# 3-Hydroxypyrroles and 1H-Pyrrol-3(2H)-ones. Part 2.[1,2] Scope and Limitations of the Synthesis of Pyrrol-3-ones by Pyrolysis of Aminomethylene Meldrum's Acid Derivatives

## Hamish McNab* and Lilian C. Monahan
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

Flash vacuum pyrolysis of *N,N*-disubstituted aminomethylene Meldrum's acid derivatives provides a route to 4,5-unsubstituted 1H-pyrrol-3(2H)-ones by a hydrogen-transfer–cyclisation sequence. Alkyl and aryl 1-substituted, 1,2-disubstituted, and 1,2,2-trisubstituted pyrrolones can be obtained. In competitive cases, there is little selectivity between hydrogen transfer from primary, secondary, or tertiary sites, although benzyl hydrogen atoms proved particularly reactive, giving a general synthesis of 2-phenyl-1H-pyrrol-3(2H)-ones.

Because of their highly electron-rich nature, and potential sensitivity to common reagents, there are few synthetic routes to simple derivatives of the 1H-pyrrol-3(2H)-one (3-hydroxypyrrole) system (1). Derivatives lacking electron-withdrawing

(1)
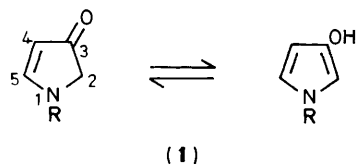
groups, or other substituents in the 4- and/or 5-positions are particularly rare and, in a single example, Momose *et al.* prepared a variety of 1-substituted compounds in a multi-step sequence involving hydrolysis and carefully controlled decarboxylation of 4-carboxylic esters:[3,4] the method appears to be inconvenient for large-scale work. However, in Part 1 of this series, we reported an example of a new flash vacuum pyrolysis method of synthesizing the 1H-pyrrol-3(2H)-one nucleus, in two steps from a simple amine[1] (Scheme). An
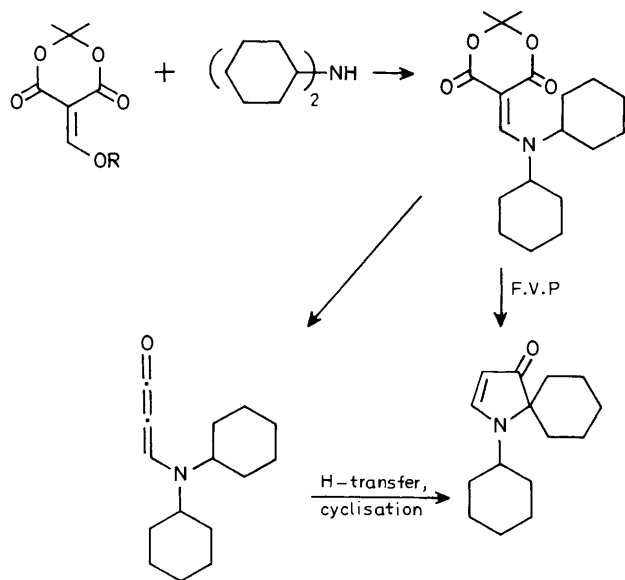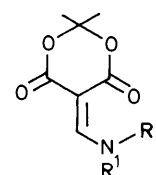

Scheme.

unusual hydrogen-transfer–cyclisation sequence is involved in the key step of the reaction. Since the pyrrolone is generated in

the gas phase, in the absence of other reagents, it was hoped that the method might have general synthetic applicability, and we report here the successful preparation of a range of alkyl and aryl 1,2,2-trisubstituted, 1,2-disubstituted, and 1-substituted 1H-pyrrol-3(2H)-ones. In its present form, the method cannot be used to prepare 1-unsubstituted examples, since the precursors undergo alternative thermolyses.[2,5,6]

The required aminomethylene derivatives (2)—(19) of

	R¹	R²
(2)	Pr^i	Pr^i
(3)	cycloheptyl	cycloheptyl
(4)	Pr^i	cyclohexyl
(5)	Et	Et
(6)	CH$_2$Ph	CH$_2$Ph
(7)	Et	Ph
(8)	CH$_2$Ph	Ph
(9)	Me	CH$_2$Ph
(10)	Pr^i	CH$_2$Ph
(11)	Me	cyclohexyl
(12)	Et	cyclohexyl
(13)	Bu^t	H
(14)	Bu^t	Me
(15)	Me	Ph
(16)	Ph	H
(17)	Me	Me
(18)	–(*o*)C$_6$H$_4$-C$_6$H$_4$(*o*)CH$_2$–	
(19)	–CHMe(CH$_2$)$_4$–	

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) were made by the action of the appropriate amine on alkoxymethylene derivatives, either *in situ* (Method A, ethoxymethylene, 2 × excess of amine[7]), or after isolation (Methods B and C, methoxymethylene, 10% excess of amine[1]). The latter method was particularly effective for the reaction of primary aromatic amines, for which the *in situ* method gives lower yields due to competitive formation of amidines [*e.g.* (16) Method B, 76%; lit.,[7] (Method A) 53%]. Further *N*-alkylation of such derivatives can also be used [Method D, *e.g.* (14), 56% from (13)], but, has not so far proved to be generally applicable.

The n.m.r. spectra of these Meldrum's acid derivatives give rise to two sets of signals representing the nitrogen substituents,

due to restricted rotation around the C–N bond. Where the nitrogen substitution is unsymmetrical, different proportions of the two rotamers are observed as a result of steric effects, together with two signals for the methylene proton at δ_H 8.0— 8.5. In addition, rotation around the formal C–C double bond can be observed in the ^{13}C n.m.r. spectra, where the carbonyl signal(s) generally appear broad as they are close to coalescence. Quantitative aspects of these phenomena will be dealt with[8] (cf. ref. 9). In the examples with a free NH [(13) and (16)], strong hydrogen bonding with the carbonyl group is reflected in the large transoid coupling to the methylene proton ($^3J_{H,H}$ 15 Hz), and in the presence of only a single rotamer.
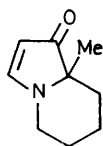
In the mass spectra, the normal breakdown pattern of Meldrum's acid derivatives (sequential loss of acetone, carbon dioxide, and carbon monoxide) is followed, although in some cases an alkyl fragment may be lost prior to cleavage of carbon dioxide (e.g. (2), m/z 154.0506; $(M - C_3H_6O - C_3H_7)^+$ requires m/z 154.0504]. The anomalous breakdown which was noted previously[1] for the N,N-dicyclohexyl derivative [viz. $(M - C_3H_6O - H_2O)^+$] is found only when saturated cyclic substituents are present [viz. in the spectra of compounds (3), (4), (11), and (12)]. Although ions of high relative abundance are formed by this route, their structures, and the rationale for this behaviour, remain unknown.

Pyrolysis of the aminomethylene derivatives (2)—(19) was carried out in the usual manner (see Experimental section), using a furnace temperature of 600 °C. Although good yields of pyrrolones* (60—80%) were obtained in most cases, the procedure has not been optimised, and slightly lower, or slightly higher temperatures might prove beneficial for specific examples.
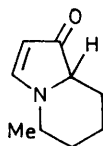
The formation of 1,2,2-trisubstituted 1H-pyrrol-3(2H)-ones[1] has been extended, with the isolation of the 1-isopropyl-2,2-dimethyl example (20) (64%) (recently prepared by Margaretha
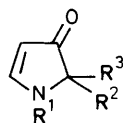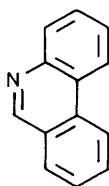
	R^1	R^2	R^3
(20)	Pr^i	Me	Me
(21)	cycloheptyl	–(CH$_2$)$_6$–	
(22)	cyclohexyl	Me	Me
(23)	Pr^i	–(CH$_2$)$_5$–	
(24)	Et	Me	H
(25)	CH$_2$Ph	Ph	H
(26)	Ph	Me	H
(27)	Ph	Ph	H
(28)	Et	–(CH$_2$)$_5$–	
(29)	cyclohexyl	Me	H
(32)	Me	Ph	H
(33)	Pr^i	Ph	H
(34)	Bu^t	H	H
(35)	Ph	H	H
(36)	cyclohexyl	H	H
(37)	Me	–(CH$_2$)$_5$–	
(38)	Me	H	H

(30)

(31)

(39)

* The question of 1H-pyrrol-3(2H)-one/3-hydroxypyrrole tautomerism and the n.m.r. spectra of these species, will be considered in later Parts of this series. The pyrrolone nomenclature is used throughout this paper.

and co-workers by a similar route[10]), and the spiro derivative (21). The method therefore provides access to typical 1,2,2-trisubstituted pyrrolones in multi-gram quantities [e.g. (20): 2.2 g obtained in a single run requiring 4.5 h]. Little selectivity is shown when an unsymmetrical derivative is pyrolysed, the 1-cyclohexyl-2,2-dimethyl- and 1-isopropyl-2,2-pentamethylene-pyrrolones (22) and (23) being obtained in 1.0:1.3 ratio from compound (4). These isomers were readily separated by chromatography on alumina, and this proved possible in general for isomers of 2,2-disubstituted 1H-pyrrol-3(2H)-ones.

1,2-Disubstituted derivatives were readily obtained when the amino compound contained an N-methylene group: once again the procedure was most convenient when precursors derived from symmetrical amines were used [e.g. the 1-ethyl-2-methyl-pyrrolone (24) (77%), obtained from the N,N-diethyl compound (5), and the 1-benzyl-2-phenylpyrrolone (25) (51%) obtained from the N,N-dibenzyl derivative (6)]. Good results were also obtained when one of the amino substituents contained no α-hydrogen atoms; the 1-phenyl-2-substituted derivatives (26) and (27) could be isolated in 73 and 56% yield respectively. 2-Monoalkyl substituted 1H-pyrrol-3(2H)-ones in particular proved to be extremely susceptible to aerial oxidation (see Part 4 of this series, and references therein[11]), which frequently precluded their purification by crystallisation or distillation. No satisfactory chromatographic conditions have so far been discovered, but the materials obtained directly from the pyrolysis were usually sufficiently pure for further reactions.

The key hydrogen-transfer step (Scheme) displayed little selectivity between secondary and tertiary sites. Thus pyrolysis of the N-cyclohexyl-N-ethyl derivative (12) gave the N-ethyl-2,2-pentamethylenepyrrolone (28) and the N-cyclohexyl-2-methyl-pyrrolone (29) in 1.0:1.35 ratio, giving a preference for tertiary over secondary reaction of only 1.0:0.7 after statistical correction. The cyclic derivative (19) showed similar behaviour, with nearly equal quantities of the isomeric indolizin-1-ones (30) and (31) being obtained.[11] This latter result establishes the principle that more complex, fused 1H-pyrrol-3(2H)-ones are directly available by this route, with suitable choice of precursor.

In marked contrast to the above examples, we have found that hydrogen transfer from a benzylic site takes place with complete specificity to give a general synthesis of 2-phenyl-1H-pyrrol-3(2H)-ones. Thus the 1-methyl- (32) (80%) and 1-iso-propyl- (33) (93%) derivatives were formed exclusively from compounds (9) and (10), respectively, notwithstanding the presence of other, potentially reactive sites. Clearly the phenyl group provides stabilisation at some stage in the hydrogen-transfer–cyclisation sequence (Scheme).

Pyrolysis of the N-methyl Meldrum's acid derivatives (14) and (15) gives simple access to 1-substituted 1H-pyrrol-3(2H)-ones with alkyl and aryl substitution, respectively. Thus the N-t-butyl example (34) (62%) was obtained as a yellow oil after distillation from a dark, crude pyrolysate, whereas the N-phenyl derivative (35) formed clean yellow crystals in 60—70% yield directly in the pyrolysis trap. The convenience of the present route to this latter compound, in two steps from N-methyl-aniline, is in marked contrast to the earlier multi-step sequence.[3,4]

Surprisingly, the hydrogen atoms of N-methyl groups proved to be rather reactive in competitive experiments. Thus the N-cyclohexylpyrrolone (36) and the N-methyl-2,2-pentamethylene derivative (37) were formed in 6.5:1.0 ratio from the Meldrum's acid derivative (11), corresponding to a preference for primary, over tertiary reaction of 2.2:1.0 after statistical correction. This result clearly excludes our initial proposal[2] of diradical intermediates in the hydrogen-transfer–cyclisation sequence, for which substantial tertiary preference would be anticipated. The reaction therefore appears to be more sensitive to steric effects.

In conclusion, we believe that the method described in this

paper provides the best synthesis of simple 4,5-unsubstituted 1H-pyrrol-3(2H)-ones which is currently available, applicable to 1-substituted, 1,2-disubstituted, and 1,2,2-trisubstituted examples. However, certain restrictions are placed on the substitution pattern, dictated either by the selectivity of the reaction, or by the sensitivity of 2-monosubstituted and 2-unsubstituted examples, which may render them unsuitable for chromatographic separation. Three further caveats may be noted. First, the 1-methylpyrrolone (38),[4] although clearly present in the complex pyrolysate from compound (17) at 600 °C, could not be cleanly isolated, possibly due to its high reactivity. Second, pyrolysis of the dihydrophenanthridyl derivative (18) under the standard conditions gave only phenanthridine (39) (43%), probably by an alternative C–N homolysis mechanism which can be a competing minor pathway in other examples (see Experimental section). Third, our preliminary attempts to introduce a substituent at the 5-position by pyrolysing condensation products derived from orthoacetate or orthopropionate derivatives have been unsuccessful, although some related work has been published recently.[12]

Experimental

Unless otherwise stated, ^{1}H n.m.r. spectra were recorded at 80 or 200 MHz, and ^{13}C n.m.r. spectra at 50 or 20 MHz, for solutions in [^{2}H]chloroform. Quaternary signals in the ^{13}C n.m.r. spectra are designated '(q).'

Preparation of Secondary Amines.—Method 1 involved alkylation of primary amines and chromatographic separation of the mixture,[13] whereas Method 2 required imine formation using a Dean and Stark trap to remove the water formed, followed by reduction.[14] The following amines were prepared: N-isopropylaniline (Method 1, 76%), b.p. 54 °C (0.3 Torr) [lit.,[15] 209 °C (712 Torr)]; dicycloheptylamine (Method 2, 83%), b.p. 135 °C (15 Torr) (previously prepared as hydrochloride[16]); 1,2-dihydrophenanthridine (Method 2, reduction step only, 70%), m.p. 89—90 °C (from ethanol) (lit.,[17] 90 °C.)

5-Aminomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione Derivatives.—Four methods were used. Method A[7] involved *in situ* treatment of 5-ethoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione with a two-fold excess of the appropriate amine, in an excess of triethyl orthoformate, as previously described.[1,5,7] Method B utilised the readily isolated 5-methoxymethylene derivative,[7] (10 mmol) which was heated under reflux for 2 h with a 10% excess of the amine, in cyclohexane (20 ml). For most purposes, these procedures have been superseded by Method C, described in Part 1,[1] in which acetonitrile is used as solvent. The reaction with the methoxymethylene derivative is complete after 30 min at 20 °C. Method D involved N-methylation of appropriate monosubstituted derivatives, as follows: sodium hydride (50% suspension in oil, 0.24 g, 5 mmol) was washed with light petroleum (× 3) (b.p. 40—60 °C) and then dried *in vacuo*. The appropriate 5-(N-monosubstituted aminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.5 mmol) was dissolved in dimethyl sulphoxide (10 ml) and the pre-washed sodium hydride was added in portions. Methyl iodide (0.8 ml, 12.5 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was then poured into methanol (10 ml) and diluted with water (20 ml). The aqueous solution was extracted with methylene dichloride (3 × 30 ml) and the combined organic layers were back-extracted with water (3 × 50 ml). The organic layer was then dried (MgSO$_4$) and the solvent was evaporated under reduced pressure to give the desired product.

This reaction could not be extended to allow the preparation of derivatives with other alkyl substitutents, possibly due to formation of the corresponding alkene occurring more readily than alkylation. Quantitative recovery of starting material observed.

The following derivatives of 5-aminomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione were prepared.

5-(N,N-*Di-isopropyl*) *derivative* (2) (Method A, 60%), m.p. 120 °C (from cyclohexane) (Found: C, 61.45; H, 8.5; N, 5.65. C$_{13}$H$_{21}$NO$_4$ requires C, 61.2; H, 8.25; N, 5.5%); δ_H 8.21 (1 H, s), 4.84 (1 H, m), 3.82 (1 H, m), 1.69 (6 H, s), 1.39 (6 H, d, ^3J 6.7 Hz), and 1.31 (6 H, d, ^3J 6.7 Hz); δ_C 163.46 (q), 155.83, 102.19 (q), 83.18 (q), 55.76, 49.15, 26.40, 23.82, and 20.04; m/z 255 (M^+, 21%), 198 (63), 197 (100), 182 (53), 154 (66), 153 (34), 138 (44), 127 (61), and 124 (75).

5-(N,N-*Dicycloheptyl*) *derivative* (3) (Method A, 52%), m.p. 125 °C (from cyclohexane) (Found: C, 69.45; H, 9.35; N, 3.75. C$_{21}$H$_{33}$NO$_4$ requires C, 69.4; H, 9.1; N, 3.85%); δ_H 8.01 (1 H, s), 4.3—4.7 (1 H, m), 3.1—3.6 (1 H, m), 1.58 (6 H, s) (clearly superimposed on methylene signals), and 1.0—2.0 (24 H, m); δ_C 163.50 (q), 156.27, 102.06 (q), 82.73 (q), 65.92, 61.63, 37.19, 32.83, 26.79 (2 signals superimposed), 26.39, 24.90, and 24.77; m/z 363 (M^+, 10%) 305 (87), 287 (100), 218 (22), 164 (27), and 124 (24).

5-(N-*Cyclohexyl*-N-*isopropyl*) *derivative* (4) (Method A, 32%), m.p. 103 °C (from cyclohexane) (Found: C, 65.0; H, 8.75; N, 4.65. C$_{16}$H$_{25}$NO$_4$ requires C, 65.1; H, 8.45; N, 4.75%); δ_H (peaks of second rotamer given in brackets) 8.02 (8.01) (1 H, s), 4.63 (3.73) (1 H, m), 4.0—4.5 (3.05—3.5) (1 H, m), 1.0—2.0 (10 H, m), 1.52 (6 H, s) (clearly superimposed on methylene signals), and 1.21 (1.13) (6 H, d, ^3J 6.7 Hz); δ_C (peaks of second rotamer given in brackets) 163.61 (163.50) (q), 156.48 (155.93), 102.25 (102.25) (q), 83.19 (82.87), (q), 64.09 (57.72), 55.84 (50.37), 34.48 (30.71), 26.50 (26.50), 25.64 (25.26), 25.03 (24.59), and 23.86 (20.20); m/z 295 (M^+, 21%), 237 (100), 219 (87), 164 (47), 150 (34), and 127 (66).

5-(N,N-*Diethyl*) *derivative* (5) (Method C, 86%), m.p. 57—58 °C (from ethanol) (Found: C, 58.4; H, 7.7; N, 6.15. C$_{11}$H$_{17}$NO$_4$ requires C, 58.15; H, 7.5; N, 6.15%); δ_H 8.02 (1 H, s), 5.49 (2 H, q, ^3J 7.2 Hz), 3.84 (2 H, q, ^3J 7.2 Hz), 1.61 (6 H, s), 1.28 (3 H, t, ^3J 7.2 Hz), and 1.15 (3 H, t, ^3J 7.2 Hz); δ_C 163.3 (q), 157.9, 102.8 (q), 83.89 (q), 47.16, 42.54, 26.27, 14.37, and 12.34; m/z 227 (M^+, 5%), 170 (35), 169 (100), 155 (20), 125 (90), 114 (37), 110 (63), and 97 (40).

5-(N,N-*Dibenzyl*) *derivative* (6) (Method A, 62%), m.p. 152 °C (from ethanol) (Found: C, 71.65; H, 5.95; N, 3.9. C$_{21}$H$_{21}$NO$_4$ requires C, 71.8; H, 6.0; N, 4.0%); δ_H 8.38 (1 H, s), 7.03—7.46 (10 H, m), 6.69 (2 H, s), 4.61 (2 H, s), and 1.47 (6 H, s); δ_C [quaternary signal(s) missing] 159.06, 133.93 (q), 133.52 (q), 129.13, 128.77, 128.46, 128.04, 127.81, 127.66, 102.80 (q), 86.12 (q), 63.90, 55.71, and 26.12; m/z 351 (M^+, <1%), 293 (100), 202 (75), 158 (95), 130 (20), and 115 (44).

5-(N-*Ethyl*-N-*phenyl*) *derivative* (7) (Method A, 49%), m.p. 163—165 °C (from ethanol) (Found: C, 65.35; H, 6.15; N, 5.05. C$_{15}$H$_{17}$NO$_4$ requires C, 65.45; H, 6.2; N, 5.1%); δ_H (peaks of minor rotamer given in brackets) 8.22 (8.27), (1 H, s), 7.0—7.5 (5 H, m), 4.32 (3.88) (2 H, q, ^3J 7.1 Hz), 1.71 (1.59) (6 H, s), and 1.23 (1.24) (3 H, t, ^3J 7.1 Hz); δ_C [peaks of major rotamer only, quaternary signal(s) missing] 158.05, 145.87 (q), 129.65, 128.26, 123.52, 102.80 (q), 86.87 (q), 49.87, 26.62, and 12.84; m/z 275 (M^+, 12%), 217 (100), 173 (20), 172 (25), 145 (18), 144 (53), 130 (34), and 104 (25).

5-(N-*Benzyl*-N-*phenyl*) *derivative* (8) (Method C, 40%), m.p. 161 °C (from ethanol) (Found: C, 70.9; H, 5.45; N, 4.1. C$_{20}$H$_{19}$NO$_4$ requires C, 71.2; H, 5.65; N, 4.15%); δ_H 8.35 (1 H, s), 7.0—7.5 (10 H, m), 5.65 (2 H, s), and 1.27 (6 H, s); δ_C 165.29 (q), 159.51 (q), 155.93, 147.65 (q), 134.34 (q), 129.62, 128.70 (2 peaks superimposed), 127.73, 127.07, 122.51, 102.84 (q), 90.16 (q), 57.79, and 25.72; m/z 337 (M^+, <1%), 280 (41), 279 (100), 250 (69), 235 (14), 234 (14), 206 (90), 193 (15), 181 (15), and 180 (12).

5-(N-*Benzyl*-N-*methyl*) *derivative* (9) (Method A, 55%), m.p.

107—109 °C (from ethanol) (Found: C, 65.0; H, 6.45; N, 4.85. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.2; N, 5.1%); δ_H (peaks of minor rotamer given in parentheses) 8.32 (8.16), (1 H, s), 7.0—7.5 (5 H, m), 4.64 (5.07) (2 H, s), 3.19 (3.32) (3 H, s), and 1.69 (1.50) (6 H, s); δ_C [peaks of minor rotamer given in parentheses, quaternary signal(s) missing] 160.40 (159.53), 133.19 (133.88) (q), 129.13 (128.84), 128.16 (128.50), 127.49 (127.81), 102.82 (102.82) (q), 84.52 (85.29) (q), 65.23 (58.15), 41.56 (47.38), and 26.47 (26.17); m/z 275 (M^+, <1%), 217 (70), 188 (45), 144 (35), and 91 (100).

5-(N-*Benzyl*-N-*isopropyl*) derivative (10) (Method A, 50%), m.p. 111.5—112 °C (from ethanol) (Found: C, 67.25; H, 6.75; N, 4.4. $C_{17}H_{21}NO_4$ requires C, 67.35; H, 6.95; N, 4.6%); δ_H 8.26 (1 H, s), 7.0—7.5 (5 H, m), 5.09 (2 H, s), 3.88 (1 H, m), 1.39 (6 H, d, ^3J 6.7 Hz), and 1.29 (6 H, s); δ_C 160.5 (q), 155.90, 134.31 (q), 128.66, 127.73, 127.41, 102.58 (q), 86.00 (q), 61.04, 54.03, 25.85, and 21.68; m/z 303 (M^+, <1%), 246 (40), 245 (100), 230 (23), 216 (70), 202 (23), 201 (27), 186 (17), 175 (23), 173 (17), 159 (27), and 158 (83).

5-(N-*Cyclohexyl*-N-*methyl*) derivative (11) (Method A, 84%), m.p. 131—132 °C (from cyclohexane) (Found: C, 62.6; H, 7.65; N, 5.3. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.25%); δ_H 8.25 (1 H, s), 3.1—3.5 (1 H, m), 3.23 (3 H, s), 1.72 (6 H, s), and 1.2—2.0 (10 H, m); δ_C [quaternary signal(s) missing] 158.36, 102.51 (q), 83.64 (q), 69.56, 39.14, 31.31, 26.38, 25.09, and 24.72; m/z 267 (M^+, 8%), 209 (99), 191 (100), 166 (66), 165 (94), 136 (100), 128 (55), 122 (98), 110 (69), and 55 (30).

5-(N-*Cyclohexyl*-N-*ethyl*) derivative (12) (Method A, 48%), m.p. 92 °C (from cyclohexane) (Found: C, 64.25; H, 8.4; N, 4.9. $C_{15}H_{23}NO_4$ requires C, 64.05; H, 8.2; N, 5.0%); δ_H 8.09 (1 H, s), 3.87 (2 H, q, ^3J 7.0 Hz), 3.0—3.5 (1 H, m), 1.0—2.0 (10 H, m), 1.62 (6 H, s) (clearly superimposed on methylene signals), and 1.11 (3 H, t, ^3J 7.0 Hz); δ_C 159.12 (q), 155.94, 102.18 (q), 83.92 (q), 68.68, 46.62, 32.38, 26.32, 25.26, 24.63, and 12.97; m/z 281 (M^+, 13%), 223 (64), 205 (41), 180 (18), 179 (20), 150 (46), 84 (87), and 56 (100).

5-(N-*t*-*Butyl*) derivative (13) (Method A, 87%), m.p. 151—153 °C (from cyclohexane) (Found: C, 58.05; H, 7.55; N, 6.15. $C_{11}H_{17}NO_4$ requires C, 58.15; H, 7.5; N, 6.15%); δ_H 9.7 (1 H, br d), 8.04 (1 H, d, ^3J 15.2 Hz), 1.53 (6 H, s), and 1.26 (9 H, s); δ_C 165.27 (q), 163.82 (q), 155.07, 104.10 (q), 83.54 (q), 54.69 (q), 29.13, and 26.39; m/z 227 (M^+, 100%), 170 (33), 154 (80), 125 (85), 114 (50), and 110 (60).

5-(N-*Methyl*-N-*t*-*butyl*) derivative (14) (Method A, 41%: Method B, 81%; Method D, 56%), m.p. 152—154 °C (from cyclohexane) (Found: C, 60.0; H, 7.9; N, 5.9. $C_{12}H_{19}NO_4$ requires C, 59.75; H, 7.9; N, 5.8%); δ_H 8.43 (1 H, s), 3.19 (3 H, s), 1.71 (6 H, s), and 1.47 (9 H, s); δ_C [quaternary signal(s) missing] 157.49, 102.42 (q), 83.62 (q), 62.49 (q), 38.16, 28.26, and 26.28; m/z 241 (M^+, 25%), 184 (36), 183 (100), 168 (61), 128 (54), 127 (46), 124 (33), 110 (51), and 99 (46).

5-(*N*-Methyl-*N*-phenyl) derivative (15) (Method A, 61%; Method B, 94%; Method D, 58%), m.p. 121—122 °C (lit.,[7] 124 °C).

5-(*N*-Phenyl) derivative (16) (Method B, 76%), m.p. 156—158 °C (from ethanol) lit.,[7] 157 °C).

5-(*N*,*N*-Dimethyl) derivative (17) (Method C, 56%) (in this case, the amine was added slowly as an acetonitrile solution; the reaction is very exothermic), m.p. 152 °C (lit.,[7] 153—154.5 °C).

Also 2,2-*dimethyl*-5-[5-(5,6-*dihydrophenanthridinyl*)*methylene*]-1,3-*dioxane*-4,6-*dione* (18) (Method A, 88%), m.p. 220 °C (from ethanol) (Found: C, 71.4; H, 4.95; N, 4.0. $C_{20}H_{17}NO_4$ requires C, 71.6; H, 5.05; N, 4.2%); δ_H 8.40 (1 H, s), 7.0—8.0 (8 H, m), 5.10 (2 H, s), and 1.78 (6 H, s); δ_C (quaternary signal missing) 165.28 (q), 160.47 (q), 156.52, 138.66 (q), 131.38 (q), 129.16, 128.61, 128.53, 128.41, 127.44 (q), 126.17, 123.67, 123.13, 122.30, 103.34 (q), 89.29 (q), 58.09, 54.63, and 26.80; m/z 335 (M^+,

<1%), 277 (58), 249 (13), 248 (39), 205 (52), 204 (100), 180 (26), and 179 (48).

2,2-*Dimethyl*-5-[1-(2-*methylpiperidino*)*methylene*]-1,3-*dioxane*-4,6-*dione* (19) (Method A, 90%), m.p. 80—82 °C (from cyclohexane), crystallised with inclusion of cyclohexane (Found: C, 64.45; H, 8.3; N, 5.0. $C_{13}H_{19}NO_4\cdot0.4C_6H_{12}$ requires C, 64.5; H, 8.3; N, 4.9%); δ_H (100 MHz) 8.18 and 8.05 (minor) (1 H, 2 × s), 3.78 (3 H, br s), 1.5—2.0 (12 H, m), and 1.42 (3 H, d) (also peak at δ_H 1.40 due to cyclohexane); δ_C (peaks of minor rotamer given in parentheses where appropriate) 162.9 (q), 156.56 (157.88), 101.88 (q), 82.16 (q), 61.34 (54.52), 49.62 (52.78), 31.99 (29.89), 26.22, 25.45, 19.15 (17.08), 17.99 (15.78), and peak at δ_C 25.97 due to cyclohexane; m/z 253 (M^+, 9%), 196 (16), 195 (39), 151 (14), 122 (100), 65 (15), and 41 (18).

Preparation of 1H-*Pyrrol*-3(2H)-*ones*.—The appropriate aminomethylene Meldrum's acid derivative (2—10 mmol) was sublimed into the furnace tube (silica, 35 × 2.5 cm) at 10^{-2}—10^{-3} Torr, and the products were collected in a trap cooled by liquid nitrogen. The entire pyrolysate was then dissolved in acetone, and the solution was concentrated under reduced pressure to give the crude pyrrolone, which was purified by bulb-to-bulb distillation. 1,2,2-Trisubstituted isomers could be separated if necessary by column chromatography on alumina, with ethyl acetate–light petroleum (b.p. 40—60 °C) (60:40) as eluant. In general, the pyrolysis conditions have not been optimised, but repeated preparations of the 1-isopropyl-2,2-dimethyl and particularly the 1-phenyl derivatives on multi-gram scales (with Mr. G. A. Hunter) have led to the following observations. First, large-scale pyrolyses requiring high inlet temperatures for extended periods may result in alternative radical cleavage to give the parent amine: *N*-methylaniline, in particular, is difficult to remove. This may be overcome by using a lower pressure (10^{-3}—10^{-4} Torr, diffusion pump) and a higher furnace temperature (*e.g.* 650 °C). The *N*-phenylpyrrolone usually crystallises at the exit point of the furnace; it can be suspended in a small amount of ether or acetone, and the pure product filtered off. Large-scale distillation is not successful in this case. The 2-monosubstituted pyrrolones are highly susceptible to aerial oxidation (see Part 4 of this series[11]) and were characterised by accurate mass measurement, or by partial addition of oxygen to the calculated analytical data.

The following 1H-pyrrol-3(2H)-ones were prepared by pyrolysis. The 5-aminomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione substrate, furnace temperature, and inlet temperature are quoted in parentheses.

1-*Isopropyl*-2,2-*dimethyl* derivative[10] (20) [5-(*N*,*N*-di-isopropyl), 600 °C, 120—130 °C] (64%), m.p. 70—72 °C (from hexane) (Found: C, 67.2; H, 9.9; N, 8.95. $C_9H_{15}NO$ requires C, 67.4; H, 9.9; N, 8.95%); δ_H 7.86 (1 H, d), 5.02 (1 H, d), 3.59 (1 H, m), 1.26 (6 H, d), and 1.19 (6 H, s); δ_C 204.68 (q), 158.78, 94.28, 67.56 (q), 45.23, 23.73, and 21.71; m/z 153 (M^+, 100%), 138 (50), and 110 (90).

1-*Cycloheptyl*-2,2-*hexamethylene* derivative (21) [5-(*N*,*N*-dicycloheptyl), 600 °C, 155—175 °C] (64%), m.p. 125 °C (from hexane) (Found: C, 78.0; H, 10.55; N, 5.55. $C_{17}H_{27}NO$ requires, C, 78.15; H, 10.35; N, 5.35%); δ_H 7.78 (1 H, d), 4.93 (1 H, d), 3.0—3.75 (1 H, m), and 1.0—2.5 (24 H, m); δ_C 205.89 (q), 158.86, 93.59, 71.86 (q), 56.19, 36.96, 34.71, 31.47, 27.20, 24.75, and 22.62; m/z 261 (M^+, 100%), 192 (95), 164 (49), and 55 (54).

1-*Isopropyl*-2,2-*pentamethylene* derivative (23) [5-(*N*-cyclohexyl-*N*-isopropyl), 600 °C, 140 °C] (22%), m.p. 75—76 °C (from hexane) (Found: C, 74.5; H, 9.85; N, 7.4. $C_{12}H_{19}NO$ requires C, 74.35; H, 9.9; N, 7.0%); δ_H 7.84 (1 H, d), 4.99 (1 H, d), 3.65 (1 H, m), 1.0—2.5 (10 H, m), and 1.25 (6 H, d) (clearly superimposed on methylene signals); δ_C 205.56 (q), 157.94, 94.60, 68.04 (q), 44.35, 30.20, 24.29, 23.72, and 19.40; m/z 193 (M^+, 100%), 150 (85), and 138 (95), separated by chromato-

graphy from the 1-*cyclohexyl*-2,2-*dimethyl derivative* (**22**) [5-(*N*-cyclohexyl-*N*-isopropyl), 600 °C, 140 °C] (21.5%), m.p. 81—83 °C (from hexane) (Found: C, 74.35; H, 9.9; N, 7.0. $C_{12}H_{19}NO$ requires C, 74.35; H, 9.9; N, 7.0%); δ_H 7.86 (1 H, d), 5.04 (1 H, d), 3.1 (1 H, m), 1.0—2.0 (10 H, m), and 1.22 (6 H, s) (clearly superimposed on methylene signals); δ_C 204.61 (q), 159.22, 94.02, 67.61 (q), 53.54, 34.68, 25.80, 24.29, and 21.85; *m/z* 193 (M^+, 100%), 150 (90), and 110 (90).

1-*Ethyl*-2-*methyl derivative* (**24**) [5-(*N,N*-diethyl), 600 °C, 120—135 °C] (77%), b.p. 123—124 °C (0.3 Torr) (Found: M^+, 125.084. $C_7H_{11}NO$ requires M^+, 125.084); δ_H (two tautomers present in chloroform; oxo tautomer quoted) 7.71 (1 H, d), 4.92 (1 H, d), 3.44 (1 H, q), 3.27 (2 H, q), 1.22 (3 H, d), and 1.13 (3 H, t); δ_C 203.91 (q), 163.93, 96.46, 61.85, 42.37, 14.24, and 14.03; *m/z* 125 (M^+, 100%), 124 (56), 110 (39), 98 (35), and 96 (48).

1-*Benzyl*-2-*phenyl derivative* (**25**) [5-(*N,N*-dibenzyl), 600 °C, 170—195 °C] (51%), b.p. 180—182 °C (0.3 Torr) (Found: C, 81.85; H, 6.25; N, 5.45. $C_{17}H_{15}NO$ requires C, 81.95; H, 6.0; N, 5.6%); δ_H (two tautomers present in chloroform; oxo tautomer quoted) 8.18 (1 H, d), 6.8—7.7 (10 H, m), 5.55 (1 H, d), 5.15 (1 H, d), 4.43 (1 H, s), and 4.20 (1 H, d); δ_C 201.31 (q), 166.13, 125—140 (complex pattern of aromatic signals), 97.30, 69.89, and 52.25; *m/z* 249 (M^+, 34%), 160 (40), 158 (12), 134 (32), 105 (17), and 91 (100).

2-*Methyl*-1-*phenyl derivative* (**26**) [5-(*N*-ethyl-*N*-phenyl), 600 °C, 155 °C] (73%), b.p. *ca.* 140 °C (0.3 Torr), this compound was occasionally obtained as a yellow solid directly on pyrolysis but generally could not be satisfactorily distilled or recrystallised due to its rapid oxidation. Its b.p. was inconsistent on attempted distillation (Found: M^+, 173.084. $C_{11}H_{11}NO$ requires M^+, 173.084); δ_H 8.30 (1 H, d), 7.0—7.5 (5 H, m), 5.42 (1 H, d), 4.15 (1 H, q), and 1.41 (3 H, d); δ_C 202.92 (q), 158.59, 137.76 (q), 129.67, 123.55, 117.09, 101.41, 61.08, and 15.29; *m/z* 173 (M^+, 100%), 147 (83), 130 (33), 119 (27), 104 (53), and 77 (80).

1,2-*Diphenyl derivative* (**27**) [5-(*N*-benzyl-*N*-phenyl), 600 °C, 180 °C] (56%), b.p. 190 °C (0.5 Torr) (Found: M^+, 235.099. $C_{16}H_{13}NO$ requires M^+, 235.100); δ_H (two tautomers present in chloroform solution; oxo tautomer quoted) 8.62 (1 H, d), 6.8—7.8 (10 H, m), 5.45 (1 H, d), and 5.04 (1 H, s); δ_C 199.81 (q), 159.60, 123—138 (complex pattern of aromatic signals), 101.26, and 69.39; *m/z* 235 (M^+, 64%), 206 (20), 146 (50), 105 (23), 104 (27), 103 (18), 91 (23), and 77 (100).

1-*Methyl*-2-*phenyl derivative* (**32**) [5-(*N*-benzyl-*N*-methyl), 600 °C, 180 °C] (80%) as an oil which oxidised rapidly in air, b.p. 170 °C (0.05 Torr) (Found: C, 74.5; H, 6.2; N, 7.85. $C_{11}H_{11}NO\cdot0.25O$ requires C, 74.55; H, 6.2; N, 7.9%); δ_H (two tautomers present in chloroform solution; oxo tautomer quoted) 7.86 (1 H, d), 7.0—7.5 (5 H, m), 5.08 (1 H, d), 4.34 (1 H, s), and 2.97 (3 H, s); (oxo tautomer insufficient for ^{13}C n.m.r. determination); *m/z* 173 (M^+, 100%), 144 (14), and 77 (12).

1-*t*-*Butyl derivative* (**34**) [5-(*N*-methyl-*N*-t-butyl), 600 °C, 135 °C] (62%) as a hygroscopic liquid, b.p. 115—117 °C (0.4 Torr) (Found: C, 66.65; H, 9.2; N, 9.5. $C_8H_{13}NO\cdot0.25H_2O$ requires C, 66.9; H, 9.4; N, 9.75%); δ_H 7.93 (1 H, d), 5.09 (1 H, d), 3.95 (2 H, d), and 1.54 (9 H, s); δ_C 199.76 (q), 162.58; 99.13, 54.80 (q), 54.19, and 28.32; *m/z* 139 (M^+, 40%), 124 (16), and 83 (100).

1-*Phenyl derivative*[4] (**35**) [5-(*N*-methyl-*N*-phenyl), 600 °C, 120—150 °C] (63%), m.p. 80—81 °C (from methanol), b.p. 157—158 °C (0.5 Torr) (Found: C, 75.6; H, 5.65; N, 8.8. $C_{10}H_9NO$ requires C, 75.5; H, 5.65; N, 8.8%); δ_H 8.40 (1 H, d), 6.9—7.5 (5 H, m), 5.46 (1 H, d), and 4.10 (2 H, d); δ_C 198.71 (q), 158.31, 139.28 (q), 129.62, 122.97, 114.67, 103.81, and 55.65; *m/z* 159 (M^+, 100%), 131 (95), 105 (73), and 104 (87).

A number of small-scale pyrolyses (*ca.* 50 mg) were carried out without isolation of the products which were identified by ^{1}H n.m.r. spectroscopy. The following derivatives of 5-aminomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione were pyrolysed. The pyrolysis parameters and 1*H*-pyrrol-3(2*H*)-one(s) produced are recorded; where two isomers were produced the ratio is given after the second product, after allowing for the presence of enol tautomers, where necessary.

5-(*N*-Benzyl-*N*-isopropyl), 600 °C, 175 °C, 20 min, 1-*isopropyl*-2-*phenyl derivative* (**33**), δ_H (two tautomers present, oxo:enol, 1:9, enol tautomer quoted in brackets) 8.07 (1 H, d), 7.0—7.5 (5 H, m), 5.12 (1 H, d), 4.53 (1 H, s), 3.51 (1 H, m), 1.31 (3 H, d), and 1.14 (3 H, d), [7.0—7.5 (5 H, m), 6.58 (1 H, d), 5.91 (1 H, d), 4.25 (1 H, m), and 1.31 (6 H, d)].

5-(*N*-Cyclohexyl-*N*-methyl), 600 °C, 130 °C, 20 min, 1-*cyclohexyl derivative* (**36**), δ_H 7.83 (1 H, d), 5.06 (1 H, d), 3.68 (2 H, s), 3.0—3.3 (1 H, m), and 1.0—2.0 (10 H, m); 1-*methyl*-2,2-*pentamethylene derivative* (**37**), δ_H 7.62 (1 H, d), 4.94 (1 H, d), 3.02 (3 H, s), and 1.0—2.0 (10 H, m) (78:22).

5-(*N*-Cyclohexyl-*N*-ethyl), 600 °C, 150 °C, 20 min, 1-*cyclohexyl*-2-*methyl derivative* (**29**), δ_H (only olefinic signals quoted) 7.82 (1 H, d) and 5.00 (1 H, d); 1-*ethyl*-2,2-*pentamethylene derivative* (**28**) δ_H (only olefinic signals quoted) 7.73 (1 H, d) and 4.93 (1 H, d) (58:42).

5-(*N*-Cyclohexyl-*N*-isopropyl), 600 °C, 135 °C, 25 min, 1-*cyclohexyl*-2,2-*dimethyl* (**22**) and 1-*isopropyl*-2,2-*pentamethylene* (**23**) *derivatives*, δ_H (see preparative section) (56:44).

N,N-Dimethyl, 600 °C, 125 °C, 25 min, 1-*methyl derivative* (**28**), δ_H (two tautomers present, oxo:enol, 75:25, enol tautomer quoted in brackets) 7.68 (1 H, d), 5.05 (1 H, d), 3.65 (2 H, d), and 3.64 (3 H, s) [6.75 (1 H, m), 6.2 (2 H, m), and 3.47 (3 H, s)]. Also 2,2-dimethyl-5-[1-(2-methylpiperidino)]methylene-1,3-dioxane-4,6-dione, 600 °C, 170 °C, 30 min, gave 8a-*methyl*-5,6,7,8-*tetrahydroindolizin*-1(8aH)-*one* (**30**), δ_H (only olefinic signals quoted) 7.68 (1 H, d) and 4.99 (1 H, d); 5-*methyl*-5,6,7,8-*tetrahydroindolizin*-1(8aH)-*one* (**31**), δ_H 7.82 (1 H, d) and 5.04 (1 H, d); full details of the isolation of products from this pyrolysis will be given in Part 4.[11]

A preparative pyrolysis was carried out on the dihydrophenanthridinylmethylene derivative but this did not lead to a pyrrolone. G.c. and ^{1}H n.m.r. analysis of the white solid obtained showed it to be phenanthridine. This was presumably formed by radical cleavage of the C–N bond. Pyrolysis of the derivative (0.2 g) (600 °C, 205 °C, 30 min) gave phenanthridine (**39**) (40 mg, 43%).

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