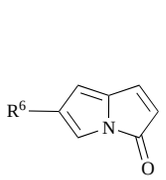
Synthesis of pyrrolizin-3-ones by flash vacuum pyrolysis of pyrrol-2-ylmethylidene Meldrum's acid derivatives and 3-(pyrrol-2-yl)propenoic esters

Shirley E. Campbell, Murray C. Comer, Paul A. Derbyshire, Xavier L. M. Despinoy, Hamish McNab,* Roderick Morrison, Craig C. Sommerville and (the late) Craig Thornley

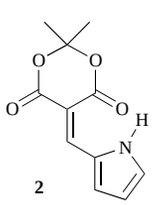
Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, UK EH9 3JJ

Monosubstituted pyrrolizin-3-ones 1 with substituents at the 1-, 5-, 6- or 7-positions are prepared in excellent yield by flash vacuum pyrolysis (FVP) of appropriate Meldrum's acid derivatives 2. The mechanism involves formation of the pyrrol-2-ylmethylideneketene 29, which can also be generated thermally from 3-(pyrrol-2-yl)propenoate esters (*e.g.* 30). This alternative route has been used to make a range of 2-substituted pyrrolizin-3-ones, again in excellent yield. The 3-oxo-3*H*-pyrrolizine-2-carboxylic acid 42 could not be made in this way owing to facile decarboxylation to pyrrolizinone 1, and extension to the formation of the azaazulenone 48 was again unsuccessful.

Some years ago we reported a simple and efficient synthesis of pyrrolizin-3-one **1** by flash vacuum pyrolysis (FVP) of the condensation product **2** of pyrrole-2-carbaldehyde and Meldrum's acid.[1] Later, we applied this methodology to the crystalline 6-bromo derivative **3**,[2] and obtained the first X-ray crystallographic data for this ring system.[2] The Meldrum's acid route was also used to make certain azapyrrolizinone ring systems for the first time,[3] and their NMR spectra have been discussed in detail.[4] Since pyrrolizinones remain relatively unexplored in the literature,[5] we now report a more extensive study of the scope and mechanism of this synthetic route from which a complementary pyrolytic synthesis *via* pyrrolylpropenoic esters has evolved.[6] Our corresponding work on the azapyrrolizinones is discussed in the accompanying paper.[7]

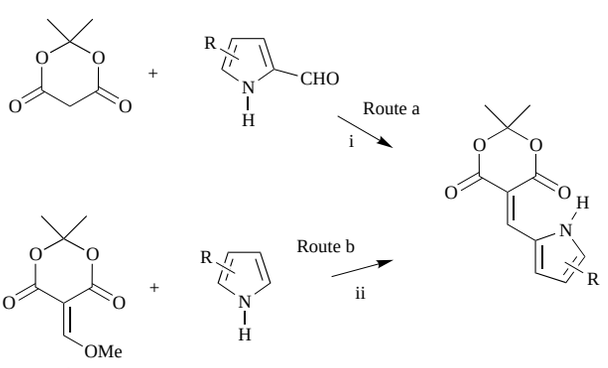


1 R^6 = H
3 R^6 = Br



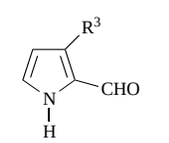
2

Two routes to the key Meldrum's acid precursors were employed (Scheme 1). The classic Knoevenagel condensation using piperidinium acetate catalyst[8] in toluene at room temperature (Scheme 1, route a) works well if the appropriate pyrrole-2-carbaldehyde is readily available. Thus, we have used the photochemical ring contraction of 4-substituted pyridine *N*-oxides[9–11] to prepare a range of 3-substituted pyrrole-2-carbaldehydes **5**–**7** containing electron donating and electron withdrawing groups, and we prepared ethyl 5-formylpyrrole-2-carboxylate **8** by Vilsmeier formylation of the ester using a literature method.[12] Yields for the Meldrum's acid condensation to give the derivatives **10**–**13** were in the range 62–98%. Condensation of Meldrum's acid with 2-acetylpyrrole **9** was achieved by the titanium tetrachloride method[13] though the yield of **18** obtained in this way was consistently lower than for the aldehyde reactions (57%).

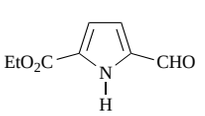


4

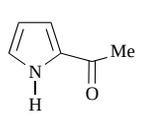
Scheme 1 *Reagents and conditions:* i, piperidinium acetate, toluene, 20 °C; ii, acetonitrile, 20 °C



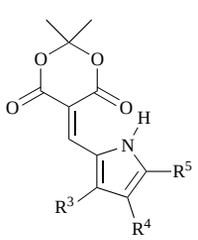
5 R^3 = Me
6 R^3 = OMe
7 R^3 = CO_2Me



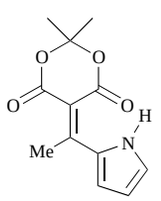
8



9



10 R^3 = Me, R^4 = R^5 = H
11 R^3 = OMe, R^4 = R^5 = H
12 R^3 = CO_2Me, R^4 = R^5 = H
13 R^3 = R^4 = H, R^5 = CO_2Et
14 R^3 = R^4 = H, R^5 = Me
15 R^3 = R^4 = H, R^5 = Ph
16 R^3 = Ph, R^4 = R^5 = H
17 R^3 = R^5 = H, R^4 = Ph



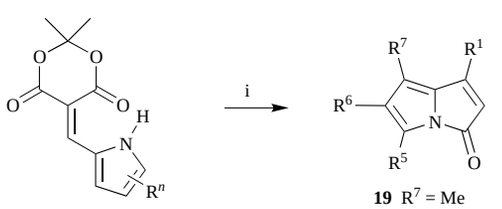
18

We have also reported a direct route to **2** by reaction of

pyrrole itself with methoxymethylidene Meldrum's acid **4**,[14] which should in effect bypass a formylation step if the simple pyrrole is available (Scheme 1, route b). Indeed 2-methylpyrrole[15] and 2-phenylpyrrole[16] gave the 5-substituted pyrrol-2-yl derivatives **14** and **15** respectively under mild conditions in 60–70% yield with total regioselectivity. Surprisingly, 3-phenylpyrrole[16] gave the 3-phenyl- and 4-phenyl-pyrrol-2-yl derivatives **16** and **17** respectively in almost equal amount. Presumably any acceleration due to the electronic stabilisation of the intermediate *en route* to **16** afforded by the phenyl group is balanced by retardation due to its steric effect. Compounds **16** and **17** were only partially separable by crystallisation, though the pyrrolizinones derived therefrom could be more readily purified (see below).

The Meldrum's acid derivatives showed characteristic features in their spectra. Where present, the N–H signal in the ^{1}H NMR spectra in [^{2}H]chloroform occurred at particularly high frequency (δ_H 12–13), consistent with strong hydrogen bonding to one of the carbonyl groups (see below). The 5-methylidene proton resonates at δ_H 8.0–8.3, except in the case of the 3-carboxylic ester **12** where the adjacent substituent causes a further deshielding of *ca.* 1 ppm. The ^{13}C NMR spectra show quaternary signals in the range δ_C 103–105 due to C(2) of the Meldrum's acid ring, but the corresponding signal for C(5) occurs over a much wider range (δ_C 95–106). As expected, electron donating groups (*e.g.* 3-methoxy) on the pyrrole cause this peak to shift to the low frequency part of the range, and electron withdrawing groups (*e.g.* 3- or 5-carboxylic esters) have the opposite effect. The carbonyl signals due to C(4) and C(6) would be expected to occur at different chemical shifts owing to the hydrogen bonding mentioned above but if [^{2}H]chloroform is used as the solvent only one signal is normally present at room temperature. The expected two signals are often observed in hydrogen bond acceptor solvents such as [^{2}H$_6$]acetone or DMSO. The 5-methylidene carbon signal is found over a wide range, centred around δ_C 140. In some examples this peak is broad, indicating that exchange processes may be operating such as those found in dialkylaminomethylidene Meldrum's acid derivatives.[17]

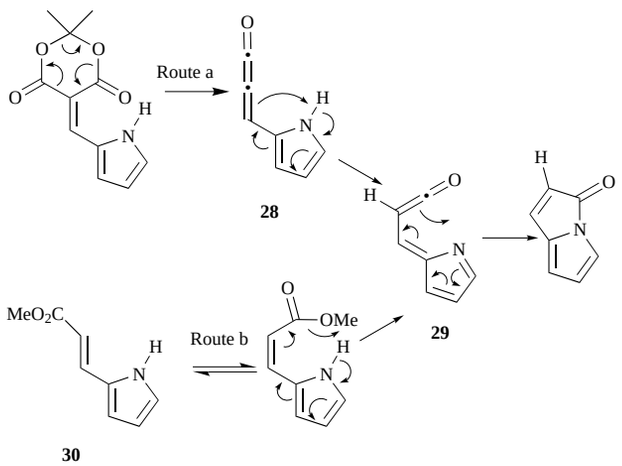
Flash vacuum pyrolysis of the Meldrum's acid derivatives **10**–**15** and **18** at *ca.* 600 °C (10^{-2}–10^{-3} Torr) gave the pyrrolizin-3-ones **19**–**25** in excellent yield (typically 70–90%) and in high purity (Scheme 2). The thermolysis conditions are therefore tolerant to the presence of electron withdrawing or electron donating groups at various positions in the pyrrole ring, or the presence of an alkyl group in the exocyclic methylidene position. Pyrolysis of the mixture **16** and **17** gave a mixture of 6- and 7-phenylpyrrolizin-3-ones **26** and **27** respectively (84% in total) which were separated by recrystallisation from *n*-hexane. The less soluble fraction was identified as the 6-phenyl isomer **26** on the basis of the small coupling constant $^4J_{5,7}$ (0.8 Hz) linking the two protons in the 'left-hand' ring. The coupling constant relating the protons in the corresponding ring of the 7-phenyl isomer **27** ($^3J_{5,6}$) is 3.3 Hz. All of the pyrrolizin-3-ones have intense orange–red colours and were characterised by their NMR spectra (see below). This methodology can therefore be applied to 1-substituted (**23**), 5-substituted (**22**, **24** and **25**), 6-substituted (**3** and **26**) and 7-substituted (**19**–**21** and **27**) pyrrolizinones with equal efficiency.



19 R^7 = Me
20 R^7 = OMe
21 R^7 = CO_2Me
22 R^5 = CO_2Et
23 R^1 = Me
24 R^5 = Me
25 R^5 = Ph
26 R^6 = Ph
27 R^7 = Ph

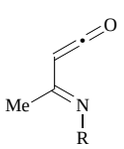
Scheme 2 *Reagents and conditions:* i, FVP (600 °C, 0.001 Torr)

The most likely mechanism for the thermolysis is shown in Scheme 3 (route a). Methylideneketenes (*e.g.* **28**) are well characterised as the key intermediates in the pyrolysis of Meldrum's acid derivatives,[18] and a [1,7] hydrogen shift involving the pyrrole NH generates the pyrrol-2-ylmethylideneketene **29** which is the immediate precursor of the pyrrolizinone by an electrocyclic ring closure. This mechanism is supported by a deuterium labelling experiment which confirms that the NH of the precursor appears exclusively at the 2-position of the pyrrolizinone product (Scheme 3, H = ^{2}H). Due to the high efficiency of the hydrogen atom as a migrating group in sigmatropic shifts it is unlikely that this route will be applicable in general for the preparation of 2-substituted pyrrolizin-3-ones. Indeed, we have shown in the corresponding indole series that *N*-alkylated precursors lead to quite different products.[19]



Scheme 3

Nevertheless, it is clear from the mechanism (Scheme 3, route a) that the methylideneketene merely serves as a route to the ketene **29**, and so we explored more direct routes to this intermediate. Chuche and co-workers have shown that related iminoketenes *e.g.* **31** can be generated by thermal elimination of

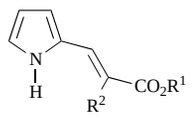


31

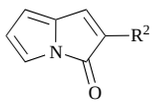
alcohols from enamino esters,[20] and, in a straightforward extension of this methodology it was easy to show that pyrrolizin-3-one **1** itself was readily formed (87%) by pyrolysis of the (*E*)-propenoate ester **30**[21,22] at 850 °C (Scheme 3, route b). We have demonstrated in a related example that the particularly high furnace temperature is required for *E*–*Z* isomerisation[23] of the propenoate precursor prior to the elimination step,[7] but the stability of the pyrrolizin-3-one system is noteworthy and these extreme conditions do not detract from the synthetic utility of the method. Indeed the ability to utilise either (*E*)- or (*Z*)-propenoates or a mixture of these isomers is a particularly attractive feature of the route.

The synthetic potential of this new method is demonstrated

by synthesis and pyrolysis of a range of 2-substituted 3-(pyrrol-2-yl)propenoates to give pyrrolizinones, many of which cannot be made by the Meldrum's acid route. Thus pyrrole-2-carbaldehyde was transformed into the parent propenoate **30** and its 2-methyl derivative **32** by the Wittig reaction,[21,22] and



32 R^1 = Et, R^2 = Me
33 R^1 = Me, R^2 = CO_2Me
34 R^1 = Et, R^2 = CO_2Et
35 R^1 = Me, R^2 = COMe
36 R^1 = Me, R^2 = CN

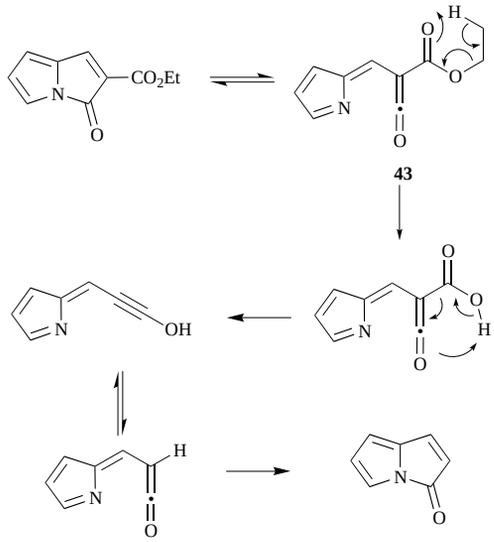


37 R^2 = Me
38 R^2 = CO_2Me
39 R^2 = CO_2Et
40 R^2 = COMe
41 R^2 = CN
42 R^2 = CO_2H

into the 2-functionalised derivatives **33**–**36** by Knoevenagel condensation under similar conditions to those employed for the Meldrum's acid derivatives. Pyrolysis of these propenoates all gave the expected pyrrolizinones **37**–**41** in *ca.* 80% yield, though the furnace temperature had to be carefully optimised for the best results. Thus the 2-methyl derivative **32** and the cyano compound **36** required furnace temperatures of 800 °C or above for complete conversion to the products **37** and **41** respectively. No deleterious results were observed by the use of the ethyl ester **32** which might be expected to eliminate ethene under these pyrolysis conditions. In contrast, pyrolysis of the malonate derivatives **33** and **34** requires furnace temperatures of only 600–650 °C to generate the pyrrolizinones **38** and **39**, since one of the ester groups is necessarily in the correct configuration for the alcohol elimination. Surprisingly, the acetyl compound **35**, which is obtained as a mixture of isomers in 5:2 ratio, was transformed to the product **40** in 76% yield at just 650 °C, which suggests that *E*–*Z* isomerisation is particularly facile for this compound.

Further insight into the pyrolizin-3-one–pyrrol-2-ylmethylideneketene equilibrium is provided by an analysis of the results of the pyrolysis of the diethyl malonate derivative **34** at various temperatures. Even at 600 °C, a small amount (6%) of pyrrolizin-3-one **1** was detected along with the 2-carboxylic ester **39** as major product, whereas at 750 °C the level of **1** had increased to 91%. No other pyrrolizinones could be detected at these, or at intermediate temperatures, and in particular the known carboxylic acid **42**[24] was absent. Repyrolysis of the isolated 3-oxo-3*H*-pyrrolizine-2-carboxylic ester **39** at temperatures in the range 650–750 °C gave similar results. Although the thermal *cis* elimination of ethene from ethyl esters is expected at such pyrolysis temperatures, the quantitative decarboxylation of an apparently unactivated carboxylic acid function does not normally occur under our conditions at temperatures below 850 °C. The most reasonable explanation is that the pyrrolizinone is in equilibrium with a corresponding pyrrol-2-ylmethylideneketene **43** and this function can participate in a concerted CO_2 elimination sequence as soon as the carboxylic acid is generated (Scheme 4). The surprising observation—particularly in view of the high thermal stability of the pyrrolizinones—is that this equilibrium must be already in place at temperatures of 650 °C and below for the decarboxylation to take place. We have reached similar conclusions in work on the decarboxylation of α-pyrone derivatives such as coumalic acid.[25]

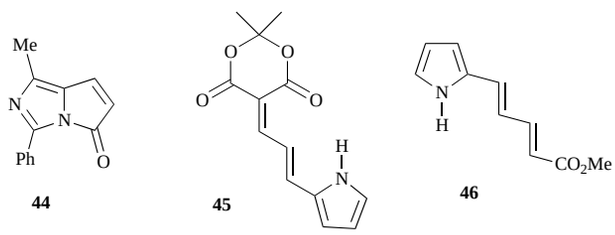
The NMR spectra of pyrrolizin-3-one itself has been studied previously,[4] but with the availability of the range of derivatives reported here the effects of substituents can now be investigated. If the ^{1}H NMR spectra are recorded with good resolution, the minor long range coupling constants expected from those of **1** could usually be identified and in particular a characteristic $^6J_{2,6}$ of *ca.* 0.8 Hz was often useful in assigning resonances. The majority of the spectra could therefore be assigned by inspection, though the 1-methyl compound **23** required a high field instrument (at least 360 MHz) for a first order spectrum to be obtained. Methyl substitution in general induces a small shielding effect at the adjacent position in both ^{1}H and ^{31}C NMR spectra, but has relatively little effect at other sites of the molecule. A ^4J of *ca.* 1.7 Hz is observed between protons on a 1- or 2-methyl group and the proton at the adjacent site, but such coupling is much smaller in magnitude when the substituent is at the 5- or 7-positions. The 7-methoxy substituent in **20** also has only a small influence on most ^{1}H and ^{13}C NMR chemical shifts, though C(7a) is shielded by *ca.* 19 ppm by comparison with the parent compound **1**.



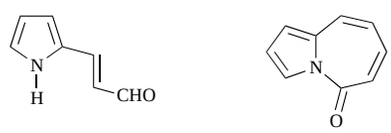
43

Scheme 4

A 5-, 6- or 7-phenyl substituent deshields adjacent protons by up to 0.4 ppm (compounds **25**–**27**); this is almost certainly a ring current effect since these substituents have very little influence on the ^{13}C NMR spectra. The chemical shifts of the *para* carbon atoms of the phenyl rings are sensitive probes of the electronic nature of the pyrrolizinone ring. Those of the 6-phenyl (δ_C 126.90) and 7-phenyl (δ_C 127.99) are both at a lower frequency than the corresponding *meta* carbon signal, indicating that the pyrrolizinone ring acts as a net electron donating group at these sites. In contrast, the signal for the *para* carbon atom of the 5-phenyl compound **25** (δ_C 128.60) is slightly deshielded relative to the *meta* carbon signal which suggests that the pyrrolizinone ring is a net electron withdrawing group at the 5-position. The effect is, however, much smaller than for the corresponding phenyl group of the azapyrrolizinone **44**[7] and may be too insignificant to be relevant to chemical reactivity (*e.g.* electrophilic substitution reactions).



44 **45** **46**



47 **48**

Table 1 $^1J_{CH}$ Values for representative pyrrolizin-3-ones

		$^1J_{CH}$/Hz					
Pyrrolizinone	Substituent	1	2	5	6	7	Alkyl
1	—	176.3	181.8	192.1	174.8	175.0	—
23	1-Me	—	179.2	192.4	173.8	174.3	128.9
37	2-Me	174.6	—	192.2	173.6	174.8	128.5
24	5-Me	175.2	181.6	—	172.1	174.4	129.4
19	7-Me	174.9	179.4	191.8	172.1	—	128.0
41	2-CN	181.5	—	194.9	179.7	177.2	—
22	5-CO_2Et	178.7	182.8	—	177.0	177.7	147.8, 127.4

Table 2 $^nJ_{CH}$ Values for representative pyrrolizin-3-ones

		$^nJ_{CH}$ [a]/Hz									
	Substituent	1,2	2,1	3,2	3,1	5,6	5,7	6,5	6,7	7,6	7,5
1	—	3.0	—	7.6	11.8	7.6	7.6	7.8	4.5	4.7	7.6
23	1-Me	6.4	5.5	8.3	—	7.7	7.7	8.0	4.3	4.8	7.6
37	2-Me	6.1	7.8	—	—	7.7	7.7	7.9	5.1	7.5	7.5
24	5-Me	—	—	—	—	—	7.8	—	4.5	4.5	—
19	7-Me	—	—	—	—	8.2	—	<5 [b]	—	—	—
41	2-CN	—	4.1	—	10.6	7.8	7.8	6.7	3.6	4.1	7.6
22	5-CO_2Et	—	—	7.6	13.0	7.8	7.8	—	4.2	4.0	—

[a] Couplings of bridgehead quaternary carbon C(7a) are not readily identified. [b] Resonance complicated by coupling of C nucleus to methyl carbon.

An ester substituent at positions 2, 5 or 7 (in **38**, **22** and **21** respectively) causes a general deshielding effect on the proton resonances of the other sites; 2-acetyl or 2-cyano groups (in **40** and **41**) have very similar effects. The situation in the ^{13}C NMR spectra of these compounds is more complex. For the compounds containing electron withdrawing groups at the 2-position (**38**, **40** and **41**) signals due to positions 1, 5, 6 and 7 are deshielded as expected, but the quaternaries at C3 and C7a are both *shielded* by 3–6 ppm.

Proton–carbon coupling constants $^nJ_{CH}$ have been measured for a representative series of substituted pyrrolizinones and are reported in Tables 1 and 2. Increases in $^1J_{CH}$ relative to the parent system **1** of up to 7 Hz are observed when the pyrrolizinone contains an electron withdrawing group. The effect is usually greatest at the adjacent position, though the significant increases at all sites of the cyano compound **41** is noteworthy. The networks of long range couplings reported in Table 2 vary little from those of the parent compound; no cross-ring interactions are observed. In systems containing a methyl group, the two-bond coupling of the *ipso* carbon atom to the methyl protons is of the order of 7.5 Hz.

The mass spectrum of **1** is dominated by ring cleavage due to loss of CO from the molecular ion, and this pattern is maintained for the simple alkyl, aryl and cyano derivatives reported here. For those compounds containing an additional carbonyl group (**21**–**22** and **38**–**40**) ionisation at this site followed by α-cleavage leads to (M − OR) peaks (from the esters) or an (M − Me) peak (from the methyl ketone) which are usually more intense than those due to ring cleavage. Loss of a methyl group under electron impact is also found for the methoxy compound **20**, but this breakdown is only about half as intense as the standard ring cleavage.

Finally, the possible extension of the pyrolytic methods to cyclisation of the vinylogous species **45** and **46** was briefly investigated. The Meldrum's acid derivative **45** was prepared by Knoevenagel condensation of the aldehyde **47**, whereas the pentadienoate **46** was obtained from pyrrole-2-carbaldehyde and the appropriate Wittig reagent.[26] However, pyrolysis of **45** at 600 °C gave a material whose ^{1}H NMR spectrum was complex with only small peaks attributable to the expected azaazulenone **48**[27] (*ca.* 13%), partly owing to the poor volatility of the precursor. Unfortunately, FVP of the volatile ester **46** at 600 °C gave only recovered starting material (TLC) whereas at 700 °C a complex mixture was obtained from which only pyrrole itself could be identified from its characteristic ^{1}H NMR spectrum (δ_H 6.24 and 6.81). Apparently no trace of **48** was formed under these conditions.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 200 (or 250) and 50 (or 63) MHz respectively for solutions in deuteriochloroform unless otherwise stated; coupling constants (*J*) are given in Hz. Infrared parameters (ν_{max}) are quoted in cm^{-1} for Nujol mulls or liquid films.

Synthesis of pyrrole precursors

2-Methylpyrrole was obtained in 72% yield by Wolff–Kishner reduction of pyrrole-2-carbaldehyde.[15] 2-Phenylpyrrole and 3-phenylpyrrole were obtained in 25 and 26% yield respectively by flash vacuum pyrolysis of 1-phenylpyrrole,[16] and were separated by dry flash chromatography on silica.

3-Substituted pyrrole-2-carbaldehydes were made by photolytic ring contraction of 4-substituted pyridine *N*-oxides in the presence of copper(II) ions. The following procedure for 3-methylpyrrole-2-carbaldehyde[10] **5** is typical. A degassed solution of 4-picoline *N*-oxide (4-methylpyridine *N*-oxide) (1.89 g, 17 mmol) and copper(II) sulfate pentahydrate (39.10 g, 0.16 mol) in deionised water (670 cm^3) was irradiated by a 400 W mercury vapour lamp for 6 h. A gentle stream of nitrogen through the solution was maintained during the photolysis. The reaction mixture was saturated with sodium chloride and continuously extracted with methylene chloride (250 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography (25% ethyl acetate–*n*-hexane) of the dark brown residue gave 3-methylpyrrole-2-carbaldehyde **5** (0.620 g, 33%) as a light brown solid, mp 92–94 °C (from *n*-hexane) (lit.,[10] 90–92 °C); δ_H 10.39 (1H, br s), 9.59 (1H, s), 7.04 (1H, t, ^3J and ^4J 2.4), 6.11 (1H, t, ^3J and ^4J 2.4) and 2.37 (3H, s) (in agreement with published data[28]); δ_C 177.49, 133.11 (q), 129.35 (q), 126.39, 112.56 and 10.48. Also made by this method were 3-methoxypyrrole-2-carbaldehyde **6** (23%), mp 131–132 °C (lit.,[9] 135–136 °C) δ_H(360 MHz) 9.80 (1H, br s), 9.50 (1H, apparent s), 6.95 (1H, td, ^3J and ^4J 2.9, ^5J 1.0), 5.87 (1H, t, ^3J and ^4J 2.8) and 3.77 (3H, s) (in agreement with published data[9]); δ_C 175.24, 158.98 (q), 127.07, 118.70 (q), 95.20 and 57.76; *m*/*z* 125 (M$^+$,

100%), 124 (17), 82 (18) and 79 (12); and methyl 2-formylpyrrole-3-carboxylate **7** (24%), mp 129–130 °C (from ethyl acetate) (lit.,[29] 129 °C), δ_H 10.20 (1H, s), 10.00 (1H, br s), 7.02 (1H, dd, ^3J 2.8 and ^4J 2.7), 6.75 (1H, dd, ^3J 2.8 and ^4J 2.7) and 3.89 (3H, s); δ_C 181.92, 163.95 (q), 132.64 (q), 124.32, 122.51 (q), 113.50 and 51.68.

Ethyl 5-formylpyrrole-2-carboxylate 8

Ethyl pyrrole-2-carboxylate was prepared by the *Organic Syntheses* method[30] and was subjected to Vilsmeier formylation.[31] Distillation of the dark red residue obtained after workup gave as the first fraction, bp 130–132 °C (2 Torr) [lit.,[31] 82–86 °C (0.05 Torr)], ethyl 5-formylpyrrole-2-carboxylate **8** (9.67 g, 58%), mp 71–73 °C (lit.,[31] 75 °C); δ_H 10.28 (1H, br s), 9.65 (1H, s), 6.91 (2H, s), 4.36 (2H, q, ^3J 7.1) and 1.35 (3H, t, ^3J 7.1) (in agreement with published data[32]); δ_C 180.30, 160.30 (q), 134.35 (q), 128.50 (q), 119.55, 115.41, 61.99 and 14.09. The residue remaining after collection of the required fraction had ^{1}H NMR spectrum (60 MHz) consistent with ethyl 4-formylpyrrole-2-carboxylate.

Condensation of pyrrole-2-carbaldehydes with active methylene compounds[8]

The active methylene compound (5 mmol), piperidine (5 drops) and glacial acetic acid (5 drops) were added to the pyrrole-carbaldehyde (5 mmol) in the minimum amount of toluene. The solution was stirred overnight at room temperature, unless otherwise stated. The solvent was removed under vacuum and the orange or yellow product was conveniently purified by bulb-to-bulb distillation or by recrystallisation.

The following derivatives were prepared by this method. The active methylene compound and aldehyde used are indicated.

5-[(3-Methylpyrrol-2-yl)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 10. Compound **10** (from Meldrum's acid and 3-methylpyrrole-2-carbaldehyde **5**) (77%) had mp 170.5–172 °C (from ethanol) (Found: C, 61.05; H, 5.7; N, 6.10. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.55; N, 5.95%); ν_{max} 3289, 1722, 1681 and 1559; δ_H 12.70 (1H, br s), 8.27 (1H, s), 7.33 (1H, apparent t, ^3J and ^4J 2.9), 6.33 (1H, apparent t, ^3J and ^4J 2.9), 2.37 (3H, s) and 1.73 (6H, s); δ_C 164.61 (q), 141.07 (q), 139.41, 131.75, 127.18 (q), 115.10, 103.87 (q), 97.86 (q), 29.51 and 26.97; *m*/*z* 235 (M^+, 42%), 177 (19), 133 (56), 105 (100), 104 (46), 78 (15), 51 (13) and 43 (15).

5-[(3-Methoxypyrrol-2-yl)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 11. Compound **11** (from Meldrum's acid and 3-methoxypyrrole-2-carbaldehyde **6**) (72%) had mp 190–191 °C (from ethanol) (Found: C, 57.2; N, 5.25; N, 5.5. $C_{12}H_{13}NO_5$ requires C, 57.35; H, 5.2; N, 5.6%); δ_H([$^2H_6$]DMSO) 11.85 (1H, br s), 7.99 (1H, d, ^5J 0.8), 7.66 (1H, dd, ^3J 2.8 and ^5J 0.8), 6.18 (1H, d, ^3J 2.8), 3.93 (3H, s) and 1.65 (6H, s); δ_C([$^2H_6$]DMSO) 164.02 (q), 162.78 (q), 136.52, 134.01, 116.61 (q), 103.47 (q), 96.30, 94.25 (q), 58.83 and 26.62; *m*/*z* 251 (M^+, 43%), 250 (68), 194 (38), 193 (30), 192 (41), 176 (28), 149 (70), 134 (48), 121 (59), 120 (100), 106 (52) and 93 (51).

2,2-Dimethyl-5-[(3-methoxycarbonylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione 12. Compound **12** (from Meldrum's acid and methyl 2-formylpyrrole-3-carboxylate **7**) (86%) had mp 191 °C (from isopropyl alcohol) (Found: C, 55.65; H, 4.85; N, 4.9. $C_{13}H_{13}NO_6$ requires C, 55.9; H, 4.7; N, 5.0%); ν_{max} 1744, 1712 and 1687; δ_H 13.08 (1H, br s), 9.34 (1H, s), 7.28 (1H, t, ^3J and ^4J 2.5), 6.96 (1H, t, ^3J and ^4J 2.5), 3.89 (3H, s) and 1.75 (6H, s); δ_C 163.58 (q), 142.39, 127.99 (q), 127.69, 126.51 (q), 116.69, 104.96 (q), 104.55 (q), 51.88 (q) and 27.19 (one quaternary signal missing); *m*/*z* 279 (M^+, 53%), 222 (20), 221 (51), 190 (20), 177 (65), 149 (97), 146 (41), 134 (100) and 118 (55).

5-[(5-Ethoxycarbonylpyrrol-2-yl)methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 13. Compound **13** (from Meldrum's acid and ethyl 5-formylpyrrole-2-carboxylate **8**) (98% after trituration with *n*-hexane) had mp 166–168 °C (from ethanol) (Found: C, 57.1; H, 5.2; N, 4.65. $C_{14}H_{15}NO_6$ requires C, 57.35; H, 5.15; N, 4.8%); ν_{max} 3200, 1715, 1695 and 1560; δ_H 12.89 (1H, br s), 8.27 (1H, s), 7.01 (2H, apparent d), 4.40 (2H, q, ^3J 7.2), 1.77 (6H, s) and 1.40 (3H, t, ^3J 7.2); δ_C 163.31 (q), 163.14 (q), 159.39 (q), 143.78, 131.98 (q), 129.61 (q), 128.18, 116.78, 105.18 (q), 104.67 (q), 61.47, 27.27 and 14.09; *m*/*z* 293 (M^+, 90%), 235 (83), 191 (89), 163 (50), 146 (90), 119 (100), 91 (31), 63 (26) and 43 (38).

Dimethyl 2-[(pyrrol-2-yl)methylidene]malonate 33. Compound **33** (from dimethyl malonate and pyrrole-2-carbaldehyde) (96%) had bp 169–174 °C (1.5 Torr) (Found: C, 57.4; H, 5.3; N, 6.9. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%); δ_H 11.31 (1H, br s), 7.61 (1H, s), 6.98 (1H, m), 6.61 (1H, m), 6.21 (1H, m), 3.72 (3H, s) and 3.68 (3H, s); δ_C 168.00 (q), 166.55 (q), 137.36, 126.72 (q), 126.17, 122.75, 112.77 (q), 111.24, 51.95 and 51.79; *m*/*z* 209 (M^+, 40%), 208 (80), 177 (62), 146 (35), 119 (100), 90 (69) and 63 (94).

Diethyl 2-[(pyrrol-2-yl)methylidene]malonate 34. Compound **34** (from diethyl malonate and pyrrole-2-carbaldehyde) (78%) had bp 100–105 °C (0.1 Torr) (Found: C, 61.8; H, 6.8; N, 6.95; M^+, 237.0991. $C_{12}H_{15}NO_4$ requires C, 60.8; H, 6.3; N, 5.95%; *M*, 237.1001); δ_H 11.31 (1H, br s), 7.63 (1H, s), 7.02 (1H, m), 6.68 (1H, m), 6.26 (1H, m), 4.28 (2H, q, ^3J 7.2), 4.23 (2H, q, ^3J 7.2), 1.29 (3H, t, ^3J 7.2) and 1.28 (3H, t, ^3J 7.2); δ_C 167.92 (q), 166.47 (q), 136.99, 127.00 (q), 125.68, 122.64, 113.48 (q), 111.13, 61.17, 60.81, 14.01 and 13.86; *m*/*z* 237 (M^+, 37%), 146 (35), 119 (27), 75 (39), 65 (100) and 53 (65).

Methyl (*E*)- and (*Z*)-2-acetyl-3-(pyrrol-2-yl)propenoate 35. Compound **35** (from methyl acetoacetate and pyrrole-2-carbaldehyde, 48 h) (72% in total) had bp 130–150 °C (1 Torr) (Found: C, 62.5; H, 6.25;. N, 7.3; M^+, 193.0737. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%; *M*, 197.0739); δ_H (major and minor isomers present in a ratio of 5:2; distinguishable minor isomer signals reported in parentheses) 12.12 (11.51) (1H, br s), 7.21 (7.62) (1H, s), 7.09 (1H, m), 6.77 (1H, m), 6.33 (1H, m), 3.79 (3.83) (3H, s) and 2.50 (2.38) (3H, s); δ_C (minor isomer in parentheses) 199.97 (197.11) (q), 168.14 (168.84) (q), 138.25 (137.72), 128.30 (127.22) (q), 126.77, 125.36 (124.74), 119.03 (120.60) (q), 112.48 (111.75), 51.81 (51.88) and 31.46 (29.36); *m*/*z* 193 (M^+, 50%), 146 (100), 91 (22), 65 (13) and 43 (47).

Methyl 2-cyano-3-(pyrrol-2-yl)propenoate 36. Compound **36** (from methyl cyanoacetate and pyrrole-2-carbaldehyde) (67%) had mp 112–114 °C (from ethanol) (Found: C, 61.0; H, 4.6; N, 15.9. $C_9H_8NO_2$ requires C, 61.35; H, 4.55; N, 15.9%); δ_H 9.94 (1H, br s), 8.01 (1H, s), 7.24 (1H, m), 6.98 (1H, m), 6.42 (1H, m) and 3.86 (3H, s); δ_C 163.81 (q), 142.53, 128.44, 126.58 (q), 124.27, 118.20 (q), 112.36, 91.16 (q) and 52.66; *m*/*z* 176 (M^+, 100%), 145 (76), 144 (84), 116 (81) and 90 (25).

2,2-Dimethyl-5-[3-(pyrrol-2-yl)prop-2-enylidene]-1,3-dioxane-4,6-dione 45. In a similar procedure, 3-(pyrrol-2-yl)propenal **47**[33] (0.36 g, 3 mmol) was reacted with Meldrum's acid (0.43 g, 3 mmol) to give compound **45** (0.68 g, 92%), mp 190–192 °C (decomp.) (from ethanol) (Found: C, 63.45; H, 5.3; N, 5.7. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.25; N, 5.65%); δ_H 10.55 (1H, br s), 8.21 (1H, d, ^3J 12.5), 7.96 (1H, t, ^3J 12.5), 7.34 (1H, d, ^3J 12.5), 7.23 (1H, m), 6.80 (1H, m), 6.38 (1H, m) and 1.74 (6H, s); δ_C 163.59 (q), 162.90 (q), 159.80, 145.24, 130.51 (q), 128.39, 121.80, 118.18, 112.69, 104.71 (q), 104.27 (q) and 27.36; *m*/*z* 247 (M^+, 60%), 189 (65), 121 (75), 117 (100) and 90 (38).

2,2-Dimethyl-5-[1-(pyrrol-2-yl)ethylidene]-1,3-dioxane-4,6-dione 18

A solution of titanium tetrachloride (9 cm^3, 82 mmol) in carbon tetrachloride (20 cm^3) was added dropwise under an atmosphere of nitrogen to ice-cold tetrahydrofuran (160 cm^3). The resulting mixture was treated with a solution of Meldrum's acid (5.96 g, 41 mmol) and 2-acetylpyrrole **9** (4.45 g, 41 mmol) in tetrahydrofuran (40 cm^3), followed by a solution of pyridine (13 cm^3) in tetrahydrofuran (20 cm^3). The mixture was stirred at 0 °C for 3.5 h and then at room temperature overnight, after

which water (40 cm^3) was added, the resulting mixture was filtered through Celite, concentrated and extracted with diethyl ether (6 × 100 cm^3). The combined organic layers were washed with brine (20 cm^3), saturated aqueous sodium hydrogen carbonate (20 cm^3) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give a crop of yellow crystals of 2,2-*dimethyl*-5-[1-(*pyrrol*-2-*yl*)*ethylidene*]-1,3-*dioxane*-4,6-*dione* **18** (5.48 g, 57%) after recrystallisation from ethanol, mp 127–129 °C (from ethanol) (Found: C, 61.3; H, 5.6; N, 5.95. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.55; N, 5.95%); ν_{max} 3260, 1780 and 1740; δ_H([$^2H_6$]DMSO) 12.10 (1H, br s), 7.39 (1H, m), 7.18 (1H, m), 6.37 (1H, m), 2.70 (3H, s) and 1.72 (6H, s); δ_C([$^2H_6$]DMSO) 162.38 (q), 157.77 (q), 130.10 (q), 128.83, 122.24, 111.74, 105.58 (q), 102.61 (q), 26.89 and 22.97; *m*/*z* 235 (M^+, 13%), 177 (39), 133 (100) and 104 (47).

Reactions of pyrroles with methoxymethylidene Meldrum's acid[14]

The appropriate pyrrole (11 mmol) was added to a solution of methoxymethylidene Meldrum's acid **4** (1.86 g, 10 mmol) in the minimum volume of acetonitrile (8 cm^3), and the mixture was stirred at room temperature for the stated length of time. Concentration of the solution under vacuum yielded a crop of yellow crystals which were washed with hexane. The following derivatives were made by this method.

2,2-Dimethyl-5-[(5-methylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione 14. Compound **14** (1.43 g, 61%) (from 2-methylpyrrole, stirred at room temperature for 40 h) had mp 136–137 °C (from ethanol) (Found: C, 61.6; H, 5.55; N, 6.0. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.55; N, 5.95%); ν_{max} 3250, 1735 and 1680; δ_H 8.04 (1H, s), 7.37 (1H, br s), 6.38 (1H, m), 2.43 (3H, s) and 1.67 (6H, s); δ_C([$^2H_6$]DMSO) 163.65 (q), 145.90 (q), 140.66, 132.07 (br), 127.92 (q), 114.94, 103.30 (q), 97.31 (q), 26.53 and 13.70 (both ^1H and ^{13}C NMR spectra show evidence of exchange processes at room temperature); *m*/*z* 235 (M^+, 24%), 177 (12), 133 (100) and 104 (40).

2,2-Dimethyl-5-[(2-phenylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione 15. Compound **15** (65%) (from 2-phenylpyrrole, stirred at room temperature overnight) had mp 139–141 °C (from ethanol) (Found: C, 68.4; H, 5.1; N, 4.7. $C_{17}H_{15}NO_4$ requires C, 68.4; H, 5.1; N, 4.7%); δ_H 8.20 (1H, s), 7.74 (2H, m), 7.4–7.5 (3H, m), 7.18 (1H, dd, ^3J 4.2 and ^4J 2.1), 6.89 (1H, dd, ^3J 4.2 and ^4J 2.3) and 1.78 (6H, s); δ_C 164.68 (q), 163.97 (q), 144.98 (q), 141.40, 131.46, 129.68, 129.41 (q), 129.14, 125.47, 112.38, 103.91 (q), 99.04 (q) and 26.98 (one quaternary signal missing); *m*/*z* 297 (M^+, 13%), 195 (85), 143 (100) and 115 (43).

2,2-Dimethyl-5-[(3-phenylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione 16 and 2,2-dimethyl-5-[(4-phenylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione 17. Reaction of 3-phenylpyrrole under similar conditions gave an equimolar mixture of compounds **16** and **17** (78%), mp 180–182 °C (from ethanol) which could only be partially separated into a major and minor isomer (**17** and **16** respectively) by recrystallisation (Found: C, 68.4; H, 5.1; N, 4.8. $C_{17}H_{15}NO_4$ requires C, 68.4; H, 5.1; N, 4.7%); δ_H(major isomer) 8.29 (1H, s), 7.71 (1H, m), 7.2–7.6 (6H, m) and 1.77 (6H, s); δ_H(minor isomer) 8.34 (1H, s), 7.2–7.6 (6H, m), 6.62 (1H, t, *J* 2.4) and 1.76 (6H, s).

Wittig reactions of pyrrole-2-carbaldehydes

A solution of the appropriate pyrrole-2-carbaldehyde and ylide in dry benzene was heated at reflux under nitrogen for the time stated. The solvent was removed and, unless otherwise stated, the products were obtained by dry flash chromatography of the residue. The following 3-(pyrrol-2-yl)propenoates were obtained by this means. The aldehyde and ylide, volume of solvent, reaction time and the eluent used in the chromatographic separation (or other workup method) are quoted.

Methyl 3-(pyrrol-2-yl)propenoate 30. Compound **30** [from pyrrole-2-carbaldehyde (0.213 g, 2.2 mmol), methyl (triphenylphosphoranylidene)acetate (0.813 g, 2.4 mmol), 20 cm^3, 1 h, sublimation] (0.236 g, 78%, ratio *E*:*Z* = 90:10) had mp 93.5–94.5 °C [from toluene–light petroleum (bp 60–80 °C)] (lit.,[21] 103 °C); λ_{max}(EtOH) (ε/dm^3 mol^{-1} cm^{-1}) 260–265 (6760) and 330 (22 900); δ_H(minor stereoisomer in square brackets) 8.81 (1H, br s) [12.22 (1H, br s)], 7.56 (1H, d, ^3J 15.9) [6.77 (1H, d, ^3J 12.5)], 6.93 (1H, m) [7.01 (1H, br d)], 6.56 (1H, m) [6.52 (1H, m)], 6.27 (1H, m) [6.27 (1H, m)], 6.00 (1H, d, ^3J 15.9) [5.53 (1H, d, ^3J 12.5)] and 3.77 (3H, s) [3.77 (3H, s)] (in agreement with literature data);[21,22] δ_C(minor stereoisomer in square brackets) 168.01 (q) [169.50 (q)], 134.30 [134.77], 128.20 (q) [128.94 (q)], 122.30 [122.90], 114.32 [118.62], 110.83 [110.05], 110.61 [106.98] and 51.39 [51.47].

Ethyl (*E*)-2-methyl-3-(pyrrol-2-yl)propenoate 32. Compound **32** [from pyrrole-2-carbaldehyde (0.201 g, 2.1 mmol), ethyl 2-(triphenylphosphoranylidene)propanoate (1.01 g, 3.0 mmol), 25 cm^3, 4 h, ethyl acetate–*n*-hexane] (0.366 g, 97%) had mp 78–79 °C [from light petroleum (bp 60–80 °C)] (lit.,[22] 79–80 °C); ν_{max} 3290, 1680 and 1630; δ_H 8.78 (1H, br s), 7.57 (1H, s), 6.94 (1H, m), 6.54 (1H, br s), 6.34 (1H, m), 4.25 (2H, q, ^3J 7.1), 2.16 (3H, d, ^4J 1.3) and 1.33 (3H, t, ^3J 7.1); δ_C 168.97 (q), 128.87 (q), 128.50, 121.03 (q), 120.82, 113.55, 110.76, 60.54, 14.20 and 13.89 (all spectroscopic data in agreement with published data[22]). Another fraction was identified as ethyl (*Z*)-2-methyl-3-(pyrrol-2-yl)propenoate (9 mg, 2%), oil; δ_H 11.99 (1H, br s), 6.92 (1H, m), 6.73 (1H, br s), 6.39 (1H, m), 6.24 (1H, m), 4.25 (2H, q, ^3J 7.1), 2.06 (3H, d, ^4J 1.2) and 1.33 (3H, t, ^3J 7.1); δ_C (three quaternaries missing) 132.33, 121.30, 117.09, 109.44, 60.47, 21.74 and 14.08 (all spectroscopic data in agreement with published data.[22]

Methyl (*E*,*E*)-5-(pyrrol-2-yl)penta-2,4-dienoate 46. Compound **46** [from pyrrole-2-carbaldehyde (0.420 g, 4.4 mmol), 3-methoxycarbonylprop-2-enylidenetriphenylphosphorane[26] (1.902 g, 5.4 mmol) in toluene (50 cm^3), 17 h, ethyl acetate, *n*-hexane] (0.400 g, 51%) was the major fraction, mp 131–132 °C (from hexane) (lit.,[21] 130 °C) δ_H 8.70 (1H, br s), 7.39 (1H, ddd, ^3J 15.2 and 11.1, ^nJ 0.6), 6.86 (1H, m), 6.75 (1H, d, ^3J 15.6), 6.40–6.50 (2H, m), 5.86 (1, d, ^3J 15.2) and 3.74 (3H, s); δ_C 167.88 (q), 145.38, 130.32, 129.74 (q), 121.13, 120.48, 117.79, 111.94, 110.58 and 51.37.

Pyrrolizinones

Pyrolysis of Meldrum's acid derivatives. The Meldrum's acid derivative was sublimed at low pressure into a horizontal quartz pyrolysis tube (35 × 2.5 cm) which was maintained at the appropriate temperature by an electrically heated furnace. The products were collected in a U-tube cooled by liquid nitrogen situated at the exit point of the furnace.

The following pyrrolizinones were obtained by pyrolysis of Meldrum's acid derivatives. The 2,2-dimethyl-5-[(pyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione substrate and pyrolysis parameters [furnace temperature (T_f), inlet temperature (T_i), pressure (*P*) and pyrolysis time (*t*)] are quoted.

7-Methylpyrrolizin-3-one 19. Compound **19** {from 2,2-dimethyl-5-[(3-methylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione **10** (2.20 g, 9 mmol)} (T_f 650 °C, T_i 120–130 °C, *P* 0.005 Torr, *t* 4 h) (1.20 g, 96%) had bp 64–66 °C (0.4 Torr) (Found: M^+, 133.0533. C_8H_7NO requires *M*, 133.0528); ν_{max} 1738 and 1526; δ_H 7.05 (1H, d, ^3J 5.8), 6.81 (1H, m, ^3J 3.2 and ^5J 0.5), 5.80 (1H, d, ^3J 3.2), 5.56 (1H, d, ^3J 5.8) and 1.98 (3H, d, ^5J 0.5); δ_C 165.66 (q), 136.69, 134.08 (q), 123.98 (q), 120.54, 119.18, 117.62 and 11.03; *m*/*z* 133 (M^+, 100%), 105 (32), 104 (71), 79 (12), 78 (18), 52 (15) and 51 (20).

7-Methoxypyrrolizin-3-one 20. Compound **20** {from 2,2-dimethyl-5-[(3-methoxypyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione **11** (0.260 g, 1.0 mmol)} (T_f 600 °C, T_i 150–180 °C, *P* 0.03 Torr, *t* 35 min) (0.058 g, 37%) had bp 90–95 °C (0.2 Torr) (Found: M^+, 149.0476. $C_8H_7NO_2$ requires *M*, 149.0477); δ_H 7.11 (1H, d, ^3J 5.8), 6.84 (1H, d, ^3J 3.3), 5.67 (1H, d, ^3J 3.3), 5.52 (1H, d, ^3J 5.8) and 3.82 (3H, s); δ_C 164.91 (q), 149.42 (q),

137.18, 120.37, 117.91, 116.88 (q), 107.53 and 58.95; *m*/*z* 149 (M^+, 100%), 134 (20), 120 (40), 106 (65), 80 (32) and 52 (49).

Methyl 3-oxo-3*H*-pyrrolizine-7-carboxylate 21. Compound **21** {from 2,2-dimethyl-5-[(3-methoxycarbonylpyrrol-2-yl)-methylidene]-1,3-dioxane-4,6-dione **12** (1.75 g, 6 mmol)} (T_f 620 °C, T_i 160–180 °C, *P* 0.01 Torr, *t* 1 h) (0.90 g, 81%) had mp 70–71 °C (from *n*-hexane) (Found: C, 61.1; H, 4.0; N, 7.75. $C_9H_7NO_3$ requires C, 61.0; H, 3.95; N, 7.9%); ν_{max} 1742, 1720, 1586 and 1524; δ_H 7.38 (1H, dd, ^3J 5.9 and ^5J 0.5), 6.84 (1H, dd, ^3J 3.3 and ^5J 0.5), 6.34 (1H, dd, ^3J 3.3 and ^6J 0.9), 5.80 (1H, dd, ^3J 5.9 and ^6J 0.9) and 3.80 (3H, s); δ_C 165.12 (q), 163.14 (q), 139.76 (q), 138.24, 123.61, 118.21, 115.84 (q), 115.08 and 51.60; *m*/*z* 177 (M^+, 100%), 146 (76), 134 (37), 118 (42), 90 (16) and 63 (33).

Ethyl 3-oxo-3*H*-pyrrolizine-5-carboxylate 22. Compound **22** {from 2,2-dimethyl-5-[(2-ethoxycarbonylpyrrol-5-yl)-methylidene]-1,3-dioxane-4,6-dione **13** (0.293 g, 1.0 mmol)} (T_f 550 °C, T_i 150–170 °C, *P* 0.002 Torr, *t* 1 h 40 min) (0.132 g, 69%) had bp 65–67 °C (0.2 Torr) (Found: M^+, 191.0579. $C_{10}H_9NO_3$ requires *M*, 191.0582); ν_{max} 1750 and 1710; δ_H 7.12 (1H, d, ^3J 6.0), 6.78 (1H, dd, ^3J 3.4 and ^6J 0.7), 6.01 (1H, d, ^3J 3.4), 5.80 (1H, dd, ^3J 6.0 and ^6J 0.7), 4.30 (2H, q, ^3J 7.1) and 1.33 (3H, t, ^3J 7.1); δ_C 163.43 (q), 158.72 (q), 141.68 (q), 136.70, 126.15 (q), 124.10, 123.84, 109.45, 60.84 and 14.08; *m*/*z* 191 (M^+, 100%), 163 (18), 146 (75), 119 (35), 91 (13) and 63 (10).

1-Methylpyrrolizin-3-one 23. Compound **23** {from 2,2-dimethyl-5-[1-(pyrrol-2-yl)ethylidene]-1,3-dioxane-4,6-dione **18** (0.58 g, 2.5 mmol)} (T_f 600 °C, T_i 130–140 °C, *P* 0.002 Torr, *t* 1 h) (0.24 g, 73%) had bp 112 °C (4 Torr) [lit.,[34] 110–130 °C (17 Torr)]; ν_{max} 1725; δ_H(360 MHz) 6.87 (1H, dd, ^3J 3.0 and ^4J 1.0), 6.00 (1H, dd, ^3J 3.0 and ^4J 1.0), 5.98 (1H, td, ^3J 3.0 and ^6J 0.7), 5.39 (1H, qd, ^4J 1.7 and ^6J 0.6) and 2.07 (3H, d, ^4J 1.7); δ_C 165.66 (q), 151.83 (q), 138.63 (q), 118.22, 117.52, 114.67, 109.09, and 13.08; *m*/*z* 133 (M^+, 100%), 118 (14), 104 (96), 94 (11), and 78 (29).

5-Methylpyrrolizin-3-one 24. Compound **24** {from 2,2-dimethyl-5-[(5-methylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione **14** (0.578 g, 2.5 mmol)} (T_f 600 °C, T_i 130–140 °C, *P* 0.005 Torr, *t* 45 min) (0.285 g, 87%) had bp 91–95 °C (21 Torr) (Found: C, 73.4; H, 5.4; N, 10.8; M^+, 133.0523. C_8H_7NO requires C, 72.2; H, 5.25; N, 10.55%; *M*, 133.0528); ν_{max} 1730 and 1585; δ_H 7.03 (1H, d, ^3J 5.9), 5.89 (1H, d, ^3J 2.9), 5.64 (1H, m), 5.60 (1H, d, ^3J 5.9) and 2.29 (3H, s); δ_C 166.50 (q), 137.36, 135.76 (q), 134.23 (q), 120.60, 112.89, 111.64 and 11.91; *m*/*z* 133 (M^+, 100%), 104 (57), 78 (19) and 63 (24).

5-Phenylpyrrolizin-3-one 25. Compound **25** {from 2,2-dimethyl-5-[(5-phenylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione **15** (0.54 g, 1.8 mmol)} (T_f 600 °C, T_i 160–180 °C, *P* 0.002 Torr, *t* 1 h) (0.31 g, 88%) had bp 97–98 °C (0.2 Torr) (Found: M^+, 195.0686. $C_{13}H_9NO$ requires *M*, 195.0684); δ_H 7.2–7.9 (5H, m), 7.10 (1H, d, ^3J 5.9), 6.19 (1H, dd, ^3J 3.3 and ^6J 0.7), 6.07 (1H, d, ^3J 3.3) and 5.09 (1H, dd, ^3J 5.8 and ^6J 0.7); δ_C 166.21 (q), 138.49 (q), 137.55, 129.60 (q), 128.60, 128.12, 126.72, 121.70, 114.67 and 112.20 (one quaternary obscured); *m*/*z* 195 (M^+, 100%), 167 (32), 166 (31), 140 (11), 139 (13) and 63 (14).

6-Phenylpyrrolizin-3-one 26 and 7-phenylpyrrolizin-3-one 27. Compounds **26** and **27** {from 2,2-dimethyl-5-[(3- and 4-phenylpyrrol-2-yl)methylidene]-1,3-dioxane-4,6-dione **16** and **17** (0.37 g, 1.25 mmol)] (T_f 600 °C, T_i 160–180 °C, *P* 0.002 Torr, *t* 1.25 h) (0.204 g, 84%) were characterised as the mixture (Found: M^+, 195.0691. $C_{13}H_9NO$ requires *M*, 195.0684); *m*/*z* 195 (M^+, 100%), 167 (29), 140 (16), 139 (37), 94 (18) and 63 (11); recrystallisation from *n*-hexane gave a fraction which was almost pure 6-phenylpyrrolizin-3-one **26** (21%), δ_H 7.2–7.5 (6H, m), 7.13 (1H, d, ^3J 6.0), 6.35 (1H, d, ^4J 0.8) and 5.73 (1H, d, ^3J 6.0); δ_C 165.57 (q), 139.90, 137.48 (q), 133.22 (q), 131.63 (q), 128.66, 126.90, 124.91, 122.47, 114.15 and 110.03; the residue after recrystallisation was predominantly 7-phenylpyrrolizin-3-one **27**, δ_H 7.3–7.5 (5H, m), 7.32 (1H, dd, ^3J 5.8 and ^5J 0.4), 6.97 (1H, dd, ^3J 3.3 and ^5J 0.4) 6.27 (1H, dd, ^3J 3.3 and ^6J 0.8) and 5.72 (1H, dd, ^3J 5.8 and ^6J 0.8); δ_C 168.32 (q), 137.87, 132.81 (q), 128.87, 127.99, 126.70, 121.02, 119.83 and 114.32 (two quaternaries not apparent).

[2-^{2}H]Pyrrolizin-3-one. Deuterium exchange of the NH of the Meldrum's acid derivative 2 was accomplished by dissolving the substrate (0.22 g, 2 mmol) in [^{2}H]chloroform (1.5 cm^3) followed by addition of [^{2}H]methanol (2 cm^3) within the inlet tube of the FVP apparatus.[35] The solvents were removed at the oil pump, and the residue was sublimed into the pyrolysis tube at 600 °C (0.002 Torr). The ^{1}H NMR spectrum of the product showed no signal at δ_H 5.62 corresponding to H(2); the level of deuterium incorporation at this position was *ca.* 96%, and there was no significant incorporation at other sites in the product.

Pyrolysis of 3-(pyrrol-2-yl)propenoic ester derivatives. Pyrolysis of the 3-(pyrrol-2-yl)propenoic ester derivatives was carried out as described above for the Meldrum's acid derivatives. However, upon completion of the pyrolysis the volatile alcohol generated in the reaction was removed into the pump trap by allowing the product trap to warm up partially while the system was still under vacuum. When no more alcohol remained, the product trap was allowed to warm to room temperature under an atmosphere of dry nitrogen. The product was removed from the trap by dissolving in acetone. After removal of the solvent, the pyrrolizinone was subjected to bulb to bulb (Kugelrohr) distillation where appropriate. The following pyrrolizin-3-ones were prepared by this means. The substrate and pyrolysis parameters are quoted as above.

Pyrrolizin-3-one 1. Compound **1** [from methyl 3-(pyrrol-2-yl)propenoate **30** (0.095 g, 0.63 mmol)] (T_f 850 °C, T_i 50 °C, *P* 0.025 Torr, *t* 15 min) (0.065 g, 87%) had bp 95–100 °C (17 Torr) [lit.,[1] 130 °C (16 Torr)]; δ_H 7.04 (1H, dd, ^3J 5.9 and ^6J 0.5), 6.86 (1H, t, ^3J 2.0), 5.96 (2H, m) and 5.62 (1H, d, ^3J 5.9) (in agreement with published data[1]).

2-Methylpyrrolizin-3-one 37. Compound **37** [from ethyl 3-(pyrrol-2-yl)-2-methylpropenoate **32** (0.177 g, 1.0 mmol)] (T_f 800 °C, T_i 90 °C, *P* 0.008 Torr, *t* 20 min) (0.115 g, 87%) had bp 45–50 °C (0.2 Torr) (Found: M^+, 133.0525. C_8H_7NO requires *M*, 133.0528); ν_{max} 1735 and 1475; δ_H 6.83 (1H, br d, ^3J 3.2), 6.68 (1H, qd, ^4J 1.7 and ^5J 0.6), 5.93 (1H, t, ^3J 3.1), 5.82 (1H, d, of apparent t, ^3J 3.2, ^4J 0.7 and ^nJ 0.7) and 1.86 (3H, d, ^4J 1.7); δ_C 166.54 (q), 136.48 (q), 132.14 (q), 131.38, 118.23, 114.98, 109.29 and 10.63; *m*/*z* 133 (M^+, 100%), 105 (29), 104 (61), 78 (15), 57 (15), 51 (15) and 39 (11).

Methyl 3-oxo-3*H*-pyrrolizine-2-carboxylate 38. Compound **38** {from dimethyl 2-[(pyrrol-2-yl)methylidene]malonate **33** (0.33 g, 1.6 mmol)} (T_f 650 °C, T_i 100–120 °C, *P* 0.002 Torr, *t* 20 min) (0.25 g, 84%) had mp 105 °C (from cyclohexane) (Found: C, 61.25; H, 4.05; N, 7.8. $C_9H_7NO_3$ requires C, 61.0; H, 3.95; N, 7.9%); δ_H 7.85 (1H, s), 7.03 (1H, d, ^3J 3.3), 6.33 (1H, d, ^3J 3.3), 6.13 (1H, t, ^3J 3.3) and 3.83 (3H, s); δ_C 161.30 (q), 160.72 (q), 145.16, 133.19 (q), 122.98 (q), 121.32, 117.14, 116.77 and 51.79; *m*/*z* 177 (M^+, 74%), 146 (100), 119 (29), 90 (39), 63 (38) and 59 (20).

Ethyl 3-oxo-3*H*-pyrrolizine-2-carboxylate 39. Compound **39** {from diethyl 2-[(pyrrol-2-yl)methylidene]malonate **34** (0.059 g, 0.25 mmol)} (T_f 600 °C, T_i 120 °C, *P* 0.008 Torr, *t* 20 min) [0.015 g, 30%; this represents a minimum yield since the (solid) product was simply scraped from the trap] had mp 59–63 °C (lit.,[24] 60–61 °C) (Found: C, 62.4; H, 4.8; N, 7.4. $C_{10}H_9NO_3$ requires C, 62.8; H, 4.7; N, 7.35%); δ_H 7.82 (1H, s), 7.03 (1H, d, ^3J 3.1), 6.31 (1H, d, ^3J 3.1), 6.12 (1H, t, ^3J 3.1), 4.28 (2H, q, ^3J 7.1) and 1.33 (3H, t, ^3J 7.1); δ_C 160.80 (2q), 144.70, 133.19 (q), 123.30 (q), 121.17, 116.85, 116.66, 60.71 and 14.08; *m*/*z* 191 (M^+, 68%), 161 (13), 146 (100), 119 (52), 91 (23), 90 (26) and 63 (18); a small amount (6%) of pyrrolizin-3-one was also detected at this temperature and was left as a liquid residue in the trap; the percentage in the pyrolysate of this product increased at higher temperatures as follows: 650 °C, 21%; 700 °C, 35%; 750 °C, 91%.

Repyrolysis of ethyl 3-oxopyrrolizine-2-carboxylate **39** as above showed clean conversion to pyrrolizin-3-one **1** with no evidence for any stable intermediates. The amounts of conversion were as follows: 650 °C, 47%; 700 °C, 53%; 750 °C, 89%.

2-Acetylpyrrolizin-3-one 40. Compound **40** [from methyl 2-acetyl-3-(pyrrol-2-yl)propenoate **35** (0.21 g, 1.1 mmol)] (T_f 650 °C, T_i 120 °C, *P* 0.003 Torr, *t* 10 min) (0.14 g, 76%) had mp 103 °C (Found: C, 66.9; H, 4.4; N, 8.6. $C_9H_7NO_2$ requires C, 67.1; H, 4.3; N, 8.7%); δ_H 7.82 (1H, d, ^5J 0.8), 7.01 (1H, apparent dt, ^3J 3.2, ^4J and ^5J 0.8), 6.37 (1H, dd, ^3J 3.2 and ^4J 0.8), 6.15 (1H, t, ^3J 3.2) and 2.46 (3H, s); δ_C 162.58 (q), 145.55, 133.53 (q), 130.55 (q), 121.00, 118.10, 117.02 and 26.90 (one quaternary signal missing); *m*/*z* 161 (M^+, 54%), 146 (100), 91 (21), 90 (24), 63 (24) and 43 (43).

2-Cyanopyrrolizin-3-one 41. Compound **41** [from methyl 2-cyano-3-(pyrrol-2-yl)propenoate **36** (1.02 g, 5.8 mmol)] (T_f 800 °C, T_i 120–130 °C, *P* 0.002 Torr, *t* 1 h) (0.68 g, 81%) had mp 137–138 °C (from ethyl acetate–cyclohexane) (Found: C, 67.0; H, 2.95; N, 19.4. $C_8H_4N_2O$ requires C, 66.65; H, 2.8; N, 19.45%); δ_H 7.67 (1H, s), 7.05 (1H, d, ^3J 3.2), 6.42 (1H, d, ^3J 3.2) and 6.20 (1H, t, ^3J 3.2); δ_C 159.46 (q), 147.47, 133.72 (q), 122.86, 118.75, 118.12, 111.65 (q) and 105.68 (q); *m*/*z* 144 (M^+, 100%), 116 (63), 89 (57), 88 (18), 63 (32) and 62 (28).

Pyrolysis of compounds 45 and 46

The Meldrum's acid derivative **45** (0.09 g, 0.35 mmol) was sublimed at 100–150 °C (0.003 Torr) during 3 h into the furnace tube which was held at 600 °C. There was considerable decomposition in the inlet and much of the pyrolysate was insoluble in [^{2}H]chloroform. However, a small amount of the azaazulenone **48** (*ca.* 13%) was present in the soluble fraction and was identified by its characteristic resonance at δ_H 8.20 (1H, m).[27]

The pyrolysate from FVP of **46** (0.027 g, 700 °C, 100 °C, 0.001 Torr, 20 min) was examined by ^{1}H NMR spectroscopy. No trace of the azaazulenone **48** was obtained and the only identifiable product was pyrrole (see Discussion section).

Acknowledgements

We are grateful to The University of Edinburgh for a Research Studentship (to C. T.), to Lonza Ltd. for a generous gift of Meldrum's acid and to Glaxo Wellcome for financial support.

References

1 H. McNab, *J. Org. Chem.*, 1981, **46**, 2809.
2 A. J. Blake, H. McNab and R. Morrison, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2145.
3 H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1987, 653.
4 H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1987, 657.
5 H. McNab and C. Thornley, *Heterocycles*, 1994, **37**, 1977.
6 H. McNab and C. Thornley, *J. Chem. Soc., Chem. Commun.*, 1993, 1570.
7 H. McNab and C. Thornley, *J. Chem. Soc., Perkin Trans. 1*, 1997, following paper.
8 H. McNab and I. Stobie, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1845 and references cited therein.
9 F. Bellamy, P. Martz and J. Streith, *Heterocycles*, 1975, **3**, 295.
10 F. Bellamy and J. Streith, *J. Chem. Res.*, (*S*), 1979, 18; (*M*), 1979, 0101.
11 F. Bellamy, J. Streith and H. Fritz, *Nouv. J. Chim.*, 1979, **3**, 115.
12 W. A. M. Davies, A. R. Pinder and I. G. Morris, *Tetrahedron*, 1962, **18**, 405.
13 G. J. Baxter and R. F. C. Brown, *Aust. J. Chem.*, 1975, **28**, 1551.
14 P. A. Derbyshire, G. A. Hunter, H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2017.
15 J. W. Cornforth and M. E. Forth, *J. Chem. Soc.*, 1958, 1091.
16 C. L. Hickson and H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1988, 339.
17 A. J. Blake, H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 2*, 1991, 2003.
18 R. F. C. Brown and F. W. Eastwood, in *Chemistry of Ketenes, Allenes and Related Compounds*, *Part 2*, ed. S. Patai, Wiley-Interscience, Chichester, 1980, p. 757.
19 D. W. M. Benzies, P. M. Fresneda, R. A. Jones and H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1651.
20 For example, A. Maujean, G. Marcy and J. Chuche, *J. Chem. Soc., Chem. Commun.*, 1980, 92.
21 Y. Badar, W. J. S. Lockley, T. P. Toube, B. C. L. Weedon and L. R. G. Valadon, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1416.
22 F. R. Ahmed and T. P Toube, *J. Chem. Res.*, (*S*), 1986, 440; (*M*), 1986, 3601.
23 C. L. Hickson and H. McNab, *J. Chem. Res.*, (*S*), 1989, 176.
24 R. Neidlein and G. Jeromin, *J. Chem. Res.*, (*S*), 1980, 223; (*M*), 1980, 3090.
25 G. A. Cartwright and H. McNab, unpublished work.
26 E. Buchta and F. Andrée, *Chem. Ber.*, 1959, **92**, 3111.
27 W. Flitsch, B. Müter and U. Wolf, *Chem. Ber.*, 1973, **106**, 1993.
28 G. S. Coumbarides, J. M. Mercy and T. P. Toube, *J. Chem. Res.*, (*S*), 1990, 151.
29 E. Bisagni, J. P. Marquet and J. Andre-Louisfert, *Bull. Soc. Chim. Fr.*, 1968, 637.
30 D. M. Bailey, R. E. Johnson and N. F. Albertson, *Org. Synth.*, **Coll. Vol. 6**, 1988, 618.
31 W. A. M. Davies, A. R. Pinder and I. G. Morris, *Tetrahedron*, 1962, **18**, 405.
32 P. Fournari, M. Farnier and C. Fournier, *Bull. Soc. Chim. Fr.*, 1972, 283.
33 For example, W. Hinz, R. A. Jones, S. U. Patel and M.-H. Karatza, *Tetrahedron*, 1986, **42**, 3753.
34 W. Flitsch and U. Neumann, *Chem. Ber.*, 1971, **104**, 2170.
35 H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1203.

Paper 7/01749I
Received 12*th March* 1997
Accepted 11*th April* 1997