Indolizine Studies. Part 2.[1] Synthesis and NMR Spectroscopic Analysis of 2-Substituted Indolizines

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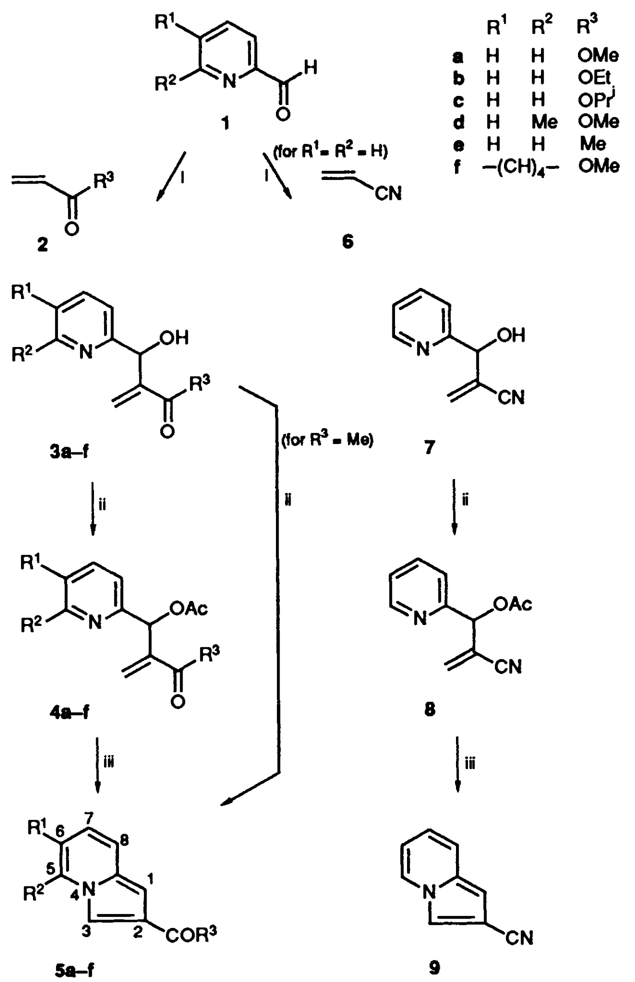
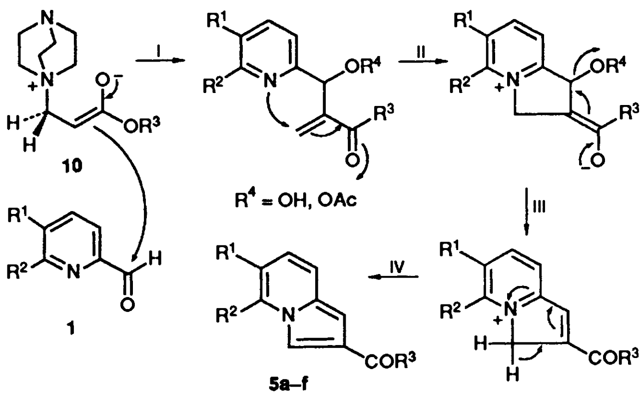
Thermal cyclisation of 3-acetoxy-3-(2-pyridyl)-2-methylenepropionate esters and related compounds provides convenient access to 2-substituted indolizines. Detailed one- and two-dimensional NMR spectroscopic analysis of the title compounds has facilitated interpretation of their ^{1}H and ^{13}C NMR spectra.

Although saturated or semi-saturated indolizine derivatives are widely distributed,[2] no natural compounds containing the discrete, aromatic indolizine nucleus† appear to have been isolated.[2,3] Synthetic indolizines, on the other hand, are relatively well known as photographic sensitisers, fabric brighteners and dyes.[3,4] They are also known to exhibit a variety of pharmacological effects[3] including CNS (central nervous system) depressant[5] and anti-inflammatory[6] activity and, in a very recent paper,[7] attention has been drawn to the potential of ethyl indolizine-2-carboxylates as fluorophores in biological markers.



Scheme 1 *Reagents and conditions:* i, DABCO, room temp.; ii, Ac_2O, 100 °C; iii, heat, 120 °C

† Two alkaloids, which contain the indolizine nucleus as part of a fused system, have been reported.[3]



Scheme 2

Methods for the preparation of indolizines have been extensively reviewed[2,8] and newer procedures have been reported by Acheson and Ansell,[9] Nugent and Murphy,[10] Eberbach and Maier,[11] Goti *et al.*[12] and Abarca *et al.*[13] Our own interest in these compounds stems from the discovery of a convenient route to 2-substituted indolizines *via* thermal cyclisation of 3-acetoxy-3-(2-pyridyl)-2-methylenepropionate esters,[1] and we now report the results of our research on the generality of this approach to 2-substituted indolizines and the ^{1}H and ^{13}C NMR spectroscopic properties of these systems.

The general approach to the 2-substituted indolizines is outlined in Scheme 1. The hydroxy precursors **3a–f** and **7** were typically obtained in good to excellent yields (Table 1) *via* the Baylis–Hillman reaction,[14] which is considered[15] to involve nucleophilic attack, by a dipolar enolate species **10** (Scheme 2; step I), on the pyridine-2-carbaldehyde **1**. Thermal cyclisation to indolizines is presumed to follow the addition–elimination sequence detailed in steps II–IV (Scheme 2)—a process which is clearly facilitated by conversion of the hydroxy function into the better leaving group, acetate. In a remarkably similar approach, Boekelheide and Windgassen[16] found it necessary to heat 3-acetoxy-3-(6-methyl-2-pyridyl)propene to 450 °C to obtain 5-methylindolizine in 30% yield, cyclisation presumably involving direct allylic displacement (S_N') of the acetoxy group. The relative ease of cyclisation of the α,β-unsaturated carbonyl and carbonitrile substrates used in our study, may be attributed to the enhanced electrophilicity of the vinyl system and the involvement of an intramolecular conjugate addition step. In certain instances, acetylation (at 100 °C) was accompanied by direct cyclisation to the corresponding indolizines **5d** (36%) and **5f** (26%), while some of the 2-acetylindolizine **5e** (5%) was even isolated together with its hydroxy precursor **3e** from the room temperature reaction of pyridine-2-carbaldehyde with methyl vinyl ketone. In fact, attempts to isolate the acetoxy intermediate **4e** were unsuccessful, affording instead the cyclised product **5e** directly. The obvious ease of cyclisation, in this case, may be attributed to the greater electrophilicity of the vinyl

Table 1 Comparative yields (%) of 2-substituted indolizines and their acetoxy and/or hydroxy precursors (for structures see Scheme 1)

Hydroxy compound[a]	Acetoxy compound[b]	Indolizine[c]
3a (94)	**4a** (78)	**5a** (68)
3b (96)	**4b** (70)	**5b** (38)
3c (51)	**4c** (62)	**5c** (26)
3d (94)	**4d** (52)[d]	**5d** (84)
3e (81)[e]	—	**5e** (53)[f]
3f (83)	**4f** (57)[g]	**5f** (86)
7 (92)	**8** (58)	**9** (32)

[a] Yield from the corresponding pyridine-2-carbaldehyde. [b] Yield from the corresponding hydroxy compound. [c] Yield from the corresponding acetoxy compound. [d] Together with 36% of compound **5d**. [e] Together with 5% of compound **5e**. [f] Cyclised directly from the hydroxy precursor **3e**. [g] Together with 26% of compound **5f**.

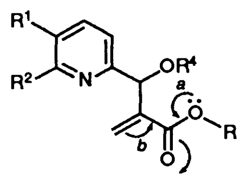


Fig. 1

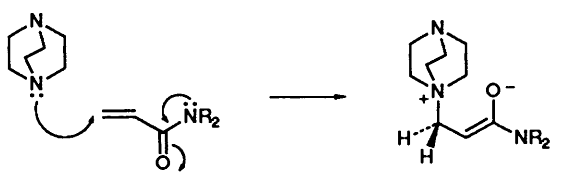


Fig. 2

ketone system in step II (Scheme 2; R^3 = Me) relative to the α,β-unsaturated ester moiety, in which alkyl-*O* lone-pair delocalisation (*a*; Fig. 1) may be expected to reduce π-delocalisation (*b*). Analogous nitrogen lone-pair delocalisation in carboxamide systems presumably inhibits formation of the dipolar enolate (Fig. 2) thus accounting for the failure, in our hands, of both acrylamide and *N,N*-dimethylacrylamide* even to undergo Baylis–Hillman hydroxyalkylation. Interestingly, in their investigation of Baylis–Hillman reactions at elevated pressure, Hill and Isaacs[17] have noted the low reactivity of acrylamide and have reported a yield of only 5% for its reaction with acetone at 5 kbar.†

Extensive polymerisation was observed when acrylaldehyde was added dropwise to a cooled (*ca.* 0 °C) solution of pyridine-2-carbaldehyde and DABCO (1,4-diazabicyclo[2.2.2]octane) in chloroform, even in the presence of the polymerisation inhibitor, hydroquinone. Acrylonitrile, on the other hand, reacts readily with pyridine-2-carbaldehyde to give the hydroxy derivative **7**, elaboration of which provides access to 2-cyano-indolizine **9** *via* its acetoxy precursor **8**.

From our results, it is apparent that the reaction sequences outlined in Scheme 1 offer convenient and relatively efficient access to 2-carbonyl- and 2-cyano-indolizines. This general approach appears to be limited only by the availability of suitably substituted pyridine-2-carbaldehydes and, presumably, by the necessity of using appropriate Baylis–Hillman 'acceptors'.‡

Several one-dimensional, and largely lowfield, NMR spectroscopic studies of a relatively small number of indolizines have been published previously.[19–23] The availability of the seven 2-substituted indolizines **5a–f**, **9** and their respective precursors has provided us with an excellent opportunity for extending these earlier studies. The 400 MHz ^1H and 100 MHz ^{13}C NMR chemical shift data tabulated for ethyl indolizine-2-carboxylate **5b** and its acetoxy- and hydroxy-precursors **4b** and **3b**, respectively (Table 2) are typical of the series of compounds examined. The signal assignments are supported by two-dimensional (COSY and HETCOR) analyses of selected, representative compounds and are essentially consistent with data published for other indolizine systems. In the case of the quinoline derivative **5f**, however, these techniques failed to permit unambiguous assignments of the signals, necessitating application of a multiple-quantum coherence (INADSY) experiment. A combination of the resulting ^{13}C–^{13}C coupling and HETCOR data finally provided the basis for the assignments detailed in Table 3 (the numbering following Mosby[8]).

A remarkable feature of the ^1H NMR spectra of indolizines and related compounds[22] is the extensive long-range ^1H–^1H coupling. By treating the protons in indolizine as a close-coupled seven-spin system, Crews *et al.*[23] have used computer simulation of 100 MHz data to derive values for all twenty-one of the possible couplings, a significant improvement on an earlier analysis by Black *et al.*[19] At 400 MHz, direct measurement of some of the smaller coupling constants becomes feasible and Fig. 3 illustrates the various ^1H–^1H couplings observed for methyl indolizine-2-carboxylate **5a**, the assignments being supported by correlation spectroscopy (COSY) data. The measured *J* values, in fact, correspond reasonably well with those derived for indolizine by Crew *et al.*[23]

Experimental

One- and two-dimensional NMR spectra were obtained from $CDCl_3$ solutions on a Bruker AMX400 NMR spectrometer and are typically referenced using the solvent signals (δ_H 7.25 and δ_C 77.0). Proton coupling constants [J_H (given in Hz)] were typically measured from routine 400 MHz spectra but, in the case of methyl indolizine-2-carboxylate **5a** resolution enhancement was obtained by Gaussian line shape transformation using appropriate line- and Gaussian-broadening factors.

The synthetic procedures are illustrated by the following examples.

Methyl 3-Hydroxy-2-methylene-3-(2-pyridyl)propionate **3a**.[14]—A solution of methyl acrylate (2.50 g, 0.029 mol), DABCO (0.15 g, 1.34 mmol) and pyridine-2-carbaldehyde (2.95 g, 0.028 mol) in $CHCl_3$ (2 cm^3) was allowed to stand at room temperature for 3 d. The solvent was evaporated and the crude product purified by flash chromatography (silica gel; elution with EtOAc) to afford as a colourless oil, methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propionate **3a** (5.08 g, 94%).

Methyl 3-Acetoxy-2-methylene-3-(2-pyridyl)propionate **4a**.[1]—The hydroxy precursor **3a** (1 g, 5.2 mmol) was heated in Ac_2O (5 cm^3) at 100 °C for 0.5 h. The cooled mixture was poured into aq. $NaHCO_3$–ice and stirred for 0.5 h. Basification, extraction (Et_2O), washing of the organic solution (aq. $NaHCO_3$ and then aq. NaCl), and evaporation of the solvent

* The unexpected formation of 2-(2,2,2-trichloro-1-hydroxyethyl)-pyridine during the attempted reaction of *N,N*-dimethylacrylamide with pyridine-2-carbaldehyde in the presence of $CHCl_3$ is being examined and will be reported elsewhere.

† 1 bar = 10^5 Pa.

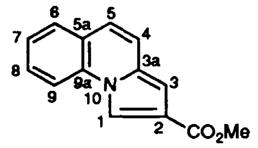
‡ Such acceptors typically include acrylonitrile, acrylate esters, vinyl ketones and phenyl vinyl sulfones; however, the presence of a β-substituent, as in crotonaldehyde, appears to inhibit Baylis–Hillman coupling.[18]

Table 2 ^1H and ^{13}C NMR chemical shift data for ethyl indolizine-2-carboxylate **5b** and its acetoxy **4b** and hydroxy **3b** precursors

Compound	Nucleus[a]	1	2	3	5	6	7	8
3b	^1H	5.53		5.84 6.24	8.37	7.06	7.53	7.30
	^{13}C	72.04	141.86	126.08	147.95	122.25	136.50	121.02
4b	^1H	5.89		6.45 6.75	8.58	7.22	7.69	7.45
	^{13}C	73.93	138.23	127.30	149.41	122.95	136.57	122.71
5b	^1H	6.83		7.79	7.83	6.49	6.65	7.34
	^{13}C	100.33	120.00	115.74	125.24	112.11	117.97	120.16

[a] For comparative purposes, nuclei are numbered to reflect their correspondence with the indolizine product **5b**; the numbers refer, in each case, to the carbon nucleus or its attached proton.

Table 3 ^1H and ^{13}C chemical shift assignments for methyl pyrrolo[1,2-*a*]quinoline-2-carboxylate **5f**



Nucleus	1	2	3	3a	4	5	5a	6	7	8	9	9a
^1H	8.38	—	6.88	—	7.24	7.00	—	7.61	7.36	7.51	7.88	—
^{13}C	115.7	118.87	103.5	131.2	118.90	120.1	124.1	128.6	124.6	128.0	114.3	132.8

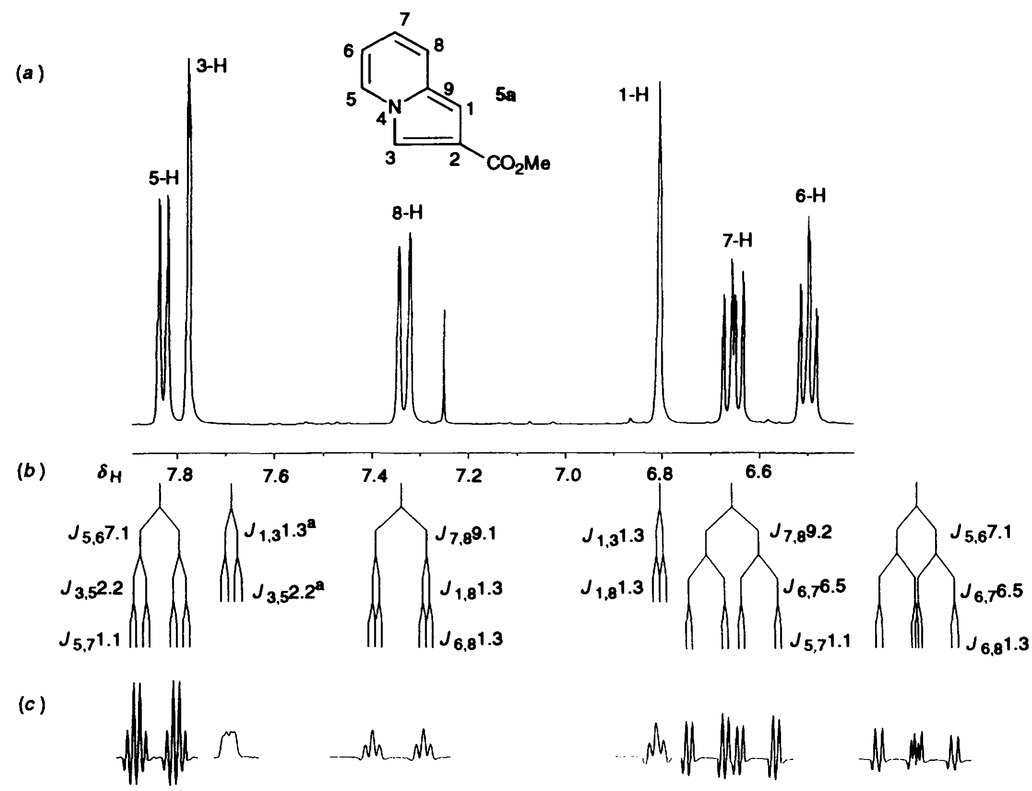


Fig. 3 ^1H–^1H Coupling interactions between the aromatic protons in methyl indolizine-2-carboxylate **5a**; (*a*) routine 400 MHz ^1H NMR spectrum; (*b*) analysis of splitting patterns with corresponding coupling constants in Hz; (*c*) resolution enhanced multiplets
[a] Resolution of the dd was poor; *J* values correspond to coupling constant values measured for 1-H and 5-H nuclei.

afforded the crude acetate **4a**. Purification by flash chromatography [silica gel; elution with hexane–EtOAc (4:6)] gave the acetate **4a** as a colourless oil (0.78 g, 78%).

Methyl Indolizine-2-carboxylate **5a**.[1]—The acetate **4a** (0.51 g, 2.2 mmol) was heated at 120 °C for 1 h and the resulting mixture was purified by flash chromatography [silica gel; elution hexane–EtOAc (7:3)] to give methyl indolizine-2-carboxylate **5a** as yellowish crystals (0.26 g, 68%).

Compounds **5a**[24] and **5e**[25] are also known; analytical data for new compounds are as follows:

Ethyl 3-*acetoxy*-2-*methylene*-3-(2-*pyridyl*)*propionate* **4b** (70%) (Found: M^+, 249.099. $C_{13}H_{15}NO_4$ requires *M*, 249.100); ν_{max}(thin film)/cm^{-1} 1745 and 1720; δ_H 1.17 (3 H, t, *J* 7.2, CH_3CH_2), 2.11 (3 H, s, CH_3CO), 4.11 (2 H, m, CH_2), 5.89 (1 H, s, *CH*OAc), 6.45 and 6.75 (2 H, 2 × s, C=CH_2), 7.22 (1 H, ddd, $J_{5',6'}$ 4.8, $J_{4',5'}$ 7.5 and $J_{3',5'}$ 1.0, 5'-H), 7.45 (1 H, d, $J_{3',4'}$ 7.8, 3'-H), 7.69 (1 H, td $J_{4',5'}$ and $J_{3',4'}$ 7.7 and $J_{4',6'}$ 1.8, 4'-H) and 8.58 (1 H, d, $J_{5',6'}$ 4.4, 6'-H); δ_C 13.9 (CH_3CH_2), 21.0 (CH_3CO), 60.8 (CH_2O), 73.9 (*C*HOAc), 122.7 (C-3'), 123.0 (C-5'), 127.2 (C=CH_2), 136.6 (C-4'), 138.2 (*C*=CH_2), 149.4 (C-6'), 157.0 (C-2') and 164.9 and 169.5 (2 × CO); *m/z* 189 (M^+ − $C_2H_4O_2$, 66%) and 117 (100%).

Ethyl indolizine-2-*carboxylate* **5b** (38%) (Found: M^+, 189.079. $C_{11}H_{11}NO_2$ requires *M*, 189.079); ν_{max}(thin film)/cm^{-1} 2975 and 1710; δ_H 1.38 (3 H, t, *J* 7.2, CH_3), 4.35 (2 H, q, *J* 7.1, CH_2), 6.49 (1 H, td, $J_{6,7}$ and $J_{5,6}$ 6.8 and $J_{6,8}$ 1.1, 6-H), 6.65 (1 H, ddd, $J_{6,7}$ 6.6, $J_{7,8}$ 9.1, and $J_{5,7}$ 1.0, 7-H), 6.83 (1 H, s, 1-H), 7.34 (1 H, d, $J_{7,8}$ 9.1, 8-H), 7.79 (1 H, m, 3-H) and 7.83 (1 H, dd, $J_{5,6}$ 7.1 and $J_{5,7}$ 1.0, 5-H); δ_C 14.4 (CH_3), 60.1 (CH_2), 100.3 (C-1), 112.1 (C-6), 115.7 (C-3), 118.0 (C-7), 120.0 (C-2), 120.2 (C-8), 125.2 (C-5), 132.7 (C-9) and 165.1 (CO); *m/z* 189 (M^+, 52%) and 117 (100%).

Isopropyl 3-*hydroxy*-2-*methylene*-3-(2-*pyridyl*)*propionate* **3c** (51%) (Found: M^+, 221.104. $C_{12}H_{15}NO_3$ requires *M*, 221.105); ν_{max}(thin film)/cm^{-1} 3390br, 2980 and 1715; δ_H 1.10 and 1.12 (6 H, 2 × d, *J* 6.3, 2 × CH_3), 4.95 {2 H, septet [*J* 6.3, *C*H($CH_3)_2$] and overlapping br s (OH)}, 5.55 (1 H, s, *CH*OH), 5.87 and 6.28 (2 H, 2 × s, C=CH_2), 7.12 (1 H, dd, $J_{5',6'}$ 5.3 and $J_{4',5'}$ 7.0, 5'-H), 7.35 (1 H, d, $J_{3',4'}$ 7.9, 3'-H), 7.60 (1 H, td, $J_{4',5'}$ and $J_{3',4'}$ 7.7 and $J_{4',6'}$ 1.6, 4'-H) and 8.45 (1 H, d, $J_{5',6'}$ 4.7, 6'-H); δ_C 21.5 (2 × CH_3), 68.1 [($CH_3)_2CH$], 72.2 (CHOH), 121.1 (C-3'), 122.3 (C-5'), 126.1 (C=CH_2), 136.6 (C-4'), 142.3 (*C*=CH_2), 148.1 (C-6'), 159.8 (C-2') and 165.5 (CO); *m/z* 221 (M^+, 1%) and 78 (100%).

Isopropyl 3-*acetoxy*-2-*methylene*-3-(2-*pyridyl*)*propionate* **4c** (62%) (Found: M^+ − $C_2H_4O_2$, 203.094. $C_{12}H_{13}NO_2$ requires *M*, 203.094); ν_{max}(thin film)/cm^{-1} 1745 and 1715; δ_H 1.03 and 1.09 (6 H, 2 × d, *J* 6.3, 2 × CH_3), 2.04 (3 H, s, CH_3CO), 4.91 [1 H, sept, *J* 6.3, *C*H($CH_3)_2$], 5.77 (1 H, s, *CH*OAc), 6.35 and 6.63 (2 H, 2 × s, C=CH_2), 7.12 (1 H, ddd, $J_{4',5'}$ 7.4, $J_{5',6'}$ 4.9 and $J_{3',5'}$ 1.1, 5'-H), 7.34 (1 H, d, $J_{3',4'}$ 7.9, 3'-H), 7.60 (1 H, td, $J_{4',5'}$ and $J_{3',4'}$ 7.7 and $J_{4',6'}$ 1.8, 4'-H) and 8.48 (1 H, dd, $J_{5',6'}$ 4.8 and $J_{4',6'}$ 0.7, 6'-H); δ_C 20.6 (CH_3CO), 21.2 and 21.3 (2 × CH_3), 68.1 [($CH_3)_2CH$], 73.7 (*C*HOAc), 122.3 (C-3'), 122.6 (C-5'), 126.5 (C=CH_2), 136.2 (C-4'), 138.6 (*C*=CH_2), 149.1 (C-6'), 157.0 (C-2') and 164.1 and 169.1 (2 × CO); *m/z* 203 (M^+ − $C_2H_4O_2$, 31%) and 161 (100%).

Isopropyl indolizine-2-*carboxylate* **5c** (26%) (Found: M^+, 203.094. $C_{12}H_{13}NO_2$ requires *M*, 203.094); ν_{max}(thin film)/cm^{-1} 2980 and 1705; δ_H 1.35 (6 H, d, *J* 6.3, 2 × CH_3), 5.24 [1 H, sept, *J* 6.3, ($CH_3)_2CH$], 6.48 (1 H, td, $J_{6,7}$ and $J_{5,6}$ 6.8 and $J_{6,8}$ 1.1, 6-H), 6.64 (1 H, ddd, $J_{7,8}$ 9.1, $J_{6,7}$ 6.5 and $J_{5,7}$ 1.0, 7-H), 6.81 (1 H, s, 1-H), 7.32 (1 H, d, $J_{7,8}$ 9.1, 8-H), 7.77 (1 H, m, 3-H) and 7.82 (1 H, dd, $J_{5,6}$ 7.1 and $J_{5,7}$ 1.0, 5-H); δ_C 22.0 (2 × CH_3), 67.3 [($CH_3)_2CH$], 100.4 (C-1), 112.1 (C-6), 115.7 (C-3), 117.9 (C-7), 120.2 (C-8), 120.5 (C-2), 125.2 (C-5), 132.7 (C-9) and 164.6 (CO); *m/z* 203 (M^+, 20%) and 161 (100%).

Methyl 3-*hydroxy*-2-*methylene*-3-(6-*methyl*-2-*pyridyl*)*propionate* **3d** (94%), m.p. 84–85 °C (from hexane) (Found: C, 63.5; H, 6.1; N, 6.6. $C_{11}H_{13}NO_3$ requires: C, 63.8; H, 6.3; N, 6.8%); ν_{max}(KBr)/cm^{-1} 3130br, 2860 and 1715; δ_H 2.52 (3 H, s, CH_3Ar), 3.73 (3 H, s, CH_3O), 5.21 (1 H, d, *J* 5.9, OH), 5.58 (1 H, d, *J* 5.7, *CH*OH), 5.92 and 6.31 (2 H, 2 × s, C=CH_2), 7.03 (1 H, d, $J_{4',5'}$ 7.6, 5'-H), 7.14 (1 H, d, $J_{3',4'}$ 7.7, 3'-H) and 7.52 (1 H, t, $J_{4',5'}$ and $J_{3',4'}$ 7.7, 4'-H); δ_C 24.2 (CH_3Ar), 51.8 (CH_3O), 71.2 (CHOH), 118.0 (C-3'), 122.1 (C-5'), 126.6 (C=CH_2), 137.0 (C-4'), 142.2 (*C*=CH_2), 157.0 (C-6'), 158.3 (C-2') and 166.6 (CO); *m/z* 207 (M^+, 5%) and 190 (100%).

Methyl 3-*acetoxy*-2-*methylene*-3-(6-*methyl*-2-*pyridyl*)*propionate* **4d** (52%)* (Found: M^+ − $C_2H_3O_2$ 190.087. $C_{11}H_{12}NO_2$ requires *M*, 190.087); ν_{max}(thin film)/cm^{-1} 1750 and 1730; δ_H 2.10 (3 H, s, CH_3CO), 2.48 (3 H, s, CH_3Ar), 3.67 (3 H, s, CH_3O), 5.78 (1 H, s, *CH*OAc), 6.41 and 6.67 (2 H, 2 × s, C=CH_2), 7.03 (1 H, d, $J_{4',5'}$ 7.7, 5'-H), 7.15 (1 H, d, $J_{3',4'}$ 7.7, 3'-H) and 7.53 (1 H, t, $J_{4',5'}$ and $J_{3',4'}$ 7.7, 4'-H); δ_C 21.0 and 24.4 (2 × CH_3), 51.8 (CH_3O), 74.0 (*C*HOAc), 119.0 (C-3'), 122.5 (C-5'), 127.6 (C=CH_2), 136.6 (C-4'), 138.4 (*C*=CH_2), 156.2 (C-6'), 158.2 (C-2') and 165.5 and 169.5 (2 × CO); *m/z* 190 (M^+ − $C_2H_3O_2$, 19%) and 83 (100%).

Methyl 5-methylindolizine-2-*carboxylate* **5d** (84%) (Found: M^+, 189.079. $C_{11}H_{11}NO_2$ requires *M*, 189.079); ν_{max}(thin film)/cm^{-1} 2950 and 1720; δ_H 2.42 (3 H, s, CH_3Ar), 3.86 (3 H, s, CH_3O), 6.36 (1 H, d, $J_{6,7}$ 6.6, 6-H), 6.65 (1 H, dd, $J_{6,7}$ 6.6 and $J_{7,8}$ 9.0, 7-H), 6.88 (1 H, m, 1-H), 7.27 (1 H, d, $J_{7,8}$ 9.3, 8-H) and 7.68 (1 H, m, 3-H); δ_C 18.2 (CH_3Ar), 51.2 (CH_3O), 100.8 (C-1), 111.2 (C-6), 112.8 (C-3), 117.8 (C-8), 118.4 (C-7), 119.3 (C-2), 132.9 (C-9), 133.3 (C-5) and 165.6 (CO); *m/z* 189 M^+, 100%).

4-*Hydroxy*-3-*methylene*-4-(2-*pyridyl*)*butan*-2-*one* **3e**† (81%); ν_{max}(thin film)/cm^{-1} 3350br and 1685; δ_H 2.19 (3 H, s, CH_3), 4.99 (1 H, br s, OH), 5.60 (1 H, s, *CH*OH), 6.03 (1 H, d, *J* 0.9, C=CH_2), 6.10 (1 H, s, C=CH_2), 7.05 (1 H, dd, $J_{5',6'}$ 5.0 and $J_{4',5'}$ 7.3, 5'-H), 7.30 (1 H, d, $J_{3',4'}$ 7.9, 3'-H), 7.52 (1 H, td, $J_{4',5'}$ and $J_{3',4'}$ 7.7 and $J_{4',6'}$ 1.8, 4'-H) and 8.37 (1 H, d, $J_{5',6'}$ 4.6, 6'-H); δ_C 26.1 (CH_3), 70.9 (CHOH), 121.2 (C-3'), 122.2 (C-5'), 126.4 (C=CH_2), 136.5 (C-4'), 147.9 (C-6'), 149.7 (*C*=CH_2), 159.9 (C-2') and 199.3 (CO); *m/z* 177 (M^+, 18%) and 78 (100%).

Methyl 3-*hydroxy*-2-*methylene*-3-(2-*quinolyl*)*propionate* **3f** (83%) (Found: M^+, 243.089. $C_{14}H_{13}NO_3$ requires *M*, 243.089); ν_{max}(thin film)/cm^{-1} 3400br, 2970 and 1735; δ_H 3.71 (3 H, s, CH_3), 5.50 (1 H, br s, OH), 5.77 (1 H, s, *CH*OH), 5.97 and 6.36 (2 H, 2 × s, C=CH_2), 7.43 (1 H, d, $J_{3',4'}$ 8.3, 3'-H), 7.51 (1 H, m, 6'-H), 7.68 (1 H, m, 7'-H), 7.77 (1 H, dd, $J_{5',6'}$ 8.3 and $J_{5',7'}$ 1.0, 5'-H), 8.07 (1 H, d, $J_{7',8'}$ 8.6, 8'-H) and 8.09 (1 H, d, $J_{3',4'}$ 8.4, 4'-H); δ_C 51.8 (CH_3), 71.8 (CHOH), 118.8 and 126.5 (2 × ArC), 127.5 (C=CH_2), 127.5 (ArC), 127.6 (*C*=CH_2), 128.7, 129.7, 137.0, 141.7, 146.3 and 159.3 (6 × ArC) and 166.5 (CO); *m/z* 243 (M^+, 11%) and 226 (100%).

Methyl 3-*acetoxy*-2-*methylene*-3-(2-*quinolyl*)*propionate* **4f** (57%)‡ (Found: M^+, 285.100. $C_{16}H_{15}NO_4$ requires *M*, 285.100); ν_{max}(thin film)/cm^{-1} 1750 and 1730; δ_H 2.16 (3 H, s, CH_3CO), 3.69 (3 H, s, CH_3O), 5.92 (1 H, s, *CH*OAc), 6.49 and 6.90 (2 H, 2 × s, C=CH_2), 7.52 [2 H, td ($J_{6',7'}$ and $J_{5',6'}$ 8.0 and $J_{6',8'}$ 1.1, 6'-H) overlapping d ($J_{3',4'}$ 8.6, 3'-H)], 7.68 (1 H, m, 7'-H), 7.78 (1 H, dd, $J_{5',6'}$ 8.1 and $J_{5',7'}$ 1.1, 5'-H), 8.07 (1 H, d, $J_{7',8'}$ 8.3, 8'-H) and 8.14 (1 H, d, $J_{3',4'}$ 8.4, 4'-H); δ_C 21.0 (CH_3CO), 52.0 (CH_3O), 74.5 (*C*HOAc), 119.9 and 126.7 (2 × ArC), 127.46 (C=CH_2), 127.53 (*C*=CH_2), 127.9, 129.5, 129.6, 136.7, 138.2, 147.6 and 157.2 (7 × ArC), 165.5 and 169.6 (2 × CO); *m/z* 285 (M^+, 0.6%) and 226 (100%).

Methyl pyrrolo[1,2-a]*quinoline*-2-*carboxylate* **5f** (86%), m.p. 109–110 °C (from hexane) (Found: M^+, 225.079. $C_{14}H_{11}NO_2$ requires *M*, 225.079); ν_{max}(KBr)/cm^{-1} 1710; δ_H 3.89 (3 H, s, CH_3), 6.88 (1 H, m, 3-H), 7.00 (1 H, d, $J_{4,5}$ 9.4, 5-H), 7.24 (1 H, d, $J_{4,5}$ 9.4, 4-H), 7.36 (1 H, td, $J_{6,7}$ and $J_{7,8}$ 7.5 and $J_{7,9}$ 1.1, 7-H), 7.51 (1 H, m, 8-H), 7.61 (1 H, dd, $J_{6,7}$ 7.8 and $J_{6,8}$ 1.4, 6-H), 7.88 (1 H, d, $J_{8,9}$ 8.3, 9-H) and 8.38 (1 H, m, 1-H); δ_C 51.4 (CH_3), 103.5 (C-3), 114.3 (C-9), 115.7 (C-1), 118.87 (C-2), 118.90 (C-4), 120.1 (C-5), 124.1 (C-5a), 124.6 (C-7), 128.0 (C-8), 128.6 (C-6), 131.2 (C-3a), 132.8 (C-9a) and 165.3 (CO); *m/z* 225 (M^+, 100%).

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* Together with 36% of compound **5d**.

† This compound decomposes rapidly and was isolated together with 5% of compound **5e**.

‡ Together with 26% of compound **5f**.

3-*Hydroxy*-2-*methylene*-3-(2-*pyridyl*)*propiononitrile* **7** (92%), m.p. 66–67 °C (from hexane) (Found: M^+, 160.064. $C_9H_8N_2O$ requires *M*, 160.064); ν_{max}(thin film)/cm^{-1} 3200br, 2225 and 1600; δ_H 5.27 (2 H, 2 × overlapping s, C*H*OH and OH), 6.05 and 6.22 (2H, 2 × s, C=CH_2), 7.29 (1 H, m, 5'-H), 7.39 (1 H, d, 3'-H), 7.76 (1 H, m, 4'-H) and 8.57 (1 H, m, 6'-H); δ_C 72.8 (CHOH), 116.7 (CN), 121.2 (C-3'), 123.7 (C-5'), 125.8 (*C*=CH_2), 130.9 (C=*C*H_2), 137.5 (C-4'), 148.5 (C-6') and 156.0 (C-2'); *m*/*z* 160 (M^+, 2%) and 143 (100%).

3-*Acetoxy*-2-*methylene*-3-(2-*pyridyl*)*propiononitrile* **8** (58%) (Found: M^+, 202.074. $C_{11}H_{10}N_2O_2$ requires *M*, 202.074); ν_{max}(thin film)/cm^{-1} 2225 and 1750; δ_H 2.14 (3 H, s, CH_3CO), 6.08 and 6.11 (2 H, 2 × s, C=CH_2), 6.33 (1 H, s, C*H*OAc), 7.22 (1 H, dd, $J_{5',6'}$ 4.8 and $J_{4',5'}$ 7.6, 5'-H), 7.43 (1 H, d, $J_{3',4'}$ 7.7, 3'-H), 7.70 (1 H, td, $J_{4',5'}$ and $J_{3',4'}$ 7.7 and $J_{4',6'}$ 1.2, 4'-H) and 8.55 (1 H, d, $J_{5',6'}$ 4.9, 6'-H); δ_C 20.7 (CH_3), 75.1 (*C*HOAc), 115.8 (CN), 121.1 (C-3'), 121.4 (*C*=CH_2), 123.6 (C-5'), 133.5 (C=*C*H_2), 137.1 (C-4'), 149.5 (C-6'), 154.8 (C-2') and 169.0 (CO); *m*/*z* 202 (M^+, 0.3%) and 143 (100%).

2-*Cyanoindolizine* **9** (32%), m.p. 67.5–69 °C (from hexane) (Found: C, 76.2; H, 4.3; N, 20.0. $C_9H_6N_2$ requires C, 76.0; H, 4.25; N, 19.7%); ν_{max}(KBr)/cm^{-1} 3110 and 2210; δ_H 6.62 (1 H, td, $J_{6,7}$ and $J_{5,6}$ 6.8 and $J_{6,8}$ 1.1, 6-H), 6.67 (1 H, s, 1-H), 6.77 (1 H, ddd, $J_{6,7}$ 6.6, $J_{7,8}$ 9.2 and $J_{5,7}$ 0.9, 7-H), 7.36 (1 H, d, $J_{7,8}$ 9.2, 8-H), 7.66 (1 H, m, 3-H) and 7.87 (1 H, dd, $J_{5,6}$ 7.1 and $J_{5,7}$ 1.0, 5-H); δ_C 97.4 (C-2), 102.5 (C-1), 113.0 (C-6), 116.4 (CN), 117.5 (C-3), 119.4 and 119.7 (C-7 and C-8), 125.1 (C-5) and 132.7 (C-9); *m*/*z* 142 (M^+, 100%).

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