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3-Hydroxypyrroles and 1*H*-Pyrrol-3(2*H*)-ones. Part 4.[1] Oxidation of 2-Monosubstituted and 2-Unsubstituted Pyrrolones, with an Electron Spin Resonance Study of a Dimeric Intermediate

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Oxidation of 2-substituted 1*H*-pyrrol-3(2*H*)-ones in air gives 2-hydroxy derivatives, which can exist in solvent-dependent equilibrium with open-chain acyl enaminones. Oxidation of 2-unsubstitued analogues by irradiation in the presence of di-t-butyl peroxide gives rise to persistent radicals, identified as pyrrolone dimers [*e.g.* (**21**)] by e.s.r. spectroscopy. The formation of the various products is rationalised by a single mechanism (Scheme 3) in which a capto-dative radical (**22**) is a key intermediate.

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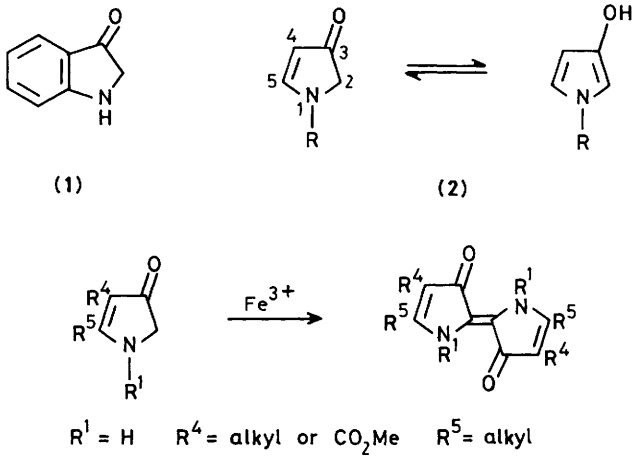
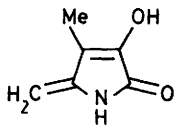
Oxidation at the 2-position of 1*H*-pyrrol-3(2*H*)-ones (3-hydroxypyrroles) (**2**) [analogous to the behaviour of indoxyl (**1**)] has been known since the first report of this ring system in 1913.[2] A variety of oxidation reactions are known to take place. Thus, 2,2-unsubstituted examples generally give dehydro-dimers (*cf.* indigo) in the presence of one-electron oxidising agents (Scheme 1): in the cases which have been studied, the 4- and/or 5-position of the ring have been substituted with electron-withdrawing[2,3] or with alkyl groups.[4–7] However, examples with a 5-alkyl group may give a monomeric product [*e.g.* (**3**)] under certain conditions.[8] 2-Monosubstituted pyrrolones may also give dimers on oxidation,[9] but the formation of the 2-hydroxy compound frequently takes place more readily, and can occur simply on exposure to air[10,11] (Scheme 2). These products are cyclic hemiaminals, which can exist in an open-chain form (Scheme 2); intermediates in the oxidation sequence may be subject also to further reactions.[12,13]

We also have noted the ease of oxidation of pyrrolones with one substituent at the 2-position,[14,15] and in this paper we give a more detailed account of three aspects of this problem. First, we discuss the preparation and tautomerism of typical 2-hydroxy 2-substituted derivatives (*cf.* Scheme 2). Secondly, we present a detailed e.s.r. characterisation of an intermediate in the controlled oxidative dimerisation of 2-unsubstituted derivatives; and thirdly we propose a unified mechanistic rationale which explains the diverse oxidative behaviour of these compounds.



Scheme 1.



Results and Discussion

All the pyrrolones used were prepared by the Meldrum's acid pyrolysis method;[15] details of the new precursors (**4**)—(**6**), and of the new pyrrolones (**8**), (**13**), and (**15**), are given in the Experimental section. The deuteriated compound (**14**) was prepared by exchange in [$^2H_4$]methanol under neutral conditions.[16]

The 1,2-disubstituted 1*H*-pyrrol-3(2*H*)-ones previously reported[15] readily underwent aerial oxidation, as shown by an (M + 16) peak in their mass spectra, and the requirement for additional oxygen to account for elemental analysis results[15] [*e.g.* for (**11**), m/z 189 (M + 16, 17%) after exposure to air]. Similarly, additional peaks may be present in the n.m.r. spectra of such pyrrolones, especially if the solutions are kept at room temperature for a period [*e.g.* for (**10**), additional peaks at $\delta_H(CDCl_3)$ 8.8 and 5.6, due to H(5) and H(4) respectively of (**16A**)]. The 2-methyl compound (**11**) undergoes particularly rapid oxidation, and the oxidation product (**17**) could be isolated (25%) after exposure to air in chloroform solution, or after treatment with potassium hexacyanoferrate(III) (40%).

After pyrolysis of the cyclic derivative (**7**) on a small scale, n.m.r. evidence[15] was obtained for the presence of two isomeric tetrahydroindolizinones (**8**) and (**9**), but only the former could be isolated by bulb-to-bulb distillation of the crude pyrolysate. However, careful aerial oxidation of the mixture gave the hydroxy derivative (**18**) as a solid which was fully characterised (see Experimental section). Only one diastereoisomer was obtained, but its configuration was not further analysed.

The ring–chain tautomerism of these oxidised derivatives is of particular interest,[17a] because Davoll obtained conflicting chemical and spectroscopic evidence[10] and Eicher apparently required extreme conditions for interconversion of a heavily substituted example.[12] There is no doubt that the bicyclic derivative (**18**) exists in the ring-closed form: the alkene protons [$\delta_H(CDCl_3)$ 7.84 and 4.99 ($^3J_{HH}$ 3.50 Hz)] are clearly part of the pyrrolone sub-unit (*cf.* ref. 15). Ring opening in this case is disfavoured, because of the resulting nine-membered ring. In contrast, the ring-chain tautomers (**17A** and **B**) were found to interconvert simply on changing solvents.[17a] The open-chain

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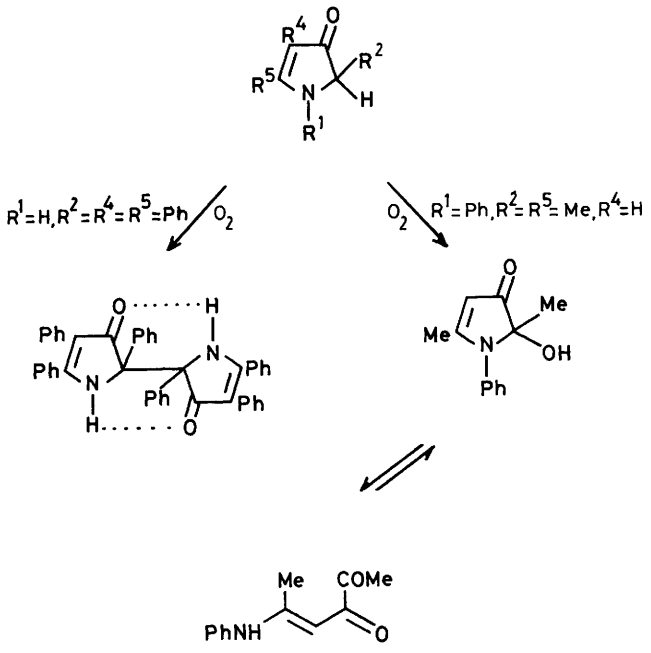

Scheme 2.

tautomer (**17B**) was exclusively present in chloroform solution, in which intramolecular hydrogen bonding would be favoured. The magnitudes of the vicinal coupling constants clearly demonstrate the *Z*-configuration of the alkene ($^3J_{HH}$ 7.5 Hz) and the *s-trans* configuration of the C–N bond ($^3J_{HH}$ 12.8 Hz) by comparison with data for closely related model compounds.[17] In contrast, the 2-hydroxypyrrolone tautomer was found in dimethyl sulphoxide solution [δ_H(alkene signals only) 8.79 and 5.27 ($^3J_{HH}$ 4.0 Hz)], in which hydrogen bonding to the solvent can increase the stability.

The types of products identified suggest that the oxidations proceed by the standard autoxidation mechanism involving free radicals, and the derived hydroperoxides, as intermediates.[12,18] The free radicals formed from the pyrrolones were investigated by e.s.r. spectroscopy. The pyrrolone, together with di-t-butyl peroxide, in a hydrocarbon solvent was irradiated in the cavity of the e.s.r. spectrometer, so that the photochemically produced t-butoxyl radicals would abstract hydrogen from the substrate. No significant signals were obtained in the absence of di-t-butyl peroxide. With a typical 2-substituted pyrrolone (**10**), weak and poorly resolved spectra from transient radicals were obtained. The hyperfine splittings (h.f.s.) could not be analysed, but it is possible that these spectra correspond to the 2-oxopyrrol-2-yl radicals (**19**).

When the 2-unsubstituted derivative (**12**) was examined the initial weak spectrum was replaced, after irradiation for some minutes at room temperature, by an extremely strong spectrum (Figure 1). The signal intensity increased with time of irradiation; optimum strength was obtained at temperatures between 250 and 273 K. The spectrum remained visible for several minutes after the u.v. irradiation was cut off; hence the radical is a persistent one with a half-life of the order of minutes. Analysis of the spectrum showed two hyperfine triplets, one quintet, and one doublet. The e.s.r. parameters, which were confirmed by computer simulation (Figure 1), are given in the Table. This pattern of h.f.s. is clearly too complex to be the result of coupling from nuclei within the five-membered ring of the initial intermediate (**20**). However, it seemed possible that spin density could be delocalised into the phenyl ring, thus accounting for the complex pattern of splittings. The 4-t-butylphenyl derivative

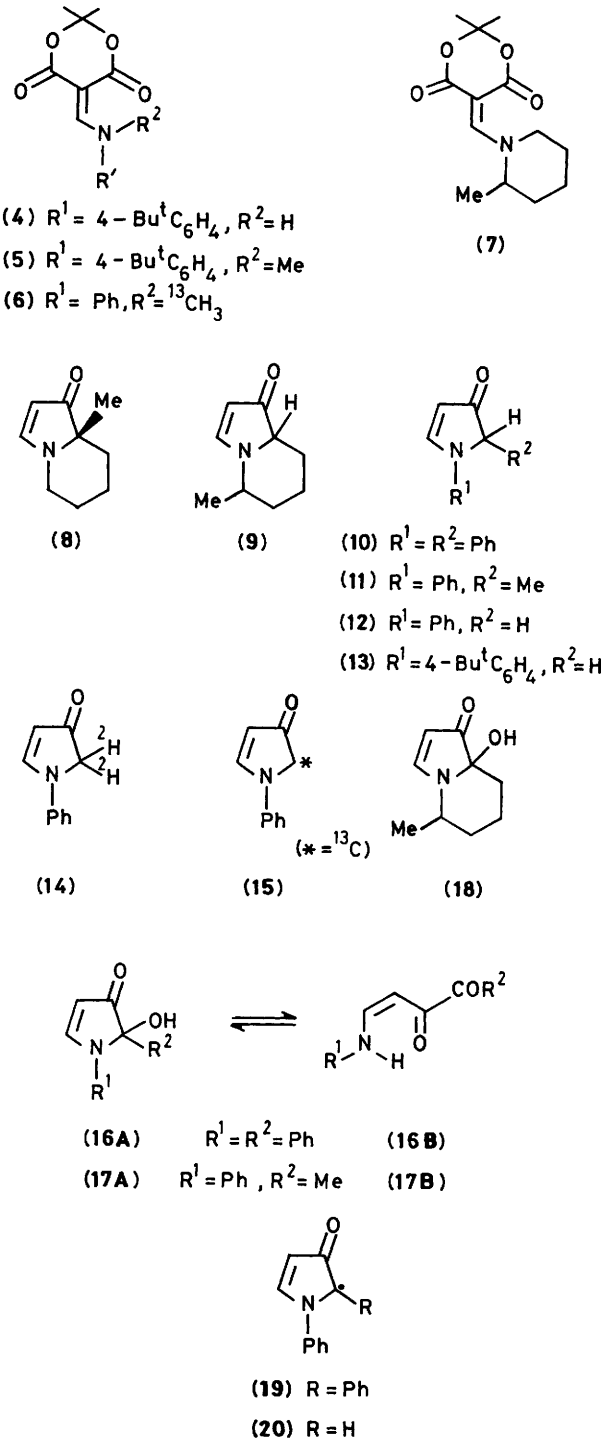

Table. E.s.r. parameters for dimeric radicals (**21**)[a]

Pyrrolone precursor	*T*/K	H.f.s. (mT) N(1,1′)	H(5,5′)	H(4,4′)	OH	^{13}C
(**12**)	250	0.135	0.485	0.085	0.055	
(**14**)	325	0.117	0.468	0.077	*b*	
(**15**)	250	0.135	0.482	0.080	0.060	0.080

[a] ΔH_{pp} *ca.* 0.02 mT in each case. [b] *a*(OD) < 0.02 mT: spectrum showed a minor amount of a second radical, probably with more D atoms incorporated.

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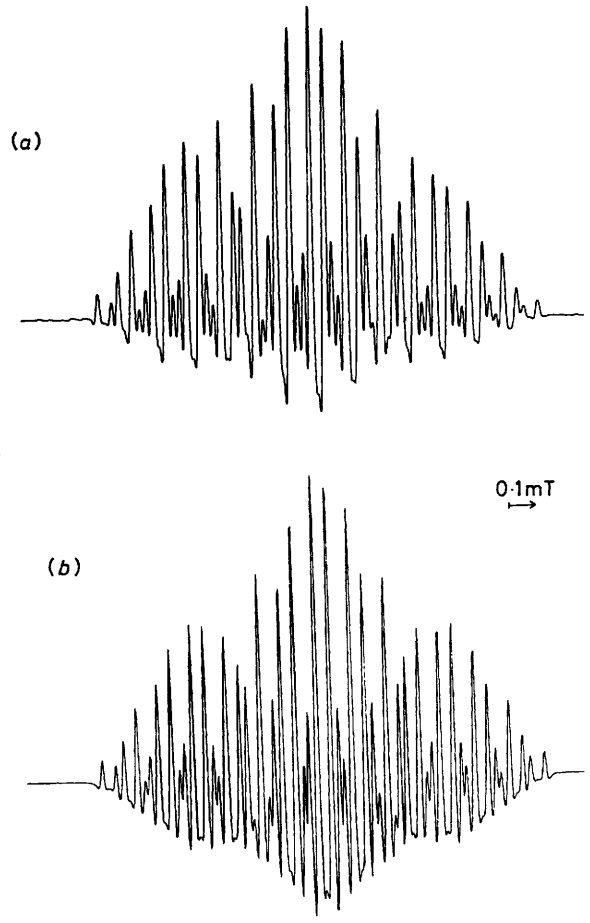
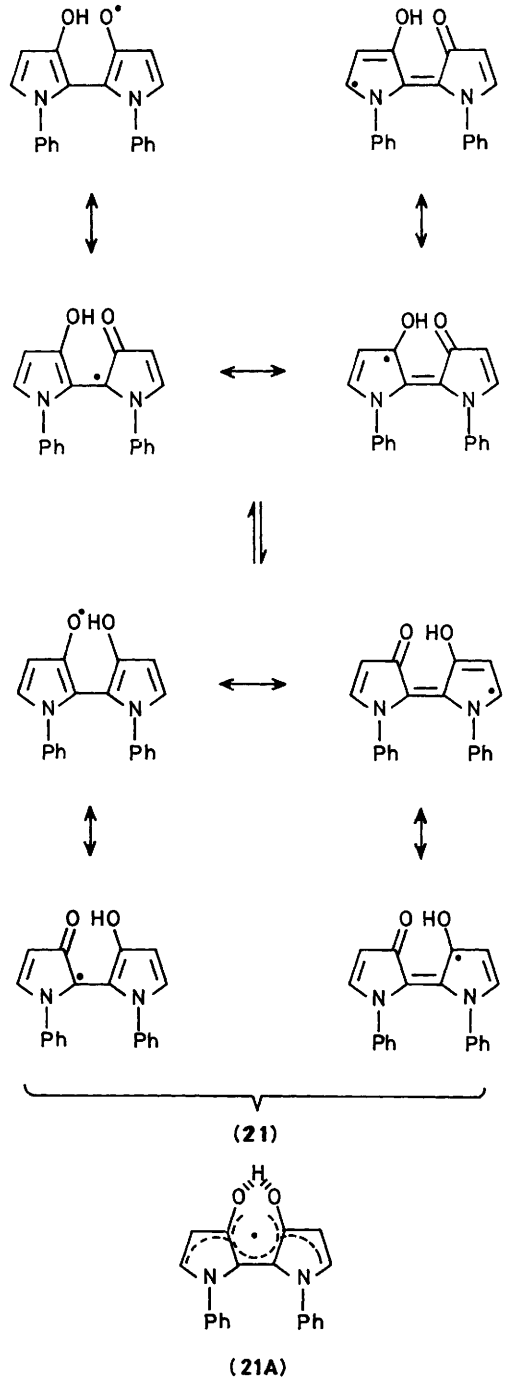


Figure 1. (*a*) 9.4 GHz second-derivative e.s.r. spectrum of dimeric radical (**21**) obtained from the pyrrolone (**12**); (*b*) simulation, using parameters given in the Table

(**13**) under the same conditions gave an essentially identical spectrum. Thus we can rule out (**20**) as the persistent species because different spectra would result from the radicals with and without substituents in the phenyl ring.

Of the numerous possible dimeric species, the 2,2′-linked radical (**21**) was an attractive candidate because of its relationship to the products of one-electron oxidation (Scheme 1). The symmetrical chelate structure, with fast proton exchange between the two sites (**21A**), has two equivalent nitrogen atoms (quintet h.f.s.), two pairs of equivalent hydrogens (two triplet h.f.s.), and one unique hydrogen (doublet h.f.s.). The large number of resonance structures (**21**) will contribute to the stabilisation and persistence of this radical. Negligible spin is expected in the phenyl rings, thus accounting for the fact that identical spectra were obtained from the phenyl (**12**) and 4-t-butylphenyl (**13**) pyrrolones. The resonance structures, and simple frontier orbital considerations, indicate that higher spin density will be associated with C(5) and C(5′) so that the larger triplet h.f.s. (0.45 mT) can be assigned to H(5) and H(5′). The complete assignments of all the h.f.s. to specific nuclei are given in the Table.

The characterisation of (**21**) was confirmed in two ways. First, the deuteriated derivative (**14**) gave a spectrum from which the doublet h.f.s (0.055 mT) was missing, but with parameters which were otherwise similar to those of the parent (Table): this confirms the assignment of the doublet h.f.s. to the chelated hydrogen atom in (**21A**). The presence of two five-membered



rings and the high symmetry of the radical were confirmed by use of the ^{13}C-labelled material (**15**). In this case the e.s.r. spectrum showed the same h.f.s. as before but with an additional triplet, *i.e. two equivalent* ^{13}C atoms were present (Figure 2 and Table). Radicals of type (**21**) have not been spectroscopically observed before although many phenoxyl radicals are known and a relationship to the prototropic 8-hydroxy-1-naphthoxyl and isomeric species[19,20] can be traced. A few 2-pyridone oxyl radicals, which are distantly related, have been reported.[21]

These and earlier results[2–13] may now be placed in a unified mechanism (Scheme 3) in which the key intermediate is the 2-oxopyrrol-2-yl radical (**22**). The spectroscopic observation of the dimer radicals (**24**) provides indirect evidence for the intermediacy of the radicals (**22**), and shows unequivocally that the

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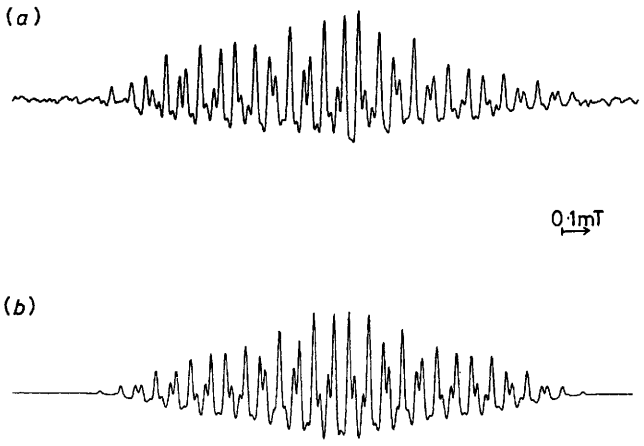
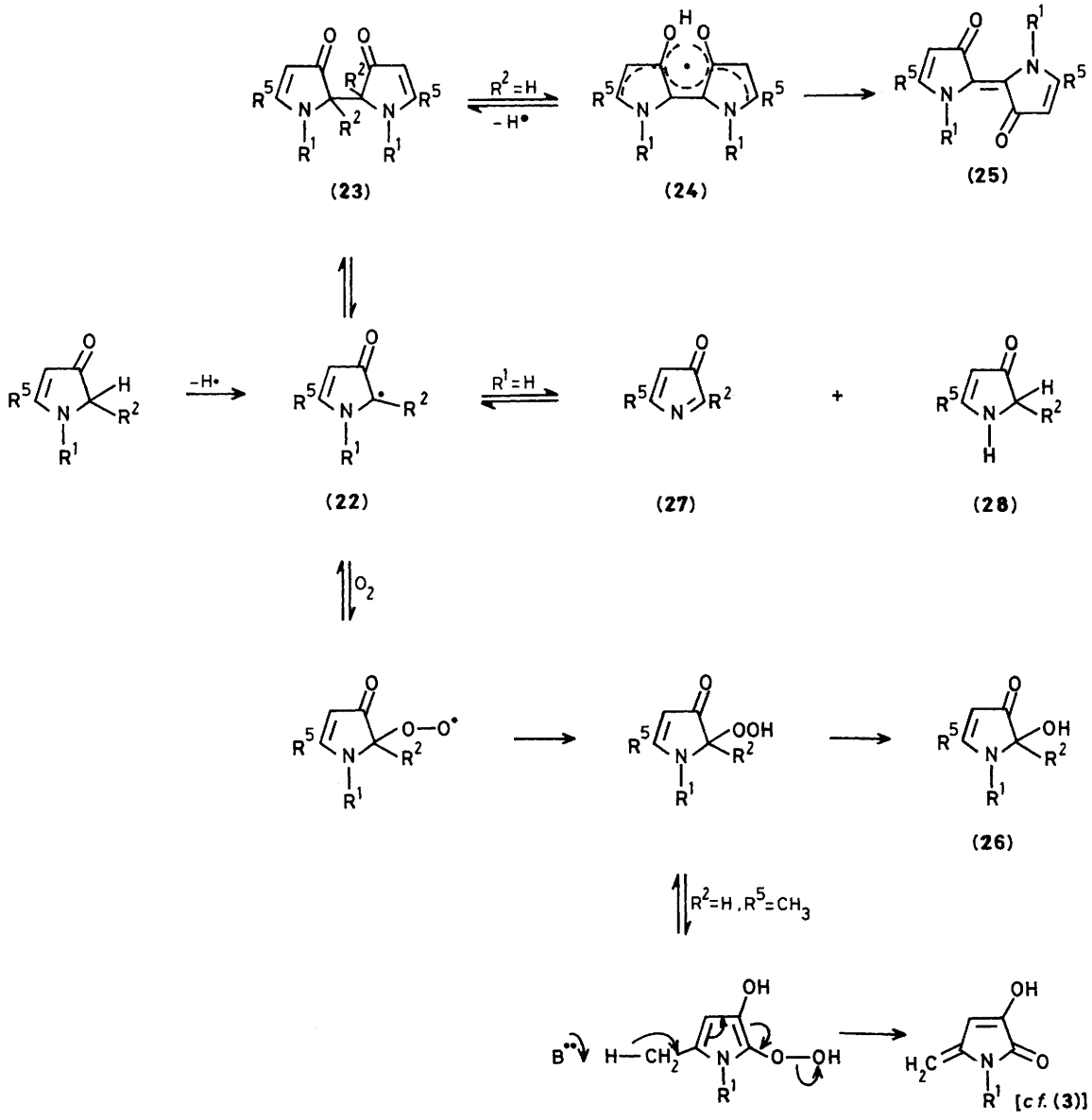


Figure 2. (*a*) 9.4 GHz second-derivative e.s.r. spectrum of dimeric radical (**21**) obtained from the ^{13}C-labelled pyrrolone (**15**); (*b*) simulation, using parameters given in the Table

primary radical reaction of pyrrolones is hydrogen abstraction at C(2). The radical centre in (**22**) is flanked by conjugatively electron-withdrawing and electron-donating groups, *i.e.* (**22**) is a capto-dative (C-D) radical, and its selective formation is readily accounted for in terms of the additional stabilisation that such species possess.[22,23] C-D Radicals are known to dimerise particularly readily,[22] and thus there are good precedents for the combination of the 2-unsubstituted radicals (**22**; R^2 = H) leading to (**23**). In the presence of an excess of oxidising agent, the dimer (**23**) may undergo a second hydrogen abstraction giving (**24**) (directly observed by e.s.r.) *en route* to the indigo-like structure (**25**) (*cf.* Scheme 1). In addition, Bauer has prepared the dimers (**23**; R^1 = R^2 = H, R^5 = CO_2Me) by an independent route, and has shown that they are readily oxidised to (**25**).[24] When the 2-position is substituted (R^2 = alkyl or aryl), such hydrogen abstraction from (**2**) cannot take place, and instead dedimerisation of (**23**) to (**22**) can initiate an autoxidation chain (Scheme 3) which normally results in the 2-hydroxy derivative (**26**)[10,11] (Scheme 2). Alternative reactions of the hydroperoxide may explain other products which are



Scheme 3.

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sometimes obtained [*e.g.* (**3**)][8] (Scheme 3): further examples are discussed in refs. 12 and 13. The dimers (**23**), which in the current hypothesis act as a reservoir of the capto-dative radical (**22**), are not normally observable, though in one case (where R^1 = H) stabilisation by hydrogen bonding may[11] lead to the possibility of isolation[9] (Scheme 2). In this example also the dimer (**23**) is found to disproportionate reversibly to (**27**) and (**28**) (Scheme 3): this behaviour is clearly possible only if the nitrogen atom is unsubstituted.[9]

Experimental

^{1}H N.m.r. spectra were recorded at 200 or 80 MHz and ^{13}C n.m.r. spectra at 50 or 20 MHz, unless otherwise stated, for solutions in [^{2}H]chloroform.

5-*Aminomethylene*-2,2-*dimethyl*-1,3-*dioxane*-4,6-*diones*.—The general methods detailed in Part 2[15] were used. The *N*-methylation procedure (ref. 15, Method D) proved particularly useful, since the independent preparation and purification of the free secondary amine could then be avoided. The following new derivatives were synthesised: 5-[N-p-(*t-butyl*)*phenyl*] (Method C,[15] 95%), m.p. 140—142 °C (from methanol) (Found: C, 66.9; H, 7.0; N, 4.6. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 6.95; N, 4.6%); δ_H 11.19 (1 H, br d), 8.60 (1 H, d), 7.43 (2 H, d), 7.15 (2 H, d), 1.73 (6 H, s), and 1.31 (9 H, s); δ_C 165.09 (q), 163.03 (q), 152.26, 149.81 (q), 135.14 (q), 126.52, 117.49, 104.52 (q), 86.69 (q), 34.23 (q), 30.88, and 26.66; *m/z* 303 (M^+, 30%), 245 (33), 186 (19), 158 (10), 144 (100), and 117 (11): 5-[N-p-(*t-butyl*)*phenyl*-N-*methyl*] (Method D,[15] 69%), m.p. 154—155 °C (from methanol) (Found: C, 67.7; H, 7.1; N, 4.45. $C_{18}H_{23}NO_4$ requires C, 68.1; H, 7.25; N, 4.4%); δ_H 8.33 (1 H, s), 7.43 (2 H, d), 7.24 (2 H, d), 3.70 (3 H, s), 1.75 (6 H, s), and 1.32 (9 H, s); δ_C(quaternary signals missing) 158.65, 151.45 (q), 144.18 (q), 126.42, 121.99, 102.75 (q), 87.14 (q), 43.35, 34.40 (q), 30.92, and 26.52; *m/z* 317 (M^+, 36%), 259 (81), 244 (100), 214 (26), 200 (17), 170 (21), 158 (69), 144 (25), and 131 (16): 5-(N-[^{13}C]*methyl*-N-*phenyl*) (Method D,[15] 90%), using a 1.5-fold excess of sodium hydride and a 2-fold excess of [^{13}C]methyl iodide.

1H-*Pyrrol*-3(2H)-*ones*.—Pyrolysis of the appropriate aminomethylene Meldrum's acid derivative at 600 °C (10^{-2} to 10^{-3} Torr) gave the pyrrolone as previously described.[15] The following new compounds were made (precursor and inlet temperature given in parentheses): 1-p-(*t-butyl*)*phenyl* {5-[*N-p*-(t-butyl)phenyl-*N*-methyl-}, 200 °C] (35%), m.p. 95—97 °C (from hexane) (Found: C, 77.3; H, 7.85; N, 6.4. $C_{14}H_{17}NO\cdot 0.1H_2O$ requires C, 77.5; H, 7.9; N, 6.45%); δ_H 8.38 (1 H, d), 7.36 (2 H, d), 6.94 (2 H, d), 5.43 (1 H, d), 4.10 (2 H, s), and 1.29 (9 H, s); δ_C 198.73 (q), 158.52, 146.28 (q), 137.10 (q), 126.48, 114.68, 103.38, 55.90, 34.10 (q), and 31.11; *m/z* 215 (M^+, 53%) and 200 (100): 1-*phenyl*-[2-^{13}C] [5-(*N*-[^{13}C]methyl-*N*-phenyl-), 180 °C] (40%); δ_H(80 MHz) 8.41 (1 H, dd, ^3J 3.7 and 3.8 Hz), 6.9—7.4 (5 H, m), 5.47 (1 H, dd, ^3J 3.7 and 4.6 Hz), and 4.11 (2 H, d, ^1J 142.1 Hz).

The 1-phenyl-1*H*-[$^2H_2$]pyrrol-3(2*H*)-one was obtained by deuterium exchange of the [$^1H_2$] analogue in neutral [$^2H_4$]-methanol.[16] The reaction was monitored at room temperature by ^{1}H n.m.r. spectroscopy, and when exchange was complete (< 2 h) the solvent was removed *in vacuo*, and the sample was immediately prepared for photolysis as described below.

8a-*Hydroxy*-5-*methyl*-5,6,7,8,*tetra*-8a-*hydroindolizin*-1(1H)-*one* (**18**) *and* 8a-*Methyl*-5,6,7,8,*tetra*-8a-*hydroindolizin*-1(1H)-*one*.—2,2-Dimethyl-5-(2-methylpiperidin-1-yl)methylene-1,3-dioxane-4,6-dione[15] (cyclohexane solvate; 2.53 g; contains 8.8 mmol of substrate) was heated at 120 °C (5×10^{-3} Torr) to remove cyclohexane. After evaporation had ceased, the inlet temperature was raised to 180 °C, and the substrate was sublimed during 90 min, through the furnace tube at 600 °C. The pyrolysate was dissolved in ether (50 ml) containing methylene dichloride (5 ml), and air was passed through the solution for 20 min. The solvent was removed, the residue was triturated with methylene dichloride, and the 8a-*hydroxy-indolizinone* was filtered off (yield 0.24 g, 16%), m.p. 170—171 °C (decomp.) (from chloroform at −20 °C) (Found: C, 64.55; H, 7.65; N, 8.25. $C_9H_{13}NO_2$ requires C, 64.65; H, 7.8; N, 8.4%); δ_H (360 MHz) 7.84 (1 H, d), 4.99 (1 H, d), 4.1 (1 H, br s), 3.71 (1 H, m), 1.2—2.1 (6 H, m), and 1.35 (3 H, d); δ_C 204.65 (q), 159.33, 92.64, 86.71 (q), 49.91, 36.45, 33.27, 19.14, and 17.52; *m/z* 167 (M^+, 100%), 139 (73), 138 (55), 124 (70), 96 (63), 70 (58), and 55 (59); $\lambda_{max.}$($CHCl_3$) 340 nm (ε 6 500).

The methylene dichloride mother liquors were concentrated and distilled (Kugelrohr) to give the 8a-*methylindolizinone* (0.27 g, 20%), b.p. 154—157 °C (0.1 Torr), as a hygroscopic yellow oil (Found: C, 69.05; H, 8.9; N, 8.7. $C_9H_{13}NO\cdot 0.33H_2O$ requires C, 68.8; H, 8.7; N, 8.9%); δ_H(360 MHz) 7.68 (1 H, d), 4.99 (1 H, d), 3.52 (1 H, m), 3.32 (1 H, t of d), 1.2—1.8 (6 H, m), and 1.21 (3 H, s); δ_C 207.27 (q), 161.62, 94.24, 65.19 (q), 46.24, 32.35, 27.71, 19.53, and 16.86; *m/z* 151 (M^+, 47%), 122 (100), 97 (15), 69 (20), and 55 (20); $\lambda_{max.}$($CHCl_3$) 322 nm (ε 6 100).

2-*Hydroxy*-2-*methyl*-1-*phenyl*-1H-*pyrrol*-3(2H)-*one* (1-*Phenylaminopent*-1-*ene*-3,4-*dione*) (**17**).—2-Methyl-1-phenyl-1*H*-pyrrol-3(2*H*)-one (crude material from pyrolysis of 5 mmol of starting material) was dissolved in an ethanol–water (50:50) mixture (20 ml). Potassium hexacyanoferrate(III) (3.3 g, 10 mmol) was added and the mixture was stirred at room temperature for 3 h. The aqueous solution was then extracted with methylene dichloride (3 × 25 ml); the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Bulb-to-bulb distillation [130 °C (10 Torr)] yielded the title compound as a yellow solid (0.31 g, 40% from pyrolysis substrate), m.p. 68—70 °C [sublimed at 155 °C (0.3 Torr)] (Found: M^+, 189.079. $C_{11}H_{11}NO$ requires *M*, 189.079); δ_H(open-chain tautomer) 12.03 (1 H, br s), 7.63 (1 H, dd, ^3J 7.5 and 12.8 Hz), 7.0—7.55 (5 H, m), 6.04 (1 H, d, ^3J 7.5 Hz), and 2.42 (3 H, s); δ_C(one carbonyl resonance not observed) 184.89 (q), 147.93, 139.21 (q), 129.72, 124.78, 116.77, 90.56, and 23.96; *m/z* 189 (M^+, 11%), 147 (10) 146 (100), and 93 (10); δ_H[ring tautomer; $(CD_3)_2SO$] 8.79 (1 H, d, ^3J 4.0 Hz), 7.0—7.6 (5 H, m), 6.90 (1 H, s), 5.27 (1 H, d, ^3J 4.0 Hz), and 1.27 (3 H, s).

E.s.r. Spectra of 1H-*Pyrrol*-3(2H)-*ones*.—Samples of the pyrrolone (*ca.* 20 mg) and di-t-butyl peroxide (50 μl) were placed in Spectrosil tubes and degassed by two or three freeze–pump–thaw cycles. The solutions were irradiated with light from a 500 W super-pressure Hg arc directly in the cavity of a Bruker ER200D spectrometer operating at 9.4 GHz. Spectra were simulated using Heinzer's program.[25]

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