to data acquisition. Frequency separations at coalescence ($\Delta\nu_C$) were determined by extrapolation as described by Lai and Chen.[10]

Acknowledgements

The authors wish to thank Rhodes University and the Foundation for Research Development for generous financial support and AECI Ltd. for a post-graduate fellowship (M. L. B.)

References

1 Part 2, M. L. Bode and P. T. Kaye, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1809.
2 M. L. Bode and P. T. Kaye, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2612.
3 G. Jones and J. Stanyer, *J. Chem. Soc. C*, 1969, 901.
4 A. U. De and B. P. Saha, *J. Pharm. Sci.*, 1973, **62**, 1897.
5 J. Mahon, L. K. Mehta, R. W. Middleton, J. Parrick and H. K. Rami, *J. Chem. Res. (S)*, 1992, 362.
6 R. J. Hodgkiss, R. W. Middleton, J. Parrick, H. K. Rami, P. Wardman and G. D. Wilson, *J. Med. Chem.*, 1992, **35**, 1920.
7 D. L. Hughes, J. J. Bergan, J. S. Amato, M. Bhupathy, J. L. Leazer, J. M. McNamara, D. R. Sidler, P. J. Reider and E. J. J. Grabowski, *J. Org. Chem.*, 1990, **55**, 6252.
8 W. A. Denny, G. W. Rewcastle and B. C. Baguley, *J. Med. Chem.*, 1990, **33**, 814.
9 D. N. Davidson and P. T. Kaye, *J. Chem. Soc., Perkin Trans. 1*, 1991, 972.
10 Y. H. Lai and P. Chen, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1665.
11 L. M. Jackman, in *Dynamic Nuclear Magnetic Resonance Spectroscopy*, eds. L. M. Jackman and F. A. Cotton, Academic Press, New York, 1975, p. 212.
12 C. W. Fong, S. F. Lincoln and E. H. Williams, *Aust. J. Chem.*, 1978, **31**, 2615.
13 J. Hauer, G. Völkel and H.-D. Lüdemann, *J. Chem. Res. (S)*, 1980, 16.
14 E. T. Borrows and D. O. Holland, *J. Chem. Soc.*, 1947, 672.

Paper 4/01723D
Received 23*rd March* 1994
Accepted 17*th May* 1994