3-Hydroxypyrroles and 1*H*-Pyrrol-3(2*H*)-ones. Part 8.[1,2] Reactions of 1-Isopropyl-2,2-dimethyl-1*H*-pyrrol-3(2*H*)-one with Electrophiles

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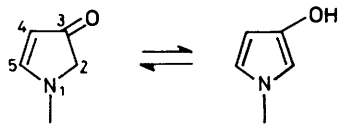
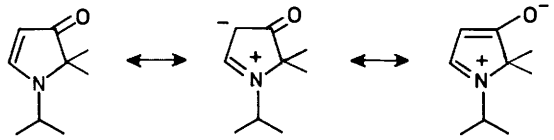
Reaction of the pyrrolone (**2**) with N-, C-, and halogen-electrophiles takes place at the 4-position to give the azo compounds (**3**)—(**5**), the 'methylene Meldrum's' derivative (**12**) and the halogeno derivatives (**16**)—(**18**). Reductive cleavage of the azo compound (**5**) gives a convenient route to the 4-aminopyrrolone (**7**), which may be diazotised and coupled with 2-naphthol. Decomposition of the Meldrum's derivative (**12**) with base leads to the malonates (**13**) and (**14**) and acrylate (**15**). Deuterium exchange at the 5-position takes place when the halogeno compounds (**16**)—(**18**) are treated with [$^2H_3$]methoxide in [$^2H_4$]methanol: the 5-anion is thought to be an intermediate. Protodehalogenation of the 4-bromo- and 4-iodo-derivatives (**17**) and (**18**) occurs on treatment with triphenylphosphine.

In this paper, we continue our studies of the properties of 1*H*-pyrrol-3(2*H*)-ones (**1A**),[1] made possible by our discovery of a simple and efficient synthetic route to this system.[3,4] In order to avoid possible complications due to tautomerism to 3-hydroxypyrroles (**1B**), we elected to concentrate at this stage on 2,2-



(**1A**) (**1B**)

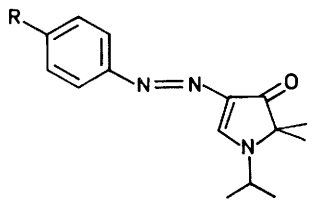


(**2**)

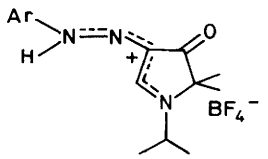
disubstituted examples of which the 1-isopropyl-2,2-dimethyl compound (**2**) is the simplest derivative conveniently made by the pyrolysis method.[3,5] Rather than being a true pyrrole, this structure is a cyclic enaminone,[6] held rigidly in a planar[7,8] *Z*-s-*E* configuration. Six π-electrons are involved in conjugation over five atoms, and so reaction with electrophiles, particularly at the electron-rich 4-position might be expected, as has been found for certain *E*-s-*E* enaminones,[6,9] and for the isoelectronic 2,3-dihydro-1,4-diazepine system.[10,11] In addition, the resonance energy of the enaminone—comparable to that of the 'aromatic' pyrrole system[8]—should cause reaction by substitution rather than addition,[12] and might influence the properties of the functional groups so obtained.

Prior to the previous paper of this series, where we considered protonation, deuterium exchange, and *O*-alkylation,[1] no reactions of 2,2-disubstituted pyrrolones with electrophiles had been reported, though some work on their photolytic behaviour,[5] including an oxidative *N*-dealkylation,[13] has appeared. The reactions with nitrogen, carbon, and halogen electrophiles, together with the chemical and spectroscopic properties of the products, are considered here.

Nitrogen Electrophiles.—Although the pyrrolone (**2**) decomposed under typical nitrating conditions (see Experimental section), it coupled smoothly with aryldiazonium fluoroborates in acetonitrile solution to give the 4-arylazo derivatives (**3**)—(**5**) in 60—70% yield. The position of substitution in these, and in later examples, was confirmed by the absence of the characteristic 4-proton signal (δ *ca.* 5.0) in the ^1H n.m.r. spectrum. The parent compound (**3**) was obtained as an oil, after chromatography, though the substituted derivatives (**4**) and (**5**) were isolated first as fluoroborate salts which gave



(**3**) R = H
(**4**) R = NO_2
(**5**) R = CO_2H

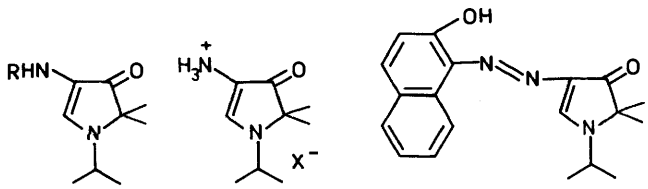


(**6**)

highly crystalline bases after careful neutralisation and extraction. Protonation presumably takes place on an exocyclic nitrogen atom, as in (**6**), to generate the stable 1,2,5-triazapentadienium conjugated system.[14] Two important points emerge from these reactions. Firstly, the pyrrolone ring must possess high reactivity to couple under mild conditions with the weakly electrophilic diazonium ion, and secondly the tendency of the system to 'retain the type' is fully borne out by the observation of substitution rather than addition behaviour.

Reductive cleavage[15] of an azo derivative provides a route to the 4-amino compound (**7**). *p*-Substituted azo derivatives are required to avoid competitive benzidine rearrangements of intermediates, and the carboxylic acid (**5**) was chosen for preparative experiments so that the resulting amines [*viz* (**7**) and *p*-aminobenzoic acid] could be readily separated by basic work-up. Since the reaction is carried out in aqueous acid solution,[15] the fluoroborate salt of (**5**) can be used directly: reduction with tin(II) chloride required 2 h at room temperature and gave the desired amino derivative (**7**) as a yellow oil by distillation (72%) or as the picrate salt (**8**; X = picrate) in 73% yield.

The free amine (**7**) appeared to be relatively stable at room temperature, though in chloroform solution it was precipitated spontaneously as a salt (presumably either hydrochloride or hydrogen carbonate) which gives an indication of its basicity. The changes observed in the ^{13}C n.m.r. spectrum of the picrate (**8**), relative to the free base (**7**), are markedly different from those observed on *O*-protonation of the 1*H*-pyrrol-3(2*H*)-one



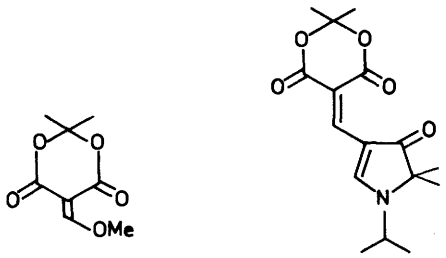
(7) R = H (8) (10)
(9) R = Ac

(2) itself;[1] the carbonyl carbon atom is shielded by only 3 p.p.m. compared to 12 p.p.m. in the parent compound, whereas C-4 is shielded by > 15 p.p.m. compared to a deshielding of 2 p.p.m. in the parent.[1] These shifts are consistent with protonation taking place at the exocyclic nitrogen atom: a dramatic shielding of the α-position is also observed on protonation of aniline.[16]

By using acetic acid at 80 °C rather than hydrochloric acid as the medium for the reduction,[15] the acetamide (**9**) was obtained directly in 41% yield.

The amine (**7**) proved to have typical 'aromatic' properties, since it could be diazotised in aqueous solution to give a stable salt which, in turn, coupled with 2-naphthol to form the deep red product (**10**).

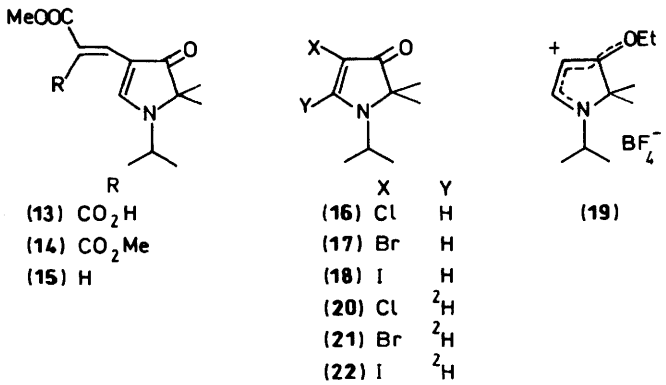
Carbon Electrophiles.—A systematic study of electrophilic substitution of pyrrolones under Vilsmeier, Friedel-Crafts *etc.* conditions has not been carried out, but we have established the principle that new C–C bonds may be formed by reaction with methoxymethylene Meldrum's acid (**11**). We have found this compound to be a useful *C*-electrophile capable of reacting with activated aromatic systems under mild conditions.[17] Thus the pyrrolone (**2**) is transformed into the 4-'methylene Meldrum's' derivative (**12**) in > 70% yield by reaction with (**11**) for just 2 h at



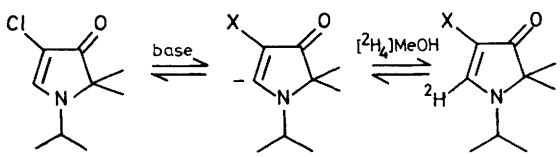
(11) (12)

room temperature in acetonitrile. It is well known that methylene Meldrum's acid derivatives can be transformed into malonates and acrylates,[18,19] and indeed the malonate half-ester (**13**) was obtained in quantitative yield by treatment of (**12**) with an excess of sodium methoxide solution at room temperature. The half-ester (**13**) was readily alkylated (MeI, DMF, K_2CO_3, 20 °C, overnight) to give the dimethyl malonate (**14**; 50%) or alternatively it could be decarboxylated by *in situ* bulb-to-bulb distillation to give the acrylate (**15**; 65%) as a single geometric isomer. From the magnitude of the vicinal coupling constant ($^3J_{H,H}$ 15.5 Hz) it is thought to be the *E*-isomer as shown. Synthetically, the sequence of activated aromatic → methylene Meldrum's derivative → malonate half-ester → acrylate is a simple and convenient source of a three-carbon unit which may find more general application.

Halogen Electrophiles.—The pyrrolone (**2**) reacts readily with *N*-halogenosuccinimides under standard 'electrophilic' conditions[9,11] (20 °C, methanol) to give the stable crystalline 4-chloro-, 4-bromo- and 4-iodo-derivatives (**16**)—(**18**) in 91, 88 and 76% yields respectively. Electrophilic bromination can also be carried out by molecular bromine (in methanol), but these conditions give a 1:1 mixture of product and starting material even in the presence of an excess of reagent. However, the addition of solid potassium carbonate to the reaction mixture resulted in total conversion into the 4-bromo compound (**17**), so it appears that the incomplete reaction may be due to the formation of an inert hydrobromide salt of the starting material (**2**). It is perhaps not surprising that (**2**), lacking the electronegative halogen atom, should be more basic than the product (**17**), and it was easy to show that the related *O*-alkylated salt (**19**)[1] is indeed inert both to *N*-bromosuccinimide



R X Y
(13) CO_2H (16) Cl H (19)
(14) CO_2Me (17) Br H
(15) H (18) I H
(20) Cl ^2H
(21) Br ^2H
(22) I ^2H



(23)

Scheme 1.

and to molecular bromine under the reaction conditions. These results emphasise the difference in reactivity of enaminonium and the isoelectronic vinamidinium systems (exemplified by the 2,3-dihydro-1,4-diazepinium salts) which normally undergo electrophilic substitution *via* the monocation,[11] and hence the relative efficiency of oxygen and nitrogen atoms as electron donors.

The 4-halogeno compounds (**16**)—(**18**) were smoothly *O*-protonated by acid (*cf.* reference 1). Electrophilic protodehalogenation was extremely slow: even the 4-iodo derivative (**18**) was unchanged after 8 h in neat trifluoroacetic acid at 65 °C and at room temperature the reaction was only *ca.* 60% complete after 5 months.

On reaction of the halogeno derivatives (**16**)—(**18**) with the hard nucleophile [$^2H_3$]methoxide ion, in refluxing [$^2H_4$]-methanol, *no* displacement of the halogen atom was detected, even from the iodo compound, but instead a totally unexpected exchange reaction took place at the normally inert 5-position to give the deuteriated products (**20**)—(**22**) in *ca.* 90% yield. The parent compound (**2**) showed no reaction under identical conditions. The relative rates of this process for the three halogeno derivatives were followed competitively in the probe of an n.m.r. spectrometer at 55 °C (see Experimental section). Good pseudo-first-order plots were obtained (Figure 1) giving the relative rates of the exchange of the chloro:bromo:iodo derivatives as 4.5:3.5:1. Rather surprisingly, the chloro compound (**16**) showed the fastest reaction, and indeed the approximate relative first-order rate constants show a linear relationship with the electronegativity of the halogen atom

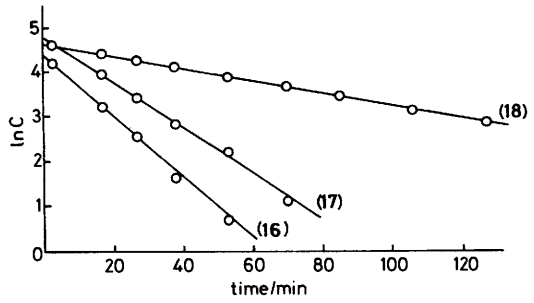


Figure 1. First order plots for competitive deuterium exchange of (**16**)—(**18**) in [$^2H_3$]MeO$^-$/[$^2H_4$]MeOH at 55 °C.

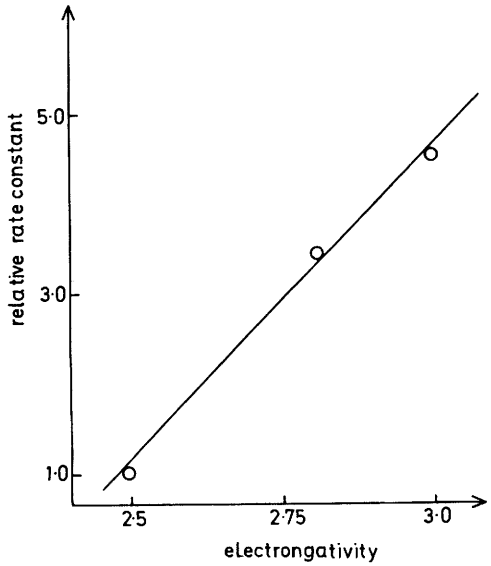
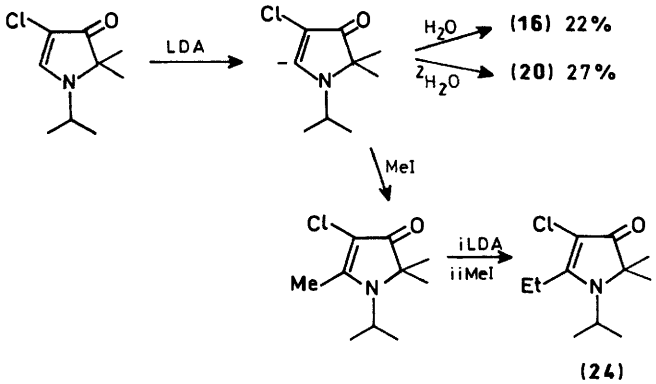


Figure 2. Correlation of relative rate constants (from Figure 1) with electronegativity of the 4-halogeno substituent.

(Figure 2). The most reasonable mechanism therefore involves the generation of a low equilibrium concentration of the vinyl anion (**23**) (Scheme 1), whch is quenched by the solvent. Related anions are thought to be involved in exchange processes of 4-pyridones.[20]

These conclusions are supported by the results of experiments in which the 4-chloro compound (**16**) was treated with lithium di-isopropylamide, and the resulting mixture was quenched with electrophiles (Scheme 2). These processes are subject to a



Scheme 2.

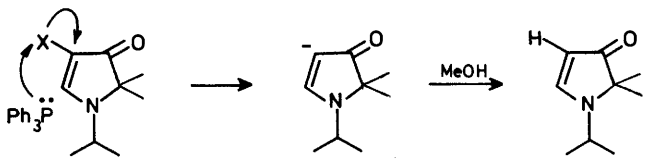
Table. ^{13}C N.m.r. additivity effects for electronegative 4-substituents in the 1*H*-pyrrol-3(2*H*)-one nucleus

Compound	4-Substituent	C-3	C-4	C-5
(**3**)	PhN_2	−10.69	+31.02	−4.57
		(−5.5)	(+24.2)	(−5.5)
(**7**)	NH_2	−6.71	+21.00	−8.99
		(−13.3)	(+18.0)	(−13.3)
(**9**)	NHAc	−9.85	+16.14	−8.47
		(−9.9)	(+11.1)	(−9.9)
(**16**)	Cl	−8.47	+4.15	−2.43
		(+0.4)	(+6.2)	(+0.4)
(**17**)	Br	−7.86	−10.67	−0.40
		(+3.4)	(−5.5)	(+3.4)
(**18**)	I	−4.57	−43.54	+3.41
		(+10.2)	(−32.0)	(+10.2)

[a] Data refer to the additivity effect of the substituent relative to the spectrum of (**2**), taking δ[C(3)–C(5)] as 204.68, 94.28 and 158.78 respectively. Figures in parentheses in the C-4 column refer to the corresponding data for the α-position in benzene derivatives while those in the C-3 and C-5 columns refer to the *ortho*-positions in benzene derivatives.[16,23]

number of unidentified side-reactions and have not been optimised, but it was nevertheless possible to isolate the deuteriated compound (**20**) and the parent compound (**16**), in comparable yield, on quenching with ^2H_2O and H_2O respectively. A mixture of products was also obtained when the vinyl anion (**23**; X = Cl) was trapped with an excess of iodomethane but the major product was identified as the 5-ethyl derivative (**24**) resulting from reaction of the initial methylation product with an excess of base followed by a second alkylation. This sequence has previously been observed for a variety of heterocyclic systems[21] and gives an indication of the reactivity of 5-alkyl groups.

Treatment of the halogeno derivatives (**16**)—(**18**) with the soft nucleophile triphenylphosphine, in methanol at room temperature, induced protodehalogenation. The iodo compound (**18**) required less than 30 min for complete reaction whereas the bromo compound (**17**) required a few hours and the chloro compound (**16**) showed less than 50% reaction even after 3 weeks. The observed rapid reaction at the soft iodine centre supports initial attack at the halogen atom[22] to give the vinyl anion (**25**) (or its equivalent) which is trapped by the solvent (Scheme 3). As expected, the 4-deuterio derivative was formed



Scheme 3.

when [$^2H_4$]methanol was used as solvent. Very similar behaviour has been well documented in the 2,3-dihydro-1,4-diazepine series.[22]

^{1}H *and* ^{13}C *N.m.r. Spectra.*—In the ^{1}H n.m.r. spectra of these 4-substituted pyrrolones, the singlet due to the residual 5-proton is particularly characteristic. Its chemical shift is remarkably constant (δ 7.6—8.0) unless the 4-substituent generates ring current effects where significant deshielding is observed [*e.g.* δ 8.6—9.3 for the azo derivatives (**3**)—(**5**) and the acetamido compound (**9**)].

Very large shifts in δ (C-4) are observed (Table) and these are

invariably in the same direction as found for the same substituent in the benzene series:[16,23] the shifts are usually larger in the pyrrolone cases however, and, for the halogens, are closer to those of the corresponding alkene.[24] The carbonyl signal (C-3) is shielded in all the examples, presumably due to a general perturbation of the enaminone system due to the substituent. There is no relation here to benzene *ortho* additivity effects. In contrast, the effect at the 5-position is usually smaller in magnitude than at the 3-position, but often in the same direction as *ortho*-shifts in aromatics[16,23] (Table). Again, the appropriate alkene is perhaps a better model for the halogen compounds (Cl, Br, I; $\Delta\delta$ −6.0, −1.3, +7.1 p.p.m. respectively[24]).

Experimental

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

Reaction with Nitrating Agents.—Attempted nitration of 1-isopropyl-2,2-dimethyl-1*H*-pyrrol-3(2*H*)-one using concentrated nitric acid under the conditions of Lloyd,[25] Barnett[26] and of Kucera and Arnold,[27] led only to decomposition.

Arenediazonium Tetrafluoroborates.—The benzene- and *p*-nitrobenzene-diazonium tetrafluoroborates[28] were prepared by literature methods. The *p*-carboxybenzenediazonium tetrafluoroborate was prepared as follows: 4-aminobenzoic acid (6.85 g, 50 mmol) was dissolved in fluoroboric acid (40%, 43.5 ml, 200 mmol) and water (50 ml). The solution was heated until the aniline was completely dissolved and then cooled on ice (some precipitation of solid occurred). Sodium nitrite (3.65 g, 53 mmol) in water (10 ml) was added dropwise while the solution was stirred. The reaction mixture was allowed to warm to room temperature and the solution was concentrated under reduced pressure to approximately half its original volume. The reaction mixture was cooled in ice before filtration to give the diazonium salt (9.7 g, 89%) which was washed with ether and dried *in vacuo*.

4-*Arylazo*-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*ones* (**3**)—(**5**).—1-Isopropyl-2,2-dimethyl-1*H*-pyrrol-3(2*H*)-one[3] (**2**) (80 mg, 0.52 mmol) was dissolved in acetonitrile (5 ml) and the solution cooled to 0 °C. The appropriate arenediazonium tetrafluoroborate (0.52 mmol) was added in portions and the reaction mixture was then allowed to warm to room temperature. Evaporation of the solvent under reduced pressure from the diazonium salt reaction mixture gave the parent phenylazo compound as a dark oil which was purified by chromatography on alumina with ethyl acetate–hexane (4:1) as eluant, but it could not be obtained in crystalline form. For the substituted examples, evaporation of solvent gave the *p*-nitro- and *p*-carboxy-phenylazo derivatives as their tetrafluoroborate salts. The free bases were obtained by careful neutralisation of a solution of the salts with aqueous potassium hydroxide and extraction with methylene dichloride. For the *p*-carboxyphenylazo case in particular, it was necessary to avoid the addition of excess of base as the acid function then prevented extraction of the compound. The following azo derivatives were obtained: 4-*phenylazo* (**3**) (104 mg, 66%) (Found: M^+, 257.1528. $C_{15}H_{19}N_3O$ requires M^+, 257.1528); δ_H 8.66 (1 H, s), 7.25—8.0 (5 H, m), 3.38 (1 H, m), 1.43 (6 H, d), and 1.41 (6 H, s); δ_C 193.99(q), 154.22, 153.42(q), 128.93(q), 128.36, 128.26, 121.38, 71.04(q), 46.55, 23.52, and 21.65; *m/z* 257 (M^+, 100%), 186(28), 180(90), and 110(59): 4-p-*nitrophenylazo* (**4**) (97 mg, 62%), m.p. 228—229 °C (from ethanol) (Found: C, 59.6; H, 5.95; N, 18.55. $C_{15}H_{18}N_4O_3$ requires C, 59.8; H, 6.0; N, 18.45%); δ_H 8.72 (1 H, s), 8.22 (2 H, d), 7.78 (2 H, d), 3.84 (1 H, m), 1.45 (6 H, d), and 1.41 (6 H, s); δ_C 193.13(q), 157.60(q), 156.02, 146.82(q), 130.08(q), 124.34, 121.89, 71.84(q), 47.24, 23.78, and 21.85; *m/z* 302 (M^+, 100%), 231(23), 180(66), 122(33), and 110(60); 4-p-*carboxyphenylazo* (**5**) (119 mg, 76%), m.p. 189—191 °C (from toluene) (Found: C, 63.8; H, 6.15; N, 13.6. $C_{16}H_{19}N_3O_3$ requires C, 63.8; H, 6.3; N, 13.95%); δ_H ([$^2H_6$]dimethyl sulphoxide) 9.28 (1 H, s), 8.01 (2 H, d), 7.64 (2 H, d), 3.98 (1 H, m), 1.38 (6 H, d), and 1.31 (6 H, s); δ_C ([$^2H_6$]dimethyl sulphoxide) 193.14(q), 167.12(q), 157.21, 156.46(q), 130.43, 129.76(q), 129.36(q), 120.79, 70.98(q), 46.96, 23.21, and 21.34; *m/z* 301 (M^+, 36%), 217(27), 180(17), 143(20), 137(90), and 120(100).

4-*Amino*-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*one* (**7**).—The 4-carboxyphenylazopyrrol-3-one (described above), as its tetrafluoroborate salt (390 mg, 1 mmol), was added in portions to a solution of tin(II) chloride dihydrate (1.33 g, 6 mmol) in concentrated hydrochloric acid (8 ml) and the reaction mixture was stirred at room temperature until the solution became opaque (*ca.* 2 h). The mixture was then cooled in ice and basified with aqueous potassium hydroxide solution. Methylene dichloride (50 ml) was added and the resulting two-phase system was filtered through Celite. The organic layer was separated and the aqueous layer was extracted with methylene dichloride (4 × 50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure, at the minimum required temperature. The residue was purified by bulb-to-bulb distillation to give the amine (**7**) (120 mg, 72%), b.p. 145 °C (0.3 Torr), δ_H 7.65 (1 H, s), 3.56 (1 H, m), 1.22 (6 H, d), and 1.19 (6 H, s); δ_C 197.97(q), 149.79, 115.28(q), 66.57(q), 44.52, 23.34, and 21.60; *m/z* 168 (M^+, 36%), 153(59), 107(82), and 106(100). Alternatively, prior to distillation, the amine was dissolved in ethanol and an excess of a saturated solution of picric acid in ethanol was added to give 4-*amino*-2,2-*dimethyl*-3-*oxo*-1-*isopropylpyrrolium picrate* (**8**) (X = $C_6H_2N_3O_7^-$) (290 mg, 73%, from azo salt), m.p. 158 °C (decomp.) (from dimethylformamide) (Found: C, 44.8; H, 5.1; N, 17.6. $C_{15}H_{19}N_5O_8$ requires C, 44.9; H, 4.75; N, 17.45%); δ_H([$^2H_6$]acetone) 8.82 (1 H, s), 8.72 (2 H, s), 4.02 (1 H, m), 3.5—4.2 (3 H, br), 1.39 (6 H, d), and 1.36 (6 H, s); δ_C([$^2H_6$]dimethyl sulphoxide) 194.91(q), 160.84(q), 155.42, 141.89(q), 125.14, 124.36(q), 99.73(q), 68.34(q), 45.68, 23.25, and 21.17.

4-*Acetamido*-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*one* (**9**).—The 4-carboxyphenylazopyrrolone (base) (301 mg, 1 mmol) was dissolved in acetic acid (2 ml) and was added to a solution of tin(II) chloride dihydrate (2 g, 9 mmol) in acetic acid (20 ml) at 80 °C. The reaction mixture was maintained at 80 °C and stirred for 2 h. The mixture was then poured into aqueous potassium hydroxide (20%; 25 ml) and extracted with methylene dichloride (3 × 30 ml); the combined organic layers were then washed again with aqueous potassium hydroxide, dried ($MgSO_4$), and evaporated under reduced pressure to give the 4-*acetamido* compound (**9**) as a yellow solid (86 mg, 41%), m.p. 192 °C (from methanol) (Found: C, 61.6; H, 8.3; N, 13.0. $C_{11}H_{18}N_2O_2 \cdot 0.25\ H_2O$ requires C, 61.5; H, 8.6; N, 13.05%); δ_H 8.81 (1 H, s), 7.98 (1 H, br), 3.62 (1 H, m), 2.08 (3 H, s), 1.29 (6 H, d), and 1.23 (6 H, s); δ_C 194.83(q), 166.83(q), 150.31, 110.42(q), 66.13(q), 45.45, 23.56, 22.86, and 21.77; *m/z* 210 (M^+, 100%), 195(68), 168(43), 153(64), and 84(54).

2,3-*Dihydro*-1-*isopropyl*-2,2-*dimethyl*-3-*oxo*-1H-*pyrrole*-4-*diazonium Chloride and Its Coupling to* 2-*Naphthol.*—The amine (85 mg, 0.5 mmol) was dissolved in dilute hydrochloric acid (0.6 ml) and the solution was cooled to 0 °C. A solution of sodium nitrite (40 mg, 0.55 mmol) in water (0.3 ml) was added dropwise. A solution of 2-naphthol (90 mg, 0.6 mmol) in sodium hydroxide (2M; 1 ml) was then added in one portion to the cooled solution. The deep red precipitate which resulted was

filtered off, dissolved in base, and extracted with methylene dichloride (3 × 10 ml). The combined extracts were dried and evaporated under reduced pressure to give 4-[1-(2-*hydroxy*-2-*naphthylazo*)-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*one* (**10**) (53 mg, 33%) (Found: M^+, 323.163. $C_{19}H_{21}N_3O_2$ requires M^+, 323.163); δ_H 8.74 (1 H, d), 8.71 (1 H, s), 7.2—7.75 (5 H, m), 3.84 (1 H, m), 1.48 (6 H, d), and 1.44 (6 H, s); δ_C 194.08(q), 151.31, 151.23(q), 132.30(q), 131.74, 129.62(q), 128.30(q), 127.80, 127.03(q), 126.84, 123.72, 121.82, 119.96, 71.09(q), 46.92, 23.94, and 22.06; *m/z* 324 (35%), 323 (M^+, 24%), 221(24), 167(42), 143(56), 115(36), 97(30), and 69(100). This material could not be satisfactorily purified.

5-[1,2-*Dihydro*-1-*isopropyl*-2,2-*dimethyl*-3-*oxo*-4-(3H-*pyrrolylmethylene*)]-2,2-*dimethyl*-1,3-*dioxane*-4,6-*dione* (**12**) *and Its Reaction with Sodium Methoxide.*—(*a*) 5-Methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione[29] (**11**) (1.02 g, 5.5 mmol) was dissolved in acetonitrile (10 ml) and 1-isopropyl-2,2-dimethyl-1*H*-pyrrol-3(2*H*)-one (0.85 g, 5.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and then evaporated under reduced pressure to give a thick oil. Trituration of this with toluene yielded a yellow solid which was recrystallised from toluene to give the title compound (**12**) (1.23 g, 73%), m.p. 188—190 °C (from toluene) (Found: C, 64.7; H, 7.1; N, 4.2. $C_{16}H_{21}NO_5 \cdot 0.25\ C_7H_8$ requires C, 64.55; H, 6.95; N, 4.25%); δ_H 9.79 (1 H, s), 7.89 (1 H, s), 3.70 (1 H, m), 1.35 (6 H, s), 1.15 (6 H, d), and 1.06 (6 H, s); δ_C 199.95(q), 165.91, 164.23(q), 163.18(q), 145.31, 107.58(q), 103.30(q), 99.83(q), 70.35(q), 47.25, 27.00, 23.60, and 21.58; *m/z* 307 (M^+, 100%), 249(50), 221(45), 206(90), and 193(30).

(*b*) The derivative prepared in (*a*) above (1 g, 3.25 mmol) was dissolved in methanol (10 ml) and sodium methoxide [from sodium (150 mg, 6.5 mmol) in methanol (5 ml)] was added. The reaction mixture was stirred at room temperature for 1 h and then poured into water (15 ml) and acidified with hydrochloric acid. The acid solution was extracted with methylene dichloride (4 × 20 ml) and the combined organic layers were dried ($MgSO_4$), and evaporated under reduced pressure to give *methyl* 1,2-*dihydro*-1-*isopropyl*-2,2-*dimethyl*-3-*oxo*-3H-*pyrrol*-4-*ylmethylenemalonate* (**13**) (1.2 g, 100%, crude product) which was not purified; δ_H 10.14 (1 H, s), 8.19 (1 H, s), 3.81 (3 H, s), 3.81 (1 H, m), 1.40 (6 H, d), and 1.30 (6 H, s); δ_C 200.57(q), 172.26(q), 166.77(q), 166.36, 143.79, 106.49(q), 103.47(q), 69.83(q), 52.54, 47.63, 23.52, and 21.58; *m/z* 281 (M^+, 58%), 237(15), 236(30), 221(15), 220(19), 219(19), 205(100), 193(23), 188(54), and 166(30). Bulb-to-bulb distillation gave a solid decarboxylated product, *methyl* 3-(1,2-*dihydro*-1-*isopropyl*-2,2-*dimethyl*-3-*oxo*-3H-*pyrrol*-4-*yl*)*propenoate* (**15**) (1.5 g, 65%), m.p. 105—107 °C (from cyclohexane) (Found: C, 65.8; H, 8.2; N, 6.1. $C_{13}H_{19}NO_3$ requires C, 65.8; H, 8.0; N, 5.9%); δ_H 8.00 (1 H, s), 7.32 (1 H, d, ^3J 15.5 Hz), 6.53 (1 H, d, ^3J 15.5 Hz), 3.67 (4 H, s and superimposed m), 1.32 (6 H, d), and 1.24 (6 H, s); δ_C 199.78(q), 168.47(q), 159.61, 134.84, 110.08, 104.97(q), 69.78(q), 45.91, 23.24, and 21.36; *m/z* 237 (M^+, 100%), 222(31), 206(38), 194(62), 166(85), and 154(46).

(*c*) Alternatively, the methanol was removed under reduced pressure from the sodium methoxide solution prepared in (*b*) above, and the residual anion was dissolved in dimethylformamide (10 ml). Potassium carbonate (0.9 g, 6.5 mmol) and methyl iodide (100 μl, 16 mmol) were added and the reaction mixture was stirred at room temperature overnight. The mixture was filtered and the filtrate was added to water (10 ml). The product was extracted into methylene dichloride (3 × 10 ml) and the extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give *dimethyl* 1,2-*dihydro*-1-*isopropyl*-2,2-*dimethyl*-3-*oxo*-3H-*pyrrol*-4-*ylmethylenemalonate* (**14**) (0.48 g, 50%), m.p. 116—117 °C (from methanol) (Found: C, 61.05; H, 7.25; N, 4.85. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.1; N, 4.75%); δ_H 8.89 (1 H, s), 7.59 (1 H, s), 3.74 (3 H, s), 3.68 (1 H, m), 3.66 (3 H, s), 1.31 (6 H, d), and 1.21 (6 H, s); δ_C 199.92(q), 167.61(q), 166.29(q), 161.40, 136.22, 113.13(q), 104.28(q), 69.24(q), 51.52 (ester methyl resonances accidentally equivalent), 46.73, 23.61, and 21.63; *m/z* 295 (M^+, 90%), 264(46), 251(25), 224(41), 220(78), 180(84), and 153(100).

4-*Halogeno*-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*ones* (**16**)—(**18**).—*Method A.* The pyrrolone (**2**) (80 mg, 0.52 mmol) was dissolved in methanol (8 ml) and the solution was cooled in ice. The appropriate *N*-halogenosuccinimide (0.52 mmol) was added in portions to the stirred solution and the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was then poured into methylene dichloride (15 ml) and washed with aqueous sodium hydrogen carbonate (20%; 3 × 15 ml). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give the 4-halogeno compounds as crystalline solids.

Method B. The pyrrolone (**2**) (80 mg, 0.52 mmol) was dissolved in methanol (8 ml) and a solution of bromine (80 mg, 0.5 mmol) in methanol (2 ml) was added. Potassium carbonate (*ca.* 1 g) was added and the mixture was stirred at room temperature overnight and then poured into water (10 ml). The solution was extracted with methylene dichloride (3 × 15 ml) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the 4-bromo compound. The following 1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*ones* were prepared: 4-*bromo* (**17**) (Method A, 106 mg, 88%; Method B, 99 mg, 82%), m.p. 114—115 °C (from methanol) (Found: C, 46.7; H, 5.85; N, 5.85. $C_9H_{14}BrNO$ requires C, 46.55; H, 6.0; N, 6.0%); δ_H 7.92 (1 H, s), 3.64 (1 H, m), 1.30 (6 H, d), and 1.26 (6 H, s); δ_C 196.82(q), 158.38, 83.61(q), 68.48(q), 46.09, 23.73, and 21.94; *m/z* 233, 231 (M^+, 33 and 31%), 163(19), 161(25), 149(25), 148(20), 147(25), 146(20), 124(50), 110(50), and 99(100): 4-*chloro*(**16**) (Method A, 89 mg, 91%), m.p. 130—131 °C (from methanol) [Found: C, 55.1; H, 7.7; N, 6.8. $C_9H_{14}ClNO \cdot 0.5\ H_2O$ requires C, 54.95; H, 7.65; N, 7.1% (analyses reproducibly as partial hydrate)]; δ_H 7.89 (1 H, s), 3.63 (1 H, m), 1.28 (6 H, d), and 1.25 (6 H, s); δ_C 196.21(q), 156.35, 98.43(q), 68.80(q), 45.94, 23.80, and 22.00; *m/z* 189, 187 (M^+, 100 and 25%), 174(31), 172(8), 144(10), 124(50), and 84(75): 4-*iodo* (**18**) (Method A, 110 mg, 76%), m.p. 127—129 °C (from methanol) (Found: C, 39.05; H, 4.85; N, 5.0. $C_9H_{14}INO$ requires C, 38.7; H, 5.0; N, 5.0%); δ_H 7.96 (1 H, s), 3.67 (1 H, m), 1.32 (6 H, d), and 1.27 (6 H, s); δ_C 200.11(q), 162.19, 67.75(q), 50.74(q), 46.37, 23.91, and 22.04; *m/z* 279 (M^+, 90%), 264(20), 236(37), 195(23), 194(27), 152(43), and 110(100).

Reaction of 4-*Halogeno*-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*ones with Sodium Methoxide in Deuteriated Methanol.*—The pyrrolone (0.1 mmol) was dissolved in [$^2H_4$]methanol (0.2 ml) and sodium methoxide [from sodium (5 mg, 0.2 mmol) in [$^2H_4$]methanol (0.3 ml)] was added carefully. The reaction mixture was placed in an n.m.r. tube and was heated by immersion in methanol at reflux. The reaction was followed to completion by periodic examination of the ^1H n.m.r. spectrum. It was then poured into water (5 ml), acidified (HCl), and extracted with methylene dichloride (3 × 10 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give the following 5-[^2H]-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*ones*: 4-*bromo* (**21**) (91%), $\delta_{^2H}$ ($CHCl_3$) 8.04; *m/z* 234, 232 (M^+, 36 and 39%), 219(14), 217(14), 191(16), 189(18), 164(20), 162(20), 125(50), 111(43), and 84(100): 4-*iodo* (**22**) (93%) $\delta_{^2H}$ ($CHCl_3$) 8.09; *m/z* 280 (M^+, 89%), 153(61), and 111(100).

An experiment in which approximate rate constants for this reaction for the 4-chloro, 4-bromo, and 4-iodo compounds were determined was carried out as follows: approximately equimolar quantities of the starting materials were added sequentially to [$^2H_4$]methanol and ^1H n.m.r. spectra obtained

between each addition in order to assign the C(5)-H resonance for each [δ_H (200 MHz, with resolution enhancement), 8.60 (bromo), 8.59 (chloro), 8.57 (iodo), and 8.44 (parent, to act as standard for integration)]. Sodium methoxide [from sodium (2 equiv.) in [$^2H_4$]methanol] was added. The reaction mixture was placed in an n.m.r. tube and heated to 55 °C in the probe of the spectrometer. The ^1H n.m.r. spectrum of the reaction mixture was monitored at intervals. The first-order plots are shown in Figure 1.

Reactions of 4-*Chloro*-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*one with Lithium Di-isopropylamide.*—All apparatus was dried overnight before use. A solution of di-isopropylamine (560 μl, 4 mmol) in dry tetrahydrofuran (20 ml) was cooled to −78 °C and stirred using a magnetic stirrer in a 3-necked flask equipped with a rubber septum. Butyl-lithium (1.5M; 2.7 ml, 4 mmol) was added by syringe and the mixture was stirred for 15 min. The pyrrolone (187 mg, 1 mmol) in tetrahydrofuran (5 ml) was added and again stirring was continued for 15 min. The electrophile was added and the mixture was stirred for a further 15 min and then allowed to warm to room temperature. The reaction mixture was then poured into hydrochloric acid (2M; 30 ml) and the acid solution was extracted with methylene dichloride (3 × 30 ml); the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give mixtures of products as shown by t.l.c. These mixtures were separated by column chromatography on alumina using ethyl acetate–hexane (60:40) as eluant.

(*a*) *Quenching with water.* Chromatography yielded starting material (40 mg, 22%), a second product (60 mg) as an oil which decomposed on attempted distillation, and a mixed fraction (30 mg).

(*b*) *Quenching with* [$^2H_2$]*water.* Chromatography yielded the 5-[^{2}H]pyrrolone (51 mg, 27%) and a thick gummy material (77 mg), which produced two peaks on analysis by g.c. (5% S.E. 30, 180 °C) but was not analysed further.

(*c*) *Quenching with methyl iodide.* Chromatography yielded a creamy solid (130 mg) which was shown by ^1H and ^{13}C n.m.r. spectroscopy to contain two products. The major one was obtained in relatively pure form by repeated recrystallisation from hexane and identified as 4-*chloro*-5-*ethyl*-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*one* (**24**) (Found: M^+, 217.103 and 215.109. $C_{11}H_{18}ClNO$ requires M^+, 217.105 and 215.108); δ_H 3.82 (1 H, m), 2.71 (2 H, q), 1.41 (6 H, d), 1.28 (3 H, t), and 1.27 (6 H, s); δ_C 194.09(q), 174.45(q), 98.03(q), 69.09(q), 46.74, 23.27, 22.27, 20.97, and 11.11; *m/z* 217, 215 (M^+, 6 and 30%), 202(13), 172(13), 152(38), 143(16), 110(38), and 84(100).

Reaction of 4-*Halogeno*-1-*isopropyl*-2,2-*dimethyl*-1H-*pyrrol*-3(2H)-*ones with Triphenylphosphine.*—The pyrrolone (0.5 mmol) was dissolved in methanol (5 ml) and triphenylphosphine (130 mg, 0.5 mmol) was added. The reaction was followed to completion (*ca.* 30 min for 4-iodo and 16 h for 4-bromo compounds) by t.l.c. on alumina plates with ethyl acetate–hexane (50:50) as eluant. Methanolic hydrochloric acid (~2M, 10 ml) was added and the hydrochloride salt obtained was washed with ether. The salt was then dissolved in sodium hydroxide (10%; 15 ml) and the solution extracted with methylene dichloride (3 × 15 ml). The combined organic fractions were dried ($MgSO_4$), evaporated under reduced pressure, and the product recrystallised from hexane to give the 4-unsubstituted compound (**2**) in *ca.* 70% yield. Melting point and mixed melting point for both examples: 70—71 °C (from hexane). The 4-chloro compound did not react under these conditions.

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