

Chemistry of pyrrolizinones. Part 1. Reactions of pyrrolizin-3-ones with electrophiles: synthesis of 3,8-didehydroheliotridin-5-one¹

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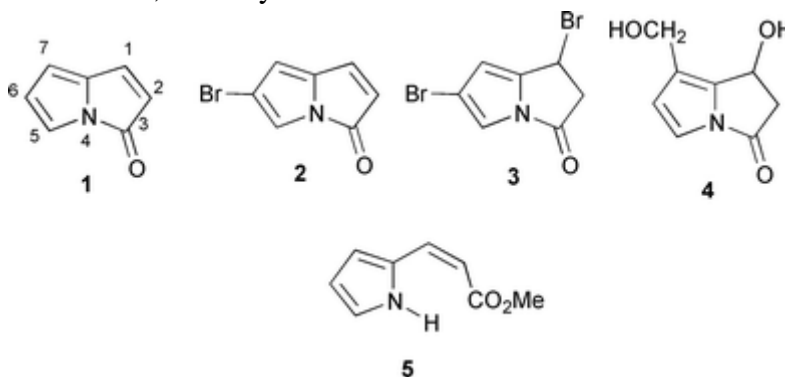
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The reaction of pyrrolizin-3-one **1** with dry hydrogen chloride gives the 1-chloro-1,2-dihydro derivative **8** (93%) by electrophilic addition. The halogen of **8** is readily displaced by *O*-nucleophiles to give **6**, **9** or **10** in 87100% yield, and this strategy has been employed in a short synthesis of the necine base didehydroheliotridin-5-one **4**. Pyrrolizinone **1** can be brominated by *N*-bromosuccinimide in the presence of nucleophiles to give **20** or **21**, or under free radical conditions to give the 2-bromopyrrolizinone **22** (55%). Vilsmeier formylation of **1** gave a variety of products including the 5-formylpyrrolizinone **26** (16%), but azo-coupling could only be observed under basic conditions to give the coupled propenoate **31** (46%) via the anion of the ring-opened species **30**.

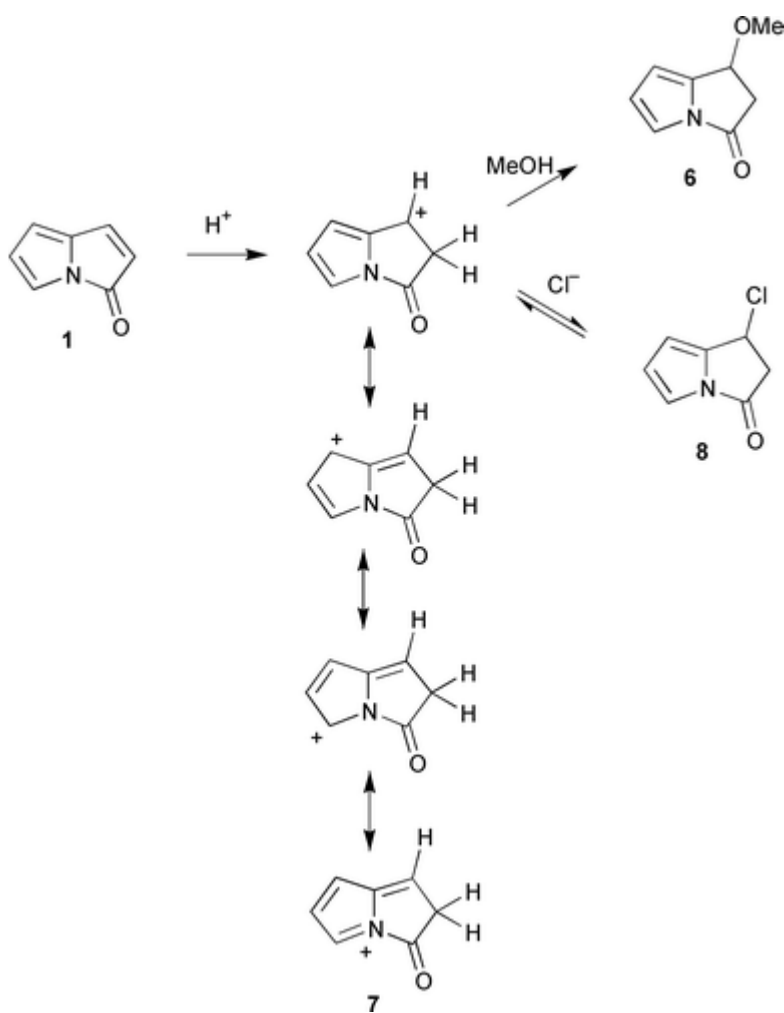
In this paper, we report the results of a systematic study of the reactions of pyrrolizin-3-one **1** with simple electrophiles.¹ Though there have been no authentic previous reports of such reactions in the literature,² we were encouraged by an earlier observation³ that in the preparation of the 6-bromo compound **2** by flash vacuum pyrolysis (FVP) a small quantity of a dibromo impurity was obtained. We speculated at the time³ that this might have been formed by adventitious addition of HBr across the 1,2-double bond to give **3**. This mode of behaviour is now confirmed, and the synthetic potential of such 1-halogeno-1,2-dihydropyrrolizin-3-ones leading to 1-hydroxy-1,2-dihydropyrrolizinones is now explored. The introduction of such functionality is an important step in the development of simple routes from pyrrolizinones^{4,5} to pyrrolizine natural products, and we illustrate our methodology with details of a concise synthesis of the *Senecio* alkaloid 3,8-didehydroheliotridin-5-one **4**.¹



Results and discussion

In view of the presence of the lactam function in pyrrolizin-3-one **1**, we expected that treatment of this compound with methanolic hydrogen chloride would lead to ring opening to the propenoate **5** as found under basic conditions.² Indeed, *N*-acyl-pyrroles and -indoles are known to be cleaved under the influence of acid catalysis.⁶ In the event, the only product which could be isolated when **1** was heated under reflux for 2 h with methanolic HCl was the methyl ether **6**. Its structure followed by analogy of its spectra with those of other 1-functionalised-1,2-dihydropyrrolizinones;¹⁷ in particular the ABX pattern of the 1- and 2-proton resonances in the ¹H NMR spectrum was characteristic [$\delta_{\text{H}}(1)$ 4.83, ³*J* 6.8 and 2.0 Hz; $\delta_{\text{H}}(2)$ 3.33, ²*J* 18.6, ³*J* 6.8 Hz, and 2.95, ²*J* 18.6, ³*J* 2.0 Hz], showing a large geminal coupling constant relating the two protons at position 2, and two vicinal ³*J*_{1,2} couplings relating protons *syn* (6.8 Hz) and *anti* (2.0 Hz) to the proton at position 1. The regiochemistry was confirmed by the presence of a minor coupling ⁴*J*_{1,7} of 0.9 Hz, which is characteristic of *ortho*-benzylic interactions.^{8,9}

Pyrrolizinone **1** is known to be stable in neutral methanol, and so the most likely mechanism for the formation of **6** is electrophilic attack of H⁺ at the 2-position to give the resonance stabilised carbocation **7**, followed by quenching by either methanol (to give **6**) or initially by chloride ion (to give **8**) (Scheme 1). In the latter case, an S_N1 process could regenerate the carbocation **7** leading to **6** in the presence of an excess of methanol. Although the yield of **6** was low (22%), this experiment nevertheless demonstrated the rather surprising reactivity of the enone moiety of **1** towards electrophiles (due to the stability of the cation **7**), together with the equally surprising stability of both **1** and its 1,2-dihydro derivatives towards ring opening under acidic conditions.

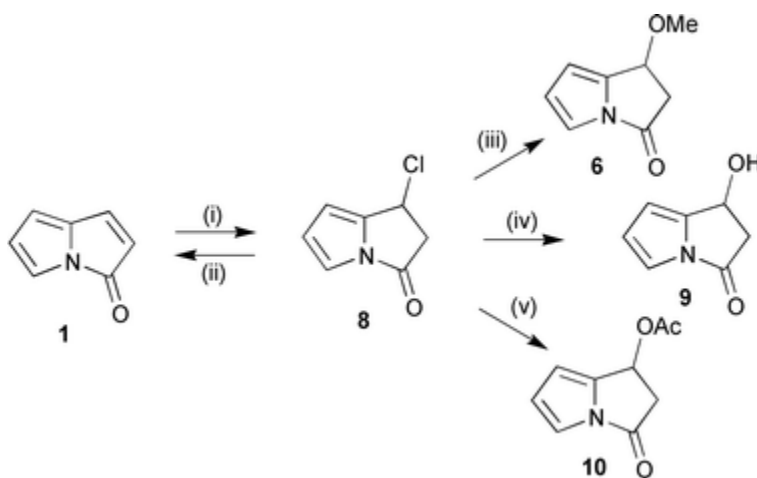


Scheme 1

These observations were further confirmed by the reaction of **1** with dry hydrogen chloride in

dichloromethane solution (*i.e.* in the absence of a competing nucleophilic solvent). After only 30 min at room temperature, a 93% yield of the 1-chloro compound **8** was obtained. This compound was characterised by its mass spectrum [m/z 157 and 155 (M^+)], by its ^1H NMR spectrum (which shows a closely similar coupling pattern to that of **6**¹⁴(see Experimental) and by the further reactions described below.

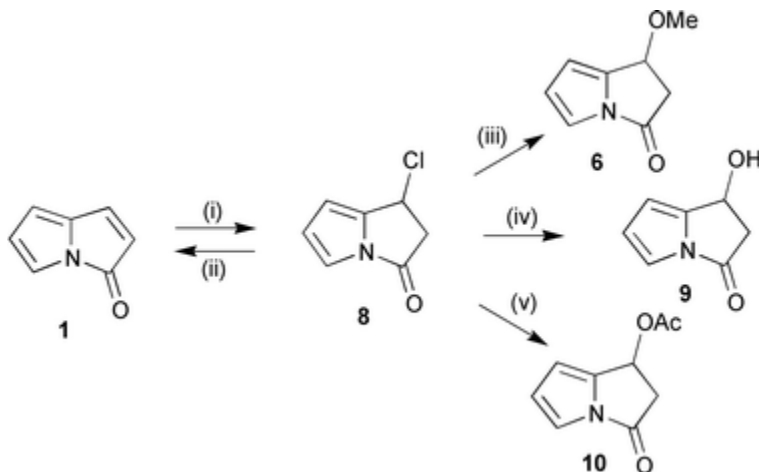
In the presence of a non-nucleophilic base such as triethylamine, clean dehydrochlorination of **8** took place at room temperature to regenerate pyrrolizin-3-one **1** in 70% yield. More usefully, **8** proved to be an exceptional alkylating agent in reactions with *O*-nucleophiles. Thus treatment with an excess of methanol at room temperature (30 min) gave the ether **6** in quantitative yield (identical with that obtained from **1** and methanolic HCl), aqueous acetone gave the alcohol **9** (93%) and a solution of sodium acetate in glacial acetic acid gave the acetoxy derivative **10** (87%) (Scheme 2). This strategy therefore allows a two-step *O*-functionalisation of the 1-position of pyrrolizin-3-ones and hence a means of incorporating a key structural feature of most pyrrolizidine alkaloids into the bicyclic framework. This transformation was not possible by conjugate addition of *O*-nucleophiles owing to preferential reaction of hard nucleophiles at the carbonyl group.^{1,3} However, these compounds contain features of the toxic pyrrolic metabolites of pyrrolizidine alkaloids, and were always handled with extreme care; the labile chloro compound **8** in particular was generally not isolated but was transformed to the other derivatives *in situ*.



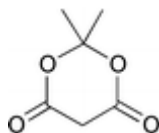
Scheme 2 Reagents and conditions: (i) HCl, CH_2Cl_2 ; (ii) Et_3N ; (iii) MeOH; (iv) H_2O ; (v) NaOAc¹⁴/HOAc.

With these¹⁴ and earlier⁵ results in place, we embarked on a preparation of the dihydropyrrolizin-3-one base 3,8-didehydroheliotridin-5-one **4** (originally named 5,7a-didehydroheliotridin-3-one) which is the base portion of a number of alkaloids isolated from various *Senecio* species of Chile, Australia and South Africa^{10,11} and has been the subject of two earlier syntheses.^{12,13} In our route (Scheme 3), the carbon skeleton of **4** was assembled from Meldrum's acid and the protected pyrrole **11**, which was obtained in 27% yield by photolytic ring contraction of the pyridine *N*-oxide **12** in aqueous copper(II) sulfate solution (*cf.* ref. **5** and references therein). Initial attempts to prepare the hydroxymethyl pyrrole **13** directly from the unprotected *N*-oxide **14** by this route were unsuccessful. Knoevenagel condensation of Meldrum's acid and **11** required rather more vigorous conditions than usual⁵ (100 °C, 2 h), presumably owing to steric effects, but the condensation product **15** was isolated in 60% yield. FVP of **15** at 600 °C produced the protected pyrrolizin-3-one **16** in 90% yield after distillation. Removal of the acetate protecting group was achieved with anhydrous potassium carbonate in methanol (20 °C, 1 h), but even under these mild basic conditions quantitative ring opening to the (*Z*)-propenoate **17** (99%) took place. However, regeneration of the lactam ring was conveniently achieved by FVP of the crude propenoate **17** at 650 °C (*cf.* ref. **5**), and by this means the deprotected pyrrolizinone **18** was obtained in 59% overall yield from **16**. (An alternative strategy, involving direct Wittig olefination of the protected aldehyde **11** did not give significant amounts of propenoate **17**, as either *E*- or *Z*-isomer.) Treatment of the pyrrolizinone **18** with gaseous hydrogen chloride

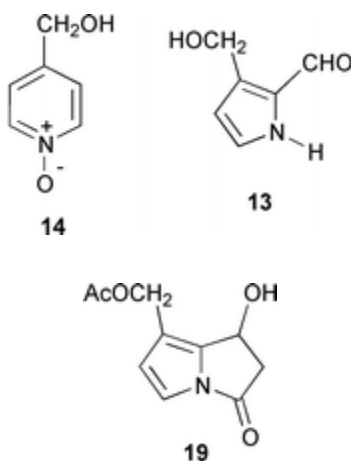
in dichloromethane followed immediately by addition of water gave a product (63%) whose mass spectrum showed the correct molecular ion and whose ^1H NMR spectrum was identical with that of **4** previously reported (see Experimental).¹³ The feasibility of this final transformation was previously established by corresponding reaction of the protected pyrrolizinone **16** to give **19** (also 63%). In summary, the base **4** has been prepared in 5 manipulative steps from the simple pyrrole **11**, in 20% overall (unoptimised) yield, and has established that the methods we have developed here, and in previous work¹⁵ give viable routes to compounds of biological interest.



Scheme 3 Reagents and conditions: (i) $h\nu$ CuSO_4 ; (ii)

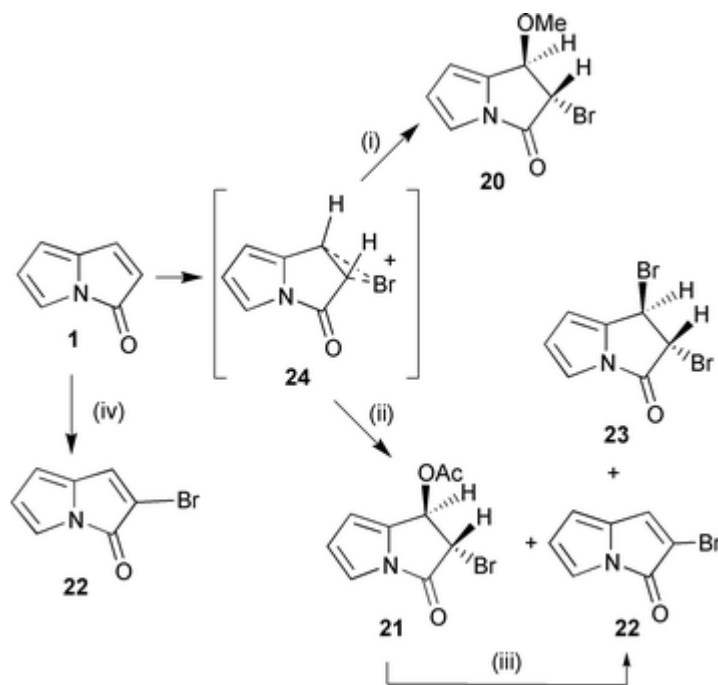


; (iii) FVP (600 °C); (iv) K_2CO_3 , MeOH; (v) FVP (650 °C); (vi) HCl, then H_2O .



The reactivity of **1** towards electrophiles was further demonstrated by its reaction with brominating agents under a variety of conditions. Although treatment with molecular bromine was unsuccessful, the use of *N*-bromosuccinimide (NBS) in methanol or acetic acid at room temperature gave the 1-methoxy-2-bromo and 1-acetoxy-2-bromo compounds **20** and **21** respectively in up to 82% yield. In practice, even these reactions could be irreproducible and on occasions the NMR spectrum of the crude product obtained after the starting material had been completely consumed (TLC) showed no pyrrole resonances whatsoever. In the successful bromination of **1** in glacial acetic acid, an inseparable mixture of products was obtained comprising the acetate **21** together with some of the elimination product **22** and a trace of the

dibromo compound **23** (MS evidence only). However, complete elimination of acetic acid from **21** could be effected by FVP of the crude reaction mixture at 600 °C, and in this way the 2-bromopyrrolizinone **22** could be obtained as the sole product in 35% overall yield from **1** (Scheme 4).



Scheme 4 Reagents and conditions: (i) NBS, MeOH; (ii) NBS, HOAc; (iii) FVP (600 °C); (iv) NBS, PhCOO₂COPh.

Pyrolytic eliminations of ester groups are invariably *syn* retro-ene-type processes, which suggests that the two substituents adopt the *anti* configuration, as expected from the most likely bromination mechanism *via* the bromonium ion **24** (Scheme 4). The regio- and stereo-chemistry of the alkoxybromination of **1** to give **20** were established unambiguously by a series of NOE experiments (Fig. 1 and Table 1). The methoxy resonance of **20** was obvious by inspection (δ_{H} 3.52), and irradiation at this position caused enhancement of one of the pyrrole signals (which identifies the latter signal as due to H-7, and confirms the location of the methoxy group at the 1-position). In addition, *both* aliphatic resonances are enhanced (which confirms that the methoxy group is on the *same* side of the molecule as H-2, and hence that *anti* addition has taken place). This assignment is further confirmed by the size of the vicinal coupling $^3J_{1,2}$ (1.9 Hz) consistent with an *anti* relationship (see above), and the corresponding coupling constant in the acetoxy compound **21** (1.7 Hz) indicated that the same stereochemistry of addition had been maintained (Table 1). [In the spectrum of **20**, a small enhancement of H-2 when H-1 is irradiated in the NOE experiment (1.5%) is probably due to a slight twist in the 5-membered ring so that these protons are relatively close in space even though they are *anti* to one another.]

Table 1 Selected ¹H NMR parameters of **20** and **21**

Compound	$\delta_{\text{H}}(1)$ ($^nJ/\text{Hz}$)	$\delta_{\text{H}}(2)$ ($^nJ/\text{Hz}$)	$\delta_{\text{H}}(5)$ ($^nJ/\text{Hz}$)	$\delta_{\text{H}}(6)$ ($^nJ/\text{Hz}$)	$\delta_{\text{H}}(7)$ ($^nJ/\text{Hz}$)
20	4.94 (1.9)	4.70 (1.9)	7.10 (3.2, 0.9)	6.55 (3.2, 3.2)	6.31 (3.2, 0.9)
21	6.05 (1.7, 1.0)	4.80 (1.7)	7.13 (3.2, 1.0)	6.57 (3.2, 3.2)	6.32 (3.2, 1.0)

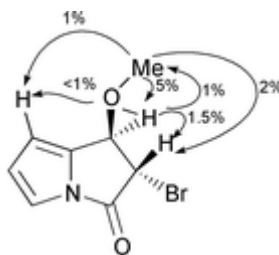
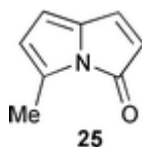
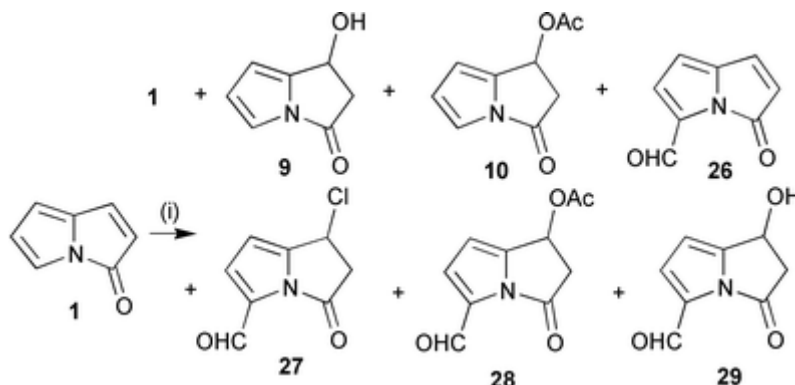


Fig. 1 NOE data for **20**.

Bromination of **1** under free radical conditions was also investigated using NBS in carbon tetrachloride solution using dibenzoyl peroxide as initiator. It was anticipated that the 1,2-dibromopyrrolizinone **23** would be the major product under such conditions, but only a trace of this material could be identified from the ^1H and ^{13}C NMR spectra of the crude reaction mixture, and it could not be isolated. Instead, the major product after 2 h under reflux was found to be 2-bromopyrrolizin-3-one **22** (55%), and this is the method of choice for its preparation. Since it is unlikely that **22** can be formed by a genuine free radical substitution mechanism, it is more probable that it arises by initial formation of the dibromo derivative **23** followed by elimination *in situ*. Unfortunately, attempts to functionalise the 5-methyl group of 5-methylpyrrolizinone **25** by free radical bromination were unsuccessful.



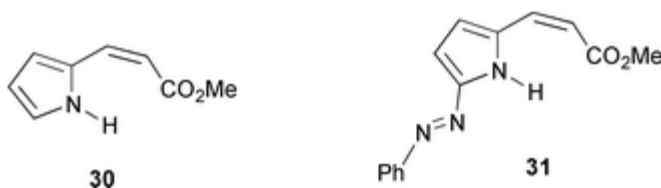
We have also studied the reaction of **1** with electrophiles which might be expected to attack the pyrrole ring of **1** under aromatic substitution conditions. Although both starting materials were recovered unchanged when **1** was treated with methoxymethylene Meldrum's acid,¹⁴ products were obtained by formylation under Vilsmeier conditions and by diazo-coupling. However, electrophilic attack of pyrrolizinone itself may not be involved in the mechanism of either of these reactions. Thus seven compounds were isolated when **1** was treated with DMF- POCl_3 in dichloroethane (15 min under reflux) followed by work-up in the presence of sodium acetate and dry-flash chromatography (Scheme 5). These include recovered starting material **1** (9%), and the hydroxy compound **9** (6%) and acetate **10** (9%), which are probably formed during work-up *via* the chloro compound **8**. Four formylated derivatives were also isolated, *viz.* just one formylated pyrrolizinone identified as **26** (16%) (see below), formed with complete regiocontrol, together with its 1-chloro-, 1-acetoxy- and 1-hydroxy-1,2-dihydro derivatives **27** (trace), **28** (2%) and **29** (1.2%) respectively. Although **28** and **29** are clearly formed in work-up in the same manner as **9** and **10**, it is not clear whether the hydrochlorination to give **27** also takes place in work-up, or by fortuitous reaction of **1** with HCl present in the excess of phosphoryl chloride prior to the actual formylation step (Scheme 5). According to this mechanism, **26** would arise by formylation of **8** to give **27**, followed by elimination of HCl during work-up. Clearly more work will be required to clarify the mechanism and optimise this process from a preparative point of view, but nevertheless we have shown that the pyrrole ring of pyrrolizinones can be functionalised by substitution processes.



Scheme 5 Reagents and conditions: (i) DMF/POCl₃.

The regiochemistry of the formylation follows from the NMR spectra of **26**, which show two ‘pyrrole’ doublets with $^3J_{\text{HH}}$ 3.5 Hz, showing that the reaction must have taken place at either the 5- or 7-positions, and the presence of a methine signal at *ca.* δ_{C} 110 is consistent with the 7-position being unsubstituted.^{5,15}

When **1** was treated with benzenediazonium tetrafluoroborate under neutral conditions, or with benzenediazonium chloride under mildly acidic conditions, no reaction took place. If the solution was basified, the conditions resulted in the cleavage of the amide linkage to give the propenoate **30** (25%) and its azo-coupled derivative **31** (46%) (see below). Coupling of benzenediazonium chloride with **30** under acidic conditions again led to recovered starting material, but basification caused some degree of coupling to occur to give **31** (43%) together with some recovered starting material. These results suggest that the azo-coupling in fact proceeds *via* the anion derived from **30** which is strongly activated towards electrophilic substitution; it is interesting to note that the *Z*-double bond of **30** is configurationally stable under these conditions. An attempt to effect ring closure to the pyrrolizinone by FVP⁵ of the propenoate **31** at 650 °C proved unsuccessful.



The regiochemistry of the coupling reaction was established by the NOE data of **31** summarised in Fig. 2. The alkene resonances were readily identified by inspection, and irradiation of the enoate β -proton caused enhancement of one of the pyrrole signals, which was also enhanced by irradiation of the other pyrrole signal. Hence, substitution must have taken place at the vacant pyrrole α -position¹⁴C5.

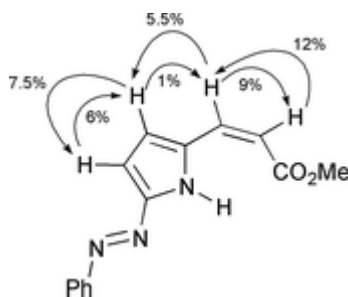


Fig. 2 NOE data for **31**.

In summary, we have demonstrated that reactions of the pyrrolizin-3-one system with electrophiles afford useful means of functionalising the 1-position (*via* the chloro compound **8**), the 2-position (*via* bromination) and in principle the 5-position (*via* Vilsmeier formylation). The reactions have been successfully applied to the synthesis of the dihydropyrrolizin-3-one base 3,8-didehydroheliotridin-5-one **4**.

Further application of these reactions as routes to pyrrolizidine alkaloids will be the subjects of future papers in this series.

Experimental

Unless otherwise stated, ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz respectively for solutions in [^2H]chloroform. Coupling constants are quoted in Hz. IR spectra were recorded for liquid films or Nujol mulls, and absorption maxima are given in cm^{-1} .

Reaction of pyrrolizin-3-one **1** with methanolic hydrogen chloride

Pyrrolizin-3-one **1**⁴ (0.123 g, 1 mmol) was dissolved in methanol (8 cm^3) and treated with a solution of hydrogen chloride in methanol (39% w/v, 2 cm^3). The solution was heated at reflux for 2 h and was then allowed to cool to room temperature. Dichloromethane (25 cm^3) was added and the solution was washed with water (25 cm^3). Solid sodium bicarbonate was added to the aqueous layer until no further evolution of carbon dioxide was observed. The aqueous layer was extracted with additional dichloromethane (25 cm^3). The combined organic layers were washed with water (3 \times 25 cm^3), dried (MgSO_4) and concentrated to give a brown oil. Trituration of the oil with ether gave a polymeric brown solid which was removed by filtration. Concentration of the filtrate gave after bulb-to-bulb (Kugelrohr) distillation *1,2-dihydro-1-methoxy-3H-pyrrolizin-3-one***6** (0.035 g, 22%), bp 6265 $^\circ\text{C}$ (0.5 Torr) (Found: M^+ , 151.0632. $\text{C}_8\text{H}_9\text{NO}_2$ requires M , 151.0633); ν_{max} 2932, 2824, 1758 and 1565; δ_{H} 7.07 (1H, dd, 3J 3.1 and 4J 0.9), 6.48 (1H, t, 3J 3.1), 6.26 (1H, dt, 3J 3.1 and 4J 0.9), 4.83 (1H, ddd, 3J 6.8, 2.0 and 4J 0.9), 3.41 (3H, s), 3.33 (1H, dd, 2J 18.6 and 3J 6.8) and 2.95 (1H, dd, 2J 18.6 and 3J 2.0); δ_{C} 169.23 (quat), 138.72 (quat), 118.78, 111.96, 107.43, 70.22, 55.92 and 42.65; m/z 151 (M^+ , 60%), 120 (100), 92 (54), 80 (53), 79 (42), 65 (35), 52 (18) and 39 (41).

1-Chloro-1,2-dihydro-3H-pyrrolizin-3-one **8**

Dry hydrogen chloride gas, generated by the action of concentrated sulfuric acid on solid ammonium chloride, was bubbled through a stirred solution of pyrrolizin-3-one **1** (0.597 g, 5 mmol) in dichloromethane (50 cm^3) until the solution became black (*ca.* 3060 min). Potassium carbonate (5 g) was added and the solution was stirred for a further 1 h. Solids were removed by filtration through Celite and the solution was evaporated with minimum heating to give, as a free flowing orange liquid which became brown on standing, *1-chloro-1,2-dihydro-3H-pyrrolizin-3-one***8** (0.724 g, 93%) (Found: M^+ , 155.0144. $\text{C}_7\text{H}_6^{35}\text{ClNO}$ requires M , 155.0138); δ_{H} (360 MHz) 7.05 (1H, dd, 3J 3.1 and 4J 0.9), 6.50 (1H, t, 3J 3.1), 6.26 (1H, dt, 3J 3.1 and 4J 0.9), 5.37 (1H, ddd, 3J 7.4, 2.1 and 4J 0.9), 3.63 (1H, dd, 2J 19.2 and 3J 7.4) and 3.21 (1H, dd, 2J 19.2 and 3J 2.1); δ_{C} 167.64 (quat), 138.36 (quat), 119.74, 112.48, 107.83, 46.57 and 45.72; m/z 157 (M^+ , 7%), 155 (M^+ , 22%), 120 (79), 119 (100), 92 (35), 91 (51), 65 (18), 64 (36), 63 (32) and 40 (31).

Reactions of 1-chloro-1,2-dihydro-3H-pyrrolizin-3-one **8**

(i) **With triethylamine.** A solution of the title compound **8** (0.155 g, 1 mmol) in sodium-dried ether (10 cm^3) was treated with triethylamine (0.17 cm^3 , 1.2 mmol) and the solution was stirred at room temperature for 3 h. Dichloromethane (15 cm^3) was added and the solution was washed with aqueous hydrochloric acid (0.2 M, 15 cm^3) and water (15 cm^3). The residue obtained after drying of the extracts (Mg_2SO_4) and removal of the solvent was subjected to bulb-to-bulb (Kugelrohr) distillation to give pyrrolizin-3-one **1** (0.083 g, 70%), bp 9395 $^\circ\text{C}$ (14 Torr) [lit.,⁴ 130 $^\circ\text{C}$ (16 Torr)]; δ_{H} (80 MHz) 7.06 (1H, dd, 3J 5.9 and 6J 0.6), 6.87 (1H, m), 5.97 (2H, m) and 5.64 (1H, dd, 3J 5.9 and 6J 0.6) (in agreement with published data⁴).

(ii) **With *O*-nucleophiles.** 1-Chloro-1,2-dihydro-3*H*-pyrrolizin-3-one **8** (1 mmol) was treated directly with the nucleophile source indicated. [Prior to treatment with water as the nucleophile, **8** was dissolved in acetone (2 cm³).] The mixture was set aside or stirred at room temperature for the time stated. Water (15 cm³) was added and the solution was extracted thoroughly with dichloromethane (3 × 15 cm³). The combined extracts were washed with water (20 cm³) and dried (Na₂SO₄). In the work-up of the reaction with glacial acetic acid/sodium acetate, additional washes with saturated aqueous sodium bicarbonate (2 × 25 cm³) and water again (25 cm³) were carried out. Removal of the solvent under vacuum gave the following compounds. The nucleophile source, its quantity and the reaction time are quoted. *1,2-Dihydro-1-hydroxy-3H-pyrrolizin-3-one* **9** [water (5 cm³), 30 min] (0.127 g, 93%), bp 118122 °C (0.8 Torr) (decomp.) (Found: M⁺, 137.0481. C₇H₇NO₂ requires M, 137.0477); ν_{\max} 3400, 2920, 1740 and 1570; δ_{H} 6.99 (1H, dd, ³J 3.1 and ⁴J 0.9), 6.45 (1H, t, ³J 3.1), 6.20 (1H, dt, ³J 3.1 and ⁴J 0.9), 5.23 (1H, ddd, ³J 7.0, 2.2 and ⁴J 0.9), 3.35 (1H, dd, ²J 18.8 and ³J 7.0), 3.23.3 (1H, br s) and 2.87 (1H, dd, ²J 18.8 and ³J 2.2); δ_{C} 169.57 (quat), 141.63 (quat), 119.15, 111.65, 106.35, 62.01 and 45.54; *m/z* 137 (M⁺, 39%), 120 (14), 95 (27), 94 (42), 71 (35), 58 (29) and 43 (100). *1,2-Dihydro-1-methoxy-3H-pyrrolizin-3-one* **6** [methanol (7 cm³), 30 min] (0.212 g, 100%), bp 6063 °C (0.2 Torr) (decomp.) (spectra identical with those of the authentic sample reported above). 1-Acetoxy-1,2-dihydro-3*H*-pyrrolizin-3-one **10** [sodium acetate (0.087 g, 1.1 mmol) in glacial acetic acid (10 cm³), 20 min] (0.157 g, 87%), bp 121122 °C (0.8 Torr) (decomp.) [lit.,¹⁶ 180 °C (decomp.)]; ν_{\max} 3130, 1760, 1745 and 1575; δ_{H} 7.04 (1H, dd, ³J 3.1 and ⁴J 1.0), 6.44 (1H, t, ³J 3.1), 6.23 (1H, dt, ³J 3.1 and ⁴J 1.0), 5.96 (1H, ddd, ³J 7.2, 2.0 and ⁴J 1.0), 3.42 (1H, dd, ²J 18.9 and ³J 7.2), 2.97 (1H, dd, ²J 18.9 and ³J 2.0) and 2.03 (3H, s); δ_{C} 170.40 (quat), 168.24 (quat), 137.47 (quat), 119.21, 112.31, 108.85, 63.80, 42.01 and 20.66 (ν_{\max} and δ_{H} in agreement with published data¹⁶).

4-(Acetoxymethyl)pyridine

Acetic anhydride (12.46 g, 0.12 mol) was added dropwise over 20 min to 4-(hydroxymethyl)pyridine (4-pyridylmethanol) (11.23 g, 0.1 mol). The resulting solution was stirred at room temperature for 90 min at which point aqueous sodium hydroxide (2 M, 80 cm³) was added carefully with cooling. The solution was extracted with dichloromethane (3 × 150 cm³). The combined extracts were washed with water (150 cm³), dried (MgSO₄) and evaporated. Distillation of the residue gave 4-(acetoxymethyl)pyridine (14.34 g, 92%), bp 130132 °C (20 Torr) [lit.,¹⁷ 126 °C (20 Torr)]; ν_{\max} 3020, 1745, 1610 and 1565; δ_{H} 8.48 (2H, br d, *J* 5.7), 7.15 (2H, dd, *J* 4.5 and 1.5), 5.01 (2H, s) and 2.05 (3H, s); δ_{C} 170.27 (quat), 149.69, 144.75 (quat), 121.68, 63.98 and 20.54.

4-(Acetoxymethyl)pyridine *N*-oxide **12**

A solution of 4-(acetoxymethyl)pyridine (15.16 g, 0.1 mol) in glacial acetic acid (60 cm³) was treated with aqueous hydrogen peroxide solution (28%, 10 cm³) and the solution was heated at 8090 °C for 3 h. Further hydrogen peroxide solution (7.5 cm³) was added and the reaction mixture was heated at 8090 °C for an additional 9 h. The solution was next cooled and concentrated to 2030 cm³ by rotary evaporation. Water (20 cm³) was added and the solution was again concentrated, to approximately 20 cm³. The concentrate was taken up in chloroform (50 cm³) and the solution was poured onto a paste of potassium carbonate (10 g) and water and shaken. The organic layer was separated, dried (MgSO₄) and evaporated to give, after bulb-to-bulb distillation, 4-(acetoxymethyl)pyridine *N*-oxide **12** (10.03 g, 60%), bp 168173 °C (1.5 Torr) (Found: M⁺, 167.0575. C₈H₉NO₃ requires M, 167.0582); ν_{\max} 1739 and 1225; δ_{H} 8.00 (2H, d, *J* 7.0), 7.10 (2H, d, *J* 7.0), 4.88 (2H, s) and 1.93 (3H, s); δ_{C} 169.81 (quat), 138.57, 134.45 (quat), 124.69, 63.98 and 20.19; *m/z* 167 (M⁺, 34%), 109 (25), 108 (75), 96 (43), 52 (27), 51 (28), 43 (100) and 39 (36). This compound has been previously reported without characterisation.¹⁸ It is highly hygroscopic and requires to be stored at -20 °C.

3-(Acetoxymethyl)pyrrole-2-carbaldehyde **11**

The pyridine *N*-oxide **12** (1.66 g, 3 mmol) was dissolved in aqueous copper(II) sulfate solution (0.2 M, 670 cm³). The solution was photolysed according to the method described in refs. [5](#) and [19](#). After work-up by continuous extraction, dry flash chromatography (ethyl acetate, *n*-hexane) gave as the first fraction 3-(acetoxymethyl)pyrrole-2-carbaldehyde**11** (0.456 g, 27%), mp 5961 °C {after distillation [bp 98100 °C (0.15 Torr)]} (Found: M⁺, 167.0582. C₈H₉NO₃ requires *M*, 167.0582); *v*_{max} 3250, 1736, 1644 and 1619; δ_{H} 10.2 (1H, br s), 9.73 (1H, d, ⁵*J* 1.0), 7.08 (1H, td, ³*J* 2.6 and ⁵*J* 1.0), 6.34 (1H, t, ³*J* 2.6), 5.28 (2H, s) and 2.08 (3H, s); δ_{C} 178.32, 170.65 (quat), 129.59 (two quat), 125.66, 112.26, 57.60 and 20.81; *m/z* 167 (M⁺, 15%), 125 (27), 108 (26), 107 (50), 105 (26), 79 (36), 53 (23) and 43 (100).

2,2-Dimethyl-5-[3-(acetoxymethyl)pyrrol-2-ylmethylidene]-1,3-dioxane-4,6-dione **15**

The pyrrole-2-carbaldehyde **11** (0.334 g, 2 mmol) was dissolved in toluene (5 cm³) and treated with piperidine (2 drops), glacial acetic acid (2 drops) and Meldrum's acid (0.29 g, 2 mmol). The solution was stirred at room temperature overnight and then heated on a steam bath for 2 h. The solvent was removed and the residue was recrystallised from ethanol to give 2,2-dimethyl-5-[3-(acetoxymethyl)pyrrol-2-ylmethylidene]-1,3-dioxane-4,6-dione**15** (0.353 g, 60%), mp 136138 °C (from ethanol) (Found: C, 57.3; H, 5.1; N, 4.6. C₁₄H₁₅NO₆ requires C, 57.35; H, 5.1; N, 4.5); *v*_{max} 3243, 1731, 1682 and 1556; δ_{H} 8.39 (1H, s), 7.36 (1H, t, ³*J* 2.7), 6.55 (1H, t, *J* 2.7), 5.23 (2H, s), 2.08 (3H, s) and 1.74 (6H, s); δ_{C} 170.45 (quat), 164.31 (quat), 163.88 (quat), 139.90, 136.27 (quat), 130.47, 126.20 (quat), 115.24, 104.23 (quat), 100.70 (quat), 57.65, 27.10 and 20.76; *m/z* 293 (M⁺, 34%), 235 (18), 149 (100), 148 (21), 121 (92), 120 (20), 104 (24), 93 (29), and 43 (54).

7-(Acetoxymethyl)-3*H*-pyrrolizin-3-one **16**

2,2-Dimethyl-5-[3-(acetoxymethyl)pyrrol-2-ylmethylidene]-1,3-dioxane-4,6-dione **15** (0.173 g, 0.6 mmol) was subjected to FVP by sublimation through a horizontal silica furnace tube using our standard apparatus. ⁵ The following parameters were used: furnace temperature 600 °C, inlet temperature 140160 °C, pressure 0.005 Torr, pyrolysis time 75 min. The product obtained from the trap was 7-(acetoxymethyl)-3*H*-pyrrolizin-3-one**16** (0.114 g, 90%), bp 104107 °C (2.5 Torr) (Found: M⁺, 191.0589. C₁₀H₉NO₃ requires *M*, 191.0582); *v*_{max} 1743 (br), 1607 and 1525; δ_{H} 7.18 (1H, d, ³*J* 5.9), 6.87 (1H, d, ³*J* 3.2), 5.98 (1H, d, ³*J* 3.2), 5.67 (1H, d, ³*J* 5.9), 4.89 (2H, s) and 2.08 (3H, s); δ_{C} (one quaternary missing) 170.47 (quat), 137.41, 135.09 (quat), 121.88, 121.37 (quat), 119.11, 115.54, 58.08, and 20.77; *m/z* 191 (M⁺, 94%), 149 (100), 132 (74), 131 (36), 120 (33), 104 (74), 103 (31), 91 (56), 51 (38), 44 (27), 43 (80) and 40 (31).

7-(Hydroxymethyl)-3*H*-pyrrolizin-3-one **18**

A solution of the (acetoxymethyl)pyrrolizin-3-one **16** (0.192 g, 1 mmol) in methanol (5 cm³) was treated with potassium carbonate (0.068 g, 0.5 mmol) and the mixture was stirred at room temperature over a period of 1 h. Water (10 cm³) was added and the solution was extracted with dichloromethane (3 × 20 cm³). The combined extracts were dried (MgSO₄) and evaporated to give methyl(*Z*)-3-[3-(hydroxymethyl)pyrrol-2-yl]propenoate**17** (0.179 g, 99%) (Found: M⁺, 181.0739. C₉H₁₁NO₃ requires *M*, 181.0739); δ_{H} 12.31 (1H, br s), 6.95 (1H, d, ³*J* 12.6), 6.94 (1H, t, ³*J* 2.6), 6.29 (1H, t, ³*J* 2.6), 5.68 (1H, d, ³*J* 12.6), 4.66 (2H, s), 3.76 (3H, s) and 1.69 (1H, br s); δ_{C} 169.56 (quat), 131.57, 130.05 (quat), 125.97 (quat), 121.73, 110.44, 107.45, 57.16 and 51.57; *m/z* 181 (M⁺, 84%), 148 (20), 132 (28), 122 (56), 121 (100), 120 (67), 94 (44), 93 (50), 92 (33) and 65 (25). This compound was used immediately for flash vacuum pyrolysis under the following conditions: furnace temperature 650 °C, inlet temperature 80100 °C, pressure range 0.0020.005 Torr, pyrolysis time 1 h. 7-(Hydroxymethyl)-3*H*-

pyrrolizin-3-one **18** (0.089 g, 60%) was thus obtained, bp 8588 °C (0.4 Torr), mp 8687 °C (Found: M^+ , 149.0469. $C_8H_7NO_2$ requires M , 149.0477); ν_{\max} 1721; δ_H 7.19 (1H, d, 3J 5.8), 6.85 (1H, d, 3J 3.2), 5.93 (1H, d, 3J 3.2), 5.62 (1H, d, 3J 5.8), 4.52 (2H, s) and 2.04 (1H, br s); δ_C (one quaternary missing) 137.89, 133.85 (quat), 127.33 (quat), 121.24, 119.36, 114.43 and 57.93; m/z 149 (M^+ , 100%), 148 (31), 132 (59), 120 (48), 104 (34), 92 (32), 65 (28), 52 (24), 51 (24) and 39 (46).

1,2-Dihydro-1-hydroxy-7-(hydroxymethyl)-3H-pyrrolizin-3-one (3,8-didehydroheliotridin-5-one) **4**

Dry hydrogen chloride gas generated from the action of concentrated sulfuric acid (3.2 cm³) on ammonium chloride (2.31 g) was passed through a stirred solution of 7-(hydroxymethyl)pyrrolizin-3-one **18** (0.076 g, 0.51 mmol) in dichloromethane (10 cm³) over a period of 10 min during which time there was a loss of the characteristic colour of the pyrrolizin-3-one. The solution was stirred at room temperature for a further 15 min at which point potassium carbonate (1 g) was added. After a further 1 h at room temperature, the solids were removed by filtration and the filtrate was evaporated. The residue (0.113 g) was taken up in acetone (2 cm³). Water (8 cm³) was added and the solution was set aside for 30 min. The aqueous solution was extracted with dichloromethane (3 × 15 cm³) and the combined extracts were dried (Na₂SO₄) and evaporated to give 1,2-dihydro-1-hydroxy-7-(hydroxymethyl)-3H-pyrrolizin-3-one **4**

(3,8-didehydroheliotridin-5-one) (0.054 g, 63%) (Found: M^+ , 167.0568. $C_8H_9NO_3$ requires M^+ 167.0582); δ_H 6.95 (1H, d, 3J 3.1), 6.32 (1H, d, 3J 3.1), 5.27 (1H, dd, 3J 7.2 and 2.5), 4.70 (1H, d, 2J 13.1), 4.59 (1H, d, 2J 13.1), 3.31 (1H, dd, 2J 18.7 and 3J 7.2) and 2.88 (1H, dd, 2J 18.7 and 3J 2.5) (identical with literature data ¹³); m/z 167 (M^+ , 74%), 150 (50), 149 (100), 121 (32), 108 (46), 104 (33), 79 (47), 71 (33), 57 (49), 52 (31), 45 (75), 43 (79) and 41 (42). Attempted purification by distillation led to decomposition.

7-(Acetoxymethyl)-1,2-dihydro-1-hydroxy-3H-pyrrolizin-3-one **19**

In a pilot reaction, treatment of a solution of 7-(acetoxymethyl)-3H-pyrrolizin-3-one **16** (0.016 g, 0.08 mmol) in dichloromethane (2 cm³) with hydrogen chloride, followed by treatment of the initial product in acetone (2 cm³) with water (3 cm³) over 20 min, as described above, gave, after the usual work-up, a lightly coloured oil (0.011 g, 63%) which was identified as 7-(acetoxymethyl)-1,2-dihydro-1-hydroxy-3H-pyrrolizin-3-one **19** on the basis of its ¹H NMR and mass spectra; δ_H 7.00 (1H, d, 3J 3.2), 6.45 (1H, d, 3J 3.2), 5.35 (1H, dd, 3J 6.9 and 2.0), 5.22 (1H, d, 2J 12.4), 4.81 (1H, d, 2J 12.4), 3.34 (1H, dd, 2J 18.7 and 3J 6.9), 2.94 (1H, dd, 2J 18.7 and 3J 2.0) and 2.05 (3H, s); m/z 209 (M^+ , 7%), 191 (3), 149 (34), 86 (68), 84 (100) and 70 (19). This product was not characterised further.

Reactions of pyrrolizin-3-one **1** with brominating agents

(i) **2-Bromo-1,2-dihydro-1-methoxy-3H-pyrrolizin-3-one 20**. A solution of pyrrolizin-3-one **1** (0.125 g, 1.0 mmol) in methanol (3 cm³) was treated with *N*-bromosuccinimide (0.230 g, 1.3 mmol). After the solution had been stirred at room temperature for 3 days, it was added to dichloromethane (25 cm³) and washed successively with saturated aqueous sodium bicarbonate solution (20 cm³) and water (20 cm³). The organic solution was dried (MgSO₄) and the solvent was removed thoroughly *in vacuo* to give *trans*-2-bromo-1,2-dihydro-1-methoxy-3H-pyrrolizin-3-one **20** (0.202 g, 82%) which underwent partial decomposition upon distillation (0.086 g, 36%), bp 122124 °C (0.1 Torr) (Found: M^+ , 230.9719 and 228.9736. $C_8H_8^{81}BrNO_2$ requires M , 230.9719 and $C_8H_8^{79}BrNO_2$ requires M , 228.9739); ν_{\max} 3140, 2940, 2830, 1765, 1720 and 1580; δ_H 7.10 (1H, dd, 3J 3.2 and 4J 0.9), 6.55 (1H, t, 3J 3.2), 6.31 (1H, dd, 3J 3.2 and 4J 0.9), 4.94 (1H, d, 3J 1.9), 4.70 (1H, d, 3J 1.9) and 3.52 (3H, s); δ_C (one quaternary missing) 135.27 (quat), 120.16, 113.00, 108.46, 80.20, 57.05 and 47.34; m/z 231 (M^+ , 65%), 229 (M^+ , 62%), 200 (63), 198 (56), 150 (44), 119 (100), 110 (29), 91 (31), 80 (72), 79 (52), 63 (24) and 43 (29).

(ii) **1-Acetoxy-2-bromo-1,2-dihydro-3H-pyrrolizin-3-one 21**. Pyrrolizin-3-one **1** (0.245 g, 2 mmol) was dissolved in glacial acetic acid (6 cm³) and treated with *N*-bromosuccinimide (0.72 g, 4 mmol). The solution was stirred at room temperature and the reaction was monitored by TLC (silica, 30% ethyl acetate in *n*-hexane). Reaction was complete after 75 min at which point the solution was added to water (30 cm³) and extracted thoroughly with dichloromethane (3 × 40 cm³). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (3 × 50 cm³) and water (50 cm³), dried (MgSO₄) and the solvent was removed thoroughly *in vacuo* to give impure *trans*-2-bromo-1-acetoxy-1,2-dihydro-3H-pyrrolizin-3-one, **21** bp 102104 °C (0.3 Torr) (decomp.) [Found (FAB): M⁺, 258.9668 and 256.9668. C₉H₈⁸¹BrNO₃ requires *M*, 258.9668 and C₉H₈⁷⁹BrNO₃ requires *M*, 256.9668]; δ_H 7.13 (1H, dd, ³J 3.2 and ⁴J 1.0), 6.57 (1H, t, ³J 3.2), 6.32 (1H, dt, ³J 3.2 and ⁴J 1.0), 6.05 (1H, dd, ³J 1.7 and ⁴J 1.0), 4.80 (1H, d, ³J 1.7) and 2.11 (3H, s); δ_C (one quaternary missing) 169.78 (quat), 164.57 (quat), 120.59, 113.54, 110.34, 72.60, 46.31 and 20.56; *m/z* (FAB) 260 [(M + H)⁺, 20%], 258 [(M + H)⁺, 33], 257 (40), 237 (41), 215 (59) and 200 (34); additional peaks were identified at *m/z* 280 (69%), 278 (100) and 276 (79) [corresponding to (C₇H₅Br₂NO – H)⁺], probably due to the dibromo compound **23**. Purification of the product could not be achieved by chromatography nor by distillation. The major contaminant was identified as 2-bromo-3H-pyrrolizin-3-one **22**.

Complete elimination of acetic acid from **21** could be effected by flash vacuum pyrolysis of the crude product under the following conditions (furnace temperature 600 °C, inlet temperature 120 °C, pressure 0.005 Torr, pyrolysis time 30 min). The dark red pyrolysate was washed from the trap with dichloromethane (10 cm³). The solution was washed with aqueous sodium bicarbonate solution (1 M, 10 cm³) and water (10 cm³), dried (MgSO₄) and concentrated to give 2-bromo-3H-pyrrolizin-3-one **22** (0.141 g, 35%), bp 6870 °C (0.3 Torr) (Found: M⁺, 198.9459 and 196.9477. C₇H₄⁸¹BrNO requires *M*, 198.9457 and C₇H₄⁷⁹BrNO requires *M*, 196.9477); *v*_{max} 3140, 1750, 1675 and 1560; δ_H 7.16 (1H, d, ⁶J 0.5), 6.95 (1H, ddd, ³J 2.9, ⁴J 1.3 and ⁶J 0.5) and 6.01 (2H, m); δ_C 160.22 (quat), 135.72, 135.53 (quat), 120.41, 115.53, 112.86 (quat) and 111.94; *m/z* 199 (M⁺, 50%), 197 (M⁺, 44), 90 (100), 63 (74) and 39 (30).

(iii) **Reaction with bromine**. A solution of pyrrolizin-3-one **1** (0.1 mmol) in [²H]chloroform (0.5 cm³) was treated with bromine (0.1, 0.2 and 0.3 mmol). In each case, there were no identifiable resonances present in the ¹H NMR spectrum (60 MHz) after 15 min.

(iv) **Reactions with NBS in the presence of radical initiator**. A solution of pyrrolizin-3-one **1** (0.119 g, 1 mmol) in carbon tetrachloride (3 cm³) was treated with *N*-bromosuccinimide (0.218 g, 1.2 mmol) and a few crystals of benzoyl peroxide. The solution was heated at reflux for 2 h. When the solution had cooled, the insoluble succinimide was removed by filtration and washed with a little fresh carbon tetrachloride. The combined filtrate and washings were evaporated. Dry flash chromatography of the residue (ethyl acetate/*n*-hexane) gave 2-bromopyrrolizin-3-one **22**, bp 6870 °C (0.03 Torr) (0.109 g, 55% after distillation) (spectra identical with sample reported above).

The ¹H NMR spectrum of the crude reaction mixture indicated the presence of a second product which could be isolated neither by chromatography nor by distillation. The compound was tentatively identified as *trans*-1,2-dibromo-1,2-dihydro-3H-pyrrolizin-3-one **23**; δ_H (one resonance hidden) 6.60 (1H, t, ³J 3.2), 6.37 (1H, dt, ³J 3.2 and ⁴J 1.0), 5.49 (1H, dd, ³J 1.4 and ⁴J 1.0) and 5.03 (1H, d, ³J 1.4); δ_C (two quaternaries missing) 121.08, 114.28, 109.86, 49.83 and 40.34.

The reaction was also carried out with 2 mmol of *N*-bromosuccinimide. ¹H NMR spectroscopy (80 MHz) showed no difference in the composition of the crude reaction mixture.

5-Methyl-3H-pyrrolizin-3-one **25**⁵ (0.068 g, 0.5 mmol) was treated with *N*-bromosuccinimide (0.102 g, 0.57 mmol) over 90 min under the conditions described above. No discernible products could be identified from the ¹H NMR spectrum (60 MHz) of the crude reaction mixture, after filtration and removal of the solvent from the filtrate.

Vilsmeier-Haack formylation of pyrrolizinone 1

N,N-Dimethylformamide (1.25 cm³) was added with stirring to phosphoryl chloride (2.5 cm³) and the temperature was kept within the range 1020 °C. 1,2-Dichloroethane (10 cm³) was added and the solution was cooled to 5 °C, and maintained at this temperature during the gradual addition, with stirring, of a solution of pyrrolizin-3-one (0.600 g, 5 mmol) in 1,2-dichloroethane (15 cm³). The solution was heated at reflux for 15 min and then allowed to cool to room temperature. The solution was cooled in an ice bath during the careful addition of sodium acetate trihydrate (18.75 g) in water (25 cm³). Further water (25 cm³) was added and the reaction mixture was extracted with ether (4 × 100 cm³). The combined extracts were washed with water (2 × 100 cm³), dried (MgSO₄) and the solvents were evaporated. Dry flash chromatography (ethyl acetate/*n*-hexane) of the residue gave the following products which were characterised by their ¹H NMR and mass spectra. Pyrrolizin-3-one **1** (0.054 g, 9%); 1-acetoxy-1,2-dihydropyrrolizin-3-one **10** (0.079 g, 9%) (identical with sample reported above); *l*-chloro-1,2-dihydro-3-oxo-3*H*-pyrrolizine-5-carbaldehyde **27** (trace) (Found: M⁺, 185.0066 and 183.0085. C₈H₆³⁷ClNO₂ requires *M*, 185.0058 and C₈H₆³⁵ClNO₂ requires *M*, 183.0087); δ_H 10.26 (1H, s), 7.36 (1H, d, ³*J* 3.7), 6.43 (1H, d, ³*J* 3.7), 5.43 (1H, dd, ³*J* 7.5 and 2.4), 3.77 (1H, dd, ²*J* 19.3 and ³*J* 7.5) and 3.34 (1H, dd, ²*J* 19.3 and ³*J* 2.4); *m/z* 185 (M⁺, 3%), 183 (M⁺, 9%), 148 (37), 147 (100), 146 (33), 119 (34), 91 (41), 64 (29) and 63 (25); 3-oxo-3*H*-pyrrolizine-5-carbaldehyde **26** (0.121 g, 16%) (Found: M⁺ 147.0416. C₈H₅NO₂ requires *M*, 147.0320); δ_H 9.97 (1H, s), 7.20 (1H, d, ³*J* 6.0), 6.89 (1H, d, ³*J* 3.5), 6.14 (1H, d, ³*J* 3.5) and 5.89 (1H, d, ³*J* 6.0); δ_C 178.98, 164.67 (quat), 141.76 (quat), 137.75, 134.17 (quat), 124.62, 123.89 and 110.79; *m/z* 147 (M⁺, 100%), 146 (29), 119 (44), 91 (88), 90 (23), 85 (21), 71 (31), 64 (45), 63 (40), 57 (49), 55 (22), 43 (41) and 41 (30); 1-acetoxy-1,2-dihydro-3-oxo-3*H*-pyrrolizine-5-carbaldehyde **28** (0.012 g, 1.2%) (Found: M⁺ 207.0536. C₁₀H₉NO₄ requires *M*, 207.0532); δ_H 10.27 (1H, d, ⁵*J* 0.5), 7.33 (1H, d, ³*J* 3.7), 6.41 (1H, dt, ³*J* 3.7 and *J* 0.8), 6.06 (1H, ddd, ³*J* 7.4, 2.2 and ⁴*J* 0.8), 3.56 (1H, dd, ²*J* 19.1 and ³*J* 7.4), 3.12 (1H, dd, ²*J* 19.1 and ³*J* 2.2) and 2.16 (3H, s); δ_C 179.27, 170.21 (quat), 168.57 (quat), 143.64 (quat), 130.19 (quat), 125.52, 110.00, 63.69, 41.52 and 30.76; *m/z* 207 (M⁺, 46%), 165 (30), 148 (62), 147 (49), 120 (25), 119 (49), 92 (27), 91 (49), 71 (26), 65 (31), 64 (22), 57 (42) and 43 (100); 1,2-dihydro-1-hydroxypyrrolizin-3-one **9** (0.038 g, 6%) (identical with sample reported above); 1,2-dihydro-1-hydroxy-3-oxo-3*H*-pyrrolizine-5-carbaldehyde **29** (0.015 g, 2%) (Found: M⁺ 165.0428. C₈H₇NO₃ requires M⁺ 165.0426); δ_H 10.14 (1H, s), 7.32 (1H, d, ³*J* 3.7), 6.38 (1H, d, ³*J* 3.7), 5.36 (1H, dd, ³*J* 7.3 and 2.4), 3.49 (1H, dd, ²*J* 18.9 and ³*J* 7.3) and 3.04 (1H, dd, ²*J* 18.9 and ³*J* 2.4); *m/z* 165 (M⁺, 60%), 123 (20), 122 (64), 94 (22), 84 (35), 57 (25), 45 (30) and 43 (100).

Azo-coupling reactions of pyrrolizin-3-one

A solution of benzenediazonium chloride (1 mmol) in water (5 cm³) was added to a stirred solution of pyrrolizin-3-one **1** (0.125 g, 1 mmol) in methanol (5 cm³) at room temperature. After stirring the solution for 20 min, aqueous sodium hydroxide (2 M, 2 cm³) was added and the solution was stirred for a further 30 min. The reaction mixture was extracted with dichloromethane (3 × 15 cm³). The combined extracts were dried (MgSO₄) and evaporated. Bulb-to-bulb distillation of the residue gave as the first fraction methyl (*Z*)-3-(pyrrol-2-yl)propenoate **30** (0.040 g, 25%), bp 5962 °C (0.5 Torr); δ_H 7.01 (1H, m), 6.78 (1H, d, ³*J* 12.5), 6.51 (1H, m), 6.27 (1H, dt, ³*J* 3.6 and ⁴*J* 2.5), 5.53 (1H, d, ³*J* 12.5) and 3.77 (3H, s) (identical with authentic sample ⁵); the second fraction was methyl(*Z*)-3-(2-phenylazopyrrol-5-yl)propenoate **31** (0.123 g, 46%), bp 175177 °C (0.5 Torr) (Found: M⁺ 255.1025. C₁₄H₁₃N₃O₂ requires *M*, 255.1008); ν_{max} 3260 (br), 1700, 1600 and 1450; λ_{max}/MeOH (ε) 247 (9400), 286 (10200) and 425 (22800); δ_H 12.69 (1H, br s), 7.92 (2H, m), 7.547.40 (3H, m), 7.00 (1H, dd, ³*J* 3.9 and ⁴*J* 1.9), 6.76 (1H, d, ³*J* 12.5), 6.60 (1H, dd, ³*J* 3.9 and ⁴*J* 1.9), 5.75 (1H, d, ³*J* 12.5) and 3.83 (3H, s); δ_C 168.48 (quat), 152.82 (quat), 147.41 (quat), 133.93, 130.58 (quat), 130.15, 128.88, 122.52, 119.89, 113.89, 112.28 and 51.90; *m/z* 255 (M⁺, 100%), 240 (18), 195 (11), 167 (10), 150 (27), 135 (10), 90 (23), 77 (78), 65 (14) and 51 (16). Without the addition of aqueous sodium

hydroxide solution, there was no evidence of any reaction after 45 min.

Methyl (*Z*)-3-(pyrrol-2-yl)propenoate **30** (0.150 g, 1 mmol) was reacted with benzenediazonium chloride (1.25 mmol) by the method described above to give unreacted propenoate **30** (0.057 g, 36%), bp 65/68 °C (0.003 Torr) and the phenylazopyrrole **31** (0.112 g, 43%), bp 138/140 °C (0.005 Torr), identical with that obtained previously.

Pyrrolizin-3-one **1** (0.031 g, 0.26 mmol) was dissolved in [²H₃]acetonitrile (0.5 cm³) and the solution was cooled to 0 °C. Benzenediazonium tetrafluoroborate (0.053 g, 0.28 mmol) was added and the solution was allowed to warm to room temperature. The reaction was monitored by ¹H NMR spectroscopy (60 MHz). After setting the sample aside overnight at room temperature no identifiable resonances could be observed.

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