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Synthesis of *N*-Substituted γ-Methylene γ-Lactams*

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N-Substituted cyanoacetamides **1** were condensed with 1,2-diketones **2** under base catalysis to form γ-hydroxy γ-lactams **3**. Treatment of **3** with acids gave novel fungicidal γ-methylene γ-lactams **4**. The exocyclic double bond of **4b** reacted reversibly with 4-toluene sulfinate.

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Introduction

The highly successful ergosterol biosynthesis-inhibiting class of fungicides includes compounds obtained by *N*-alkylation of imidazole or 1,2,4-triazole. While the fungicidal properties of many such derivatives have already been examined, opportunities remain for exploring some less common alkylating agents. Electrophilic *N*-acyliminium ions[1] are known to trap diverse nucleophiles, and these reactive entities may provide access to new azole derivatives that might have useful fungicidal properties. These *N*-acyliminium ions are usually conveniently generated by the elimination of water from a γ-hydroxy lactam[2] under acidic conditions. The hydroxy lactams are often accessed through partial reduction of readily available cyclic imides. As a potential alternative source, some γ-hydroxy γ-lactams are readily available by condensing cyanoacetamide **1a** with butane-2,3-dione[3] (**2a**; Table 1).

The reported synthesis was confined to a study of the parent unsubstituted acetamide. For our purposes it was important to determine whether the procedure could be extended to include *N*-substituted cyanoacetamides. If it could, then this extension would enable ready access to a broad and structurally diverse group of candidate compounds suitable for biological testing.

Results and Discussion

A solution of *N*-(4-chlorophenyl)cyanoacetamide **1b** in *N*,*N*-dimethylformamide containing one equivalent of butane-2,3-dione showed negligible change until a catalytic amount of a base such as morpholine was added. Following such an addition, an exothermic reaction occurred. Workup resulted in the isolation of a crystalline product with spectroscopic properties consistent with the expected γ-hydroxy lactam **3b**, such as methyl resonances in the ^{1}H NMR spectrum at δ_H 2.15 (C=C–Me) and 1.25 (C(OH)Me). Consequently, 1,2,4-triazole was added in excess to a solution of this lactam in formic acid, and the mixture was warmed with an expectation of forming the desired azole adduct. However, although **3b** reacted readily and a new crystalline product was isolated in high yield from the cooled reaction mixture, NMR examination of this material did not indicate the presence of a triazole nucleus. Instead, the product showed a new two-proton doublet at δ_H 5.01 and 5.27 (J 2.6 Hz) which, since it was accompanied by disappearance of the C(OH)Me resonance, suggested that the starting material had eliminated water to form a γ-methylene lactam[4] **4b**. Subsequent experiments with a variety of hydroxylated lactams **3** in the presence of various azoles or other potential nucleophiles confirmed that attempts at alkylation under acidic conditions led only to elimination of water and formation of a γ-methylene lactam **4**. As a result, cyano-substituted γ-methylene γ-lactams such as **4** were inadvertently found to be readily accessible. This structural motif has not been reported previously in the chemical literature and the serendipitous synthesis invited further examination. The investigation received an unexpected fillip when routine testing in agrochemical screens showed that these lactams had substantial activity against several fungal pathogens of commercial interest. To explore the potential of this new class of fungicides, a range of cyanoacetamides as well as some conceptually related compounds, **1a**–**1s**, were condensed with 1,2-diketones **2** to provide diverse candidates for biological testing.

Condensation of the cyanoacetamides **1** with 1,2-diketones **2** was catalyzed by bases such as piperidine, morpholine, *N*-methyl morpholine, and triethylamine. Overnight condensation was generally sufficient to ensure complete reaction with butane-2,3-dione, while more extensively substituted 1,2-diones sometimes required reaction for up to seven days. Although heating the reaction mixture accelerated

* Dedicated to the memory of Dr Dionne Anne Jones.

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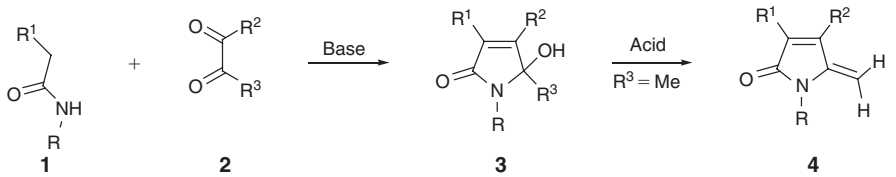
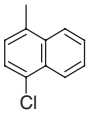
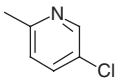
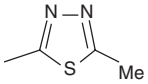
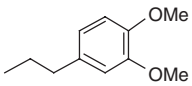
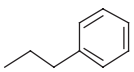
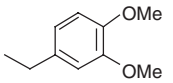
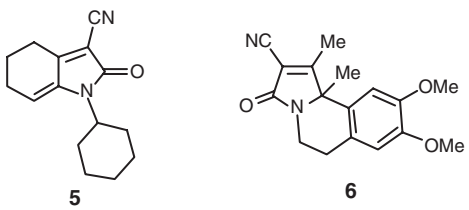
Table 1. Structures of compounds studied



1 **2** **3** **4**

	1		2		3		4	Yield [%]
	R	R^1	R^2	R^3	R^2	R^3	R^2	
a	H	CN	Me	Me	Me	Me		
b	Ph(4-Cl)	CN	Me	Me	Me	Me	Me	85
c	Cyclohexyl	CN	Ph	Me	Ph	Me	Ph	47
d	Cyclohexyl	CN	Me	Ph	Me	Ph		
e	Ph(2,6-diEt)	CN	Me	Me	Me	Me	Me	81
f	Ph(2-Cl-6-Me)	CN	Et	Me	Et	Me	Et	68
g	Ph(2-Cl-6-Me)	CN	Bu	Me	Bu	Me	Bu	42
h	Ph(2-Pr^i-6-Me)	CN	Pr^i	Me	Pr^i	Me	Pr^i	61
i	Ph(4-CN)	CN	Me	Me	Me	Me	Me	81
j	Cyclohexyl	CN	Me	Me	Me	Me	Me	92
k		CN	Me	Me	Me	Me	Me	65
l		CN	Me	Me	Me	Me	Me	51
m		CN	Me	Me	Me	Me	Me	—
n	-N=CHPh(4-Cl)	CN	Me	Me	Me	Me	Me	—
o	-COOEt	CN	Me	Me	Me	Me		
p	Ph(4-Cl)	CO_2Et	Me	Me	Me	Me	Me	58
q		CN	Me	Me	Me	Me		
r		CN	Me	Me	Me	Me	Me	56
s		CN	Me	Me	Me	Me	Me	79

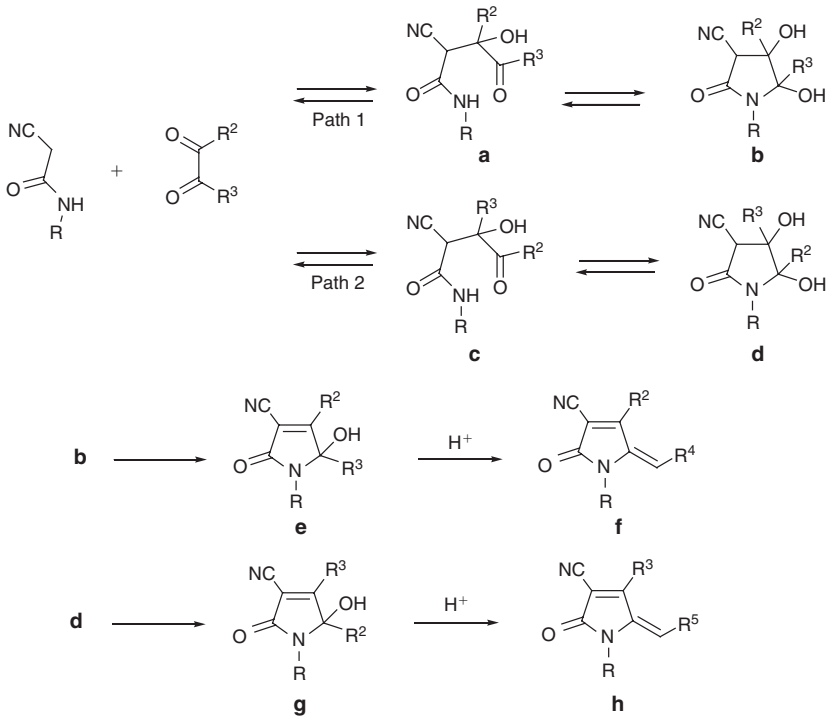
the rate of condensation, the formation of coloured by-products made this alternative unattractive. Useful results were obtained from most 1,2-diketones, including those bearing a branched alkyl chain, **2h**, cyclic 1,2-diketones such as cyclohexane-1,2-dione **5** (Fig. 1), and an arylalkyl 1,2-dione, **2c**. In the last example, the initial condensation did not discriminate significantly between the two available carbonyl groups, although these would have been expected to display substantial differences in reactivity. Thus, when the crude reaction product (which contained a mixture of both possible hydroxy compounds **3c** and **3d**), was subjected to dehydration in formic acid, products were isolated which clearly originated from the two possible condensation pathways. The methylene lactam **4c** (resulting from an initial condensation at the aroyl carbonyl) was obtained in 47% yield together with the hydroxylactam **3d**, 32% yield (arising from an initial condensation at the acetyl group, but



5 **6**

Fig. 1. Compounds **5** and **6**.

unable to eliminate water in the subsequent treatment with formic acid). However, when pentane-2,3-dione **2e** reacted with the cyanoacetamide **1f**, derived from 2-chloro-6-methyl aniline, a high degree of regioselectivity prevailed during the initial condensation since only one significant product, the methylene lactam **4f**, was obtained after dehydration of the crude hydroxy product. Similar selectivity was observed in the formation of **4g** and **4h** (starting with BuCOCOMe and



Scheme 1. Thermodynamic control during condensation.

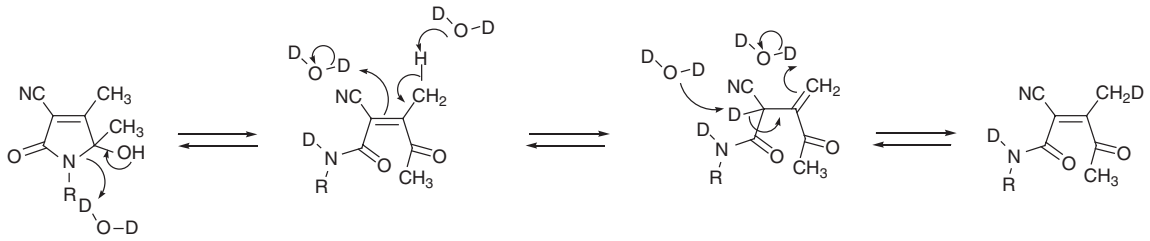
Pr^{i}COCOMe respectively). Selectivity seemed contrary to intuitive prediction, as the less electrophilic carbonyl group was the first to react.

Such unexpected chemoselectivity may arise as follows (Scheme 1). When R^2 is the smaller alkyl group, the carbonyl adjacent to R^2 (R^2 carbonyl) should usually be more reactive than the R^3 carbonyl. An initial reaction with a nucleophile should then be more rapid at the R^2 carbonyl than at the alternative R^3 carbonyl. However, the second step, the reaction of the weakly nucleophilic amide nitrogen with the remaining carbonyl to cause the ring closure, would be susceptible to steric interactions. Any such steric effect would be accentuated where there is *ortho*-substitution on the aniline, especially for 2,6-disubstituted derivatives **3f**, **3g**, and **3h**. However, if the first reaction, the formation of **a**, is reversible, there would exist an opportunity for **a** to dissociate to its precursor components and recombine to generate a small quantity of **c**. Although minor, this quantity of **c** would be continuously removed from the equilibrium by facile cyclization to **d**. This may explain why the orientation of the groups derived from the diketone was such that the smaller substituent usually furnished the eventual methylene moiety, to give thermodynamic control.

Formation of the methylene lactam was closely related to the acidity of the medium within which the dehydration was being carried out. Often elimination could be achieved by warming a solution in 98% formic acid for a few minutes or by leaving it overnight at room temperature. Because of its high solvating power and relatively high acidity, excess trifluoroacetic acid was the most generally effective medium for dehydration. This solvent also has the useful property of being relatively NMR-transparent so that the rate of progress could be monitored by ^{1}H NMR where a decrease of the methyl group signal at about δ_H 1.3 was accompanied by a proportional increase of an easily observed pair of olefinic protons at about δ_H 5. When more forceful conditions were required, methanesulfonic, trifluoromethanesulfonic, or concentrated sulfuric acid were effective alternatives.

A factor which also affected dehydration was the electron density at the nitrogen atom of the lactam. Thus, where strongly electron-withdrawing groups were present on the benzene ring, or where the *N*-pendant group was a heterocycle of a kind likely be protonated in the acidic medium, elimination was more difficult.

Subsequent screening showed that the hydroxy precursors **3** were devoid of agrochemical utility. Consequently, without an incentive to isolate this intermediate species, the crude condensation products were usually subjected to acid treatment to generate the methylene lactams without purification of the intermediate hydroxy compound. The hydroxy compounds were found to have an unexpected chemical property. Following routine confirmation of the presence of a hydroxy group in **3i** by D_2O exchange, the NMR sample was left overnight and the ^{1}H spectrum rerun the following day. One of the methyl groups (C4 at δ_H 2.30) was diminished appreciably in intensity relative to the other ^{1}H signals, including the other methyl group at δ_H 1.42. This change continued over time with the δ_H 2.30 peak steadily decreasing and becoming replaced by a diminishing cluster of peaks (presumably from CH_3, CH_2D, and CHD_2 species) over the next few days. However, the methylene lactam product **4i** was unaffected under comparable conditions. This property was also exhibited by two other hydroxy compounds, **3j** and **3m**, which were selected at random, as well as the hydrazino compound **3n**. It



Scheme 2. D_2O exchange in γ-hydroxy lactams.

appears to be an attribute peculiar to this type of compound. As the corresponding methylene lactams (**4h**, **4i**, and **4j**) do not show this effect, suggesting that appreciable acidity for the protons of the methyl group attached to the double bond is insufficient to explain these observations. Alternatively, the hydroxy lactams **3h**, **3i**, **3j**, and **3k** may be in equilibrium with a small quantity of the acyclic form[5] (Scheme 2). The acidity of the methyl group in the acyclic form is now substantially enhanced by the presence of an additional electron withdrawing group (the acetyl function) and this may be sufficient to enable a slow dissociation of a proton to occur, as shown in Scheme 2.

Many opportunities existed for increasing diversity within the pool of compounds available for testing, by varying the *N*-substituent present in the cyano acetamide starting material. Thus, the carbamate **1o** was also observed to condense readily with butane-2,3-dione to give a good yield of the hydroxy lactam **3o**. However, this failed to give a stable product upon attempted dehydration. Similarly, the hydrazone **1n** (readily obtained by condensation of commercially available cyanoacetyl hydrazide with 4-chlorobenzaldehyde) also gave the expected hydroxylactam, **3n**. Unfortunately, this formed an intractable mixture upon attempted dehydration under acidic conditions. The results of an attempt to prepare thio analogs of the methylene lactams from thiocyanocetamides have already been described.[6]

As the condensation is initiated by the formation of a carbanion from the methylene group that is activated by the flanking electron withdrawing groups (Table 1), it seemed probable that other electron withdrawing groups including thioaryl, alkyl- or aryl-sulfonyl, and acyl groups may promote a similar condensation. The malonic monoester-monoamide **1p** underwent a similar sequence of reactions to give a hydroxylactam **3p** and then the methylene lactam **4p** following elimination in trifluoroacetic acid. However, most activating groups other than cyano gave poor yields and they were not further investigated.

The failure of 1,2,4-triazole to add during the initial proposed synthesis plan resulted in the formation of methylene lactams **4**. Following the discovery of significant fungicidal activity it was speculated that such activity might have been derived from an ability of the methylene group to scavenge biological nucleophiles. These compounds, while robust under neutral or acidic conditions, were sensitive to basic conditions created by the presence of amines, alkoxides, and thioalkoxides. In each instance, reactions occurred readily to form brightly coloured solutions that failed to yield stable products upon workup. The potential for these compounds to add nucleophiles was confirmed when 4-toluenesulfinic acid reacted reversibly with **4b** under mildly acidic conditions. Thus, a solution of **4b** in formic acid showed olefinic protons at δ_H 5.1 and 5.4 (J 2.7 Hz). Following addition of sodium 4-toluenesulfinate, a crystalline precipitate was formed that consisted largely of the adduct. However, the addition was easily reversed. Attempts to purify the adduct by chromatography over silica gel led to recovery of the original methylene lactam **4b** resulting from dissociation and progressive loss of the sulfinate. Nevertheless, an irreversible trapping of this electrophilic centre might be effected by enabling an intramolecular reaction. Such an opportunity could be contrived by providing a suitably tethered electron-rich aromatic ring. When the hydroxy lactam **3q** was dissolved in formic acid, cyclization occurred readily to form a stable tricyclic product **6** by formation of an additional six-membered ring. It appears that the nucleophilic reactivity of the aromatic ring in **3q** is barely sufficient for ring closure since the analogous hydroxy lactam **3r**, which lacks the activation provided by the two methoxy groups in **3q**, merely eliminated water to give the normal methylene lactam product **4r**. Similarly, the hydroxy lactam **3s** that could have been expected to cyclize and generate a ring system analogous to **6**, gave only the methylene lactam **4s**.

Experimental

Melting points were determined on a Reichert Kofler hot-stage micromelting point apparatus and are uncorrected. Microanalyses were performed by Campbell Microanalytical Laboratory, University of Otago. Infrared spectra were recorded on a Perkin–Elmer 842 spectrophotometer and refer to paraffin mulls. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50.3 MHz respectively on a Bruker AC-200 spectrometer. Chemical shifts (δ_H) are measured in ppm with tetramethylsilane as an internal standard. Low-resolution mass spectra were recorded on a Fisons Instruments VG Platform quadrupole using either atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) in the positive-ion and/or negative-ion mode with cone voltage 30 eV for both APCI and ESI, with either 1/1 acetonitrile/water or methanol as solvent. Radial thin-layer chromatography was performed on a Harrison Research Chromatron using a 4 mm thick layer of silica (silica gel 60 PF254, Merck No. 7749). Light petroleum refers to the fraction with a bp 40–60°C.

Cyanoacetamides were prepared by applying methods described in the literature, usually by heating an amine with ethyl cyanoacetate[7] (Method A) or by condensation with cyanoacetic acid in the presence of diisopropyl carbodiimide[8,9] (Method B).

The cyanoacetamide products were recrystallized from the solvents indicated and were satisfactory for subsequent condensations without additional purification.

Preparations following Method A

N-*(4-Chlorophenyl)-2-cyanoacetamide* ***1b***

A mixture of ethyl cyanoacetate (11.3 g, 100 mmol), *N*,*N*-dimethylformamide (50 mL) and 4-chloroaniline (12.8 g, 100 mmol) was heated at 100°C for 10 h, diluted slowly with water (150 mL), and the precipitate was collected, washed with water, and recrystallized from ethanol to afford the cyanoacetamide **1b** (14.1 g, 73%) mp 207–208°C (lit.[5] 203°C). δ_H ($CDCl_3$/$(CD_3)_2SO$ 10/1) 3.74 (2H, s, CH_2), 7.19 (2H, d, *J* 8.2, ArH), 7.49 (2H, d, *J* 8.2, ArH), 10.2 (1H s, NH).

2-Cyano-N-*cyclohexylacetamide* ***1c***

Prepared in 64% yield, mp 130–132°C (ethyl acetate) (lit.[10] 132°C). δ_H ($CDCl_3$) 1.0–1.80 (10H, m, cyclohexyl), 3.42–3.54 (1H, m, NCH), 3.56 (1H, s, $COCH_2$), 8.08 (1H, d, *J* 7.3, NH).

2-Cyano-N-*(2,6-diethylphenyl)acetamide* ***1e***

Prepared in 49% yield, mp 79–180°C (aqueous ethanol). δ_H ($CDCl_3$) 1.19 (3H, t, *J* 7.3, Me), 2.57 (2H q, *J* 7.3, CH_2), 3.57 (2H, s, CH_2), 7.11–7.34 (4H, m, 4ArH), 7.42 (1H, br s, NH).

N-*(2-Chloro-6-methylphenyl)-2-cyanoacetamide* ***1g***

δ_H ($CDCl_3$/$(CD_3)_2SO$ 10/1) 2.17 (3H, s, Me), 3.49 (2H, s, CH_2), 6.95–7.11 (3H, m, 3ArH).

N-*(4-Cyanophenyl)-2-cyanoacetamide* ***1i***

Prepared in 46% yield, mp 204–205°C (isopropyl alcohol/dichloromethane). δ_H ($CDCl_3$/$(CD_3)_2SO$ 10/1) 3.78 (2H, s, CH_2), 7.39 (2H, d, *J* 8.1, ArH), 7.83 (2H, d, *J* 8.1, ArH), 10.4 (1H, s, NH).

N-*(4-Chloronaphthalen-1-yl)-2-cyanoacetamide* ***1k***

Obtained in 49% yield, mp 218–220°C (ethanol). δ_H ($CDCl_3$/$(CD_3)_2$ SO 10/1) 4.11 (2H, s, CH_2), 7.62–7.80 (4H, m, 4ArH), 8.16–8.25 (2H, m, 2ArH), 10.36 (1H, s, NH).

Preparations following Method B

2-Cyano-N-*(5-methyl[1,3,4]thiadiazol-2-yl)acetamide* ***1m***

To a stirred suspension of 2-amino-5-methyl-1,3,4-thiadiazole (10.0 g, 86.8 mmol) and cyanoacetic acid (7.4 g, 86.8 mmol) in DMF at 0–5°C under argon was added 1,3-diisopropylcarbodiimide (13.3 g, 104.2 mmol) dropwise. The reaction mixture was left stirring at room temperature for 2 days, poured into water, and the precipitate was collected by filtration, washed with water then dichloromethane to give a pale yellow solid (22.5 g) after drying under vacuum. Trituration with hot methanol and filtration gave **1m** as a pale yellow solid (12.3 g, 78%), mp 247–251°C (dec.). δ_H ($CDCl_3$/$(CD_3)_2SO$ 10/1) 2.01 (3H, s, Me), 3.24 (2H, s, CH_2).

2-Cyano-N-*(2-isopropyl-6-methylphenyl)acetamide* ***1h***

Prepared in 71% yield, mp 124–126°C (aqueous ethanol). δ_H ($CDCl_3$/$(CD_3)_2SO$ 10/1) 1.09 (6H, br s, Me_2CH), 2.28 (3H, s, Me), 3.04 (1H, m, Me_2CH), 3.79 (2H, s, CH_2), 7.03–7.58 (3H, m, 3ArH).

N-*(5-Chloropyridin-2-yl)-2-cyanoacetamide* ***1l***

Prepared in 77% yield, mp 195–196°C (aqueous ethanol). δ_H ($(CD_3)_2SO$) 4.03 (2H, s, CH_2), 7.8–8.4 (3H, m, pyH), 10.96 (1H, br s, NH).

Cyanoacetic Acid (4-Chlorobenzylidene)hydrazide ***1n***

This hydrazone was prepared from 4-chlorobenzaldehyde and cyanoacethydrazide in acetic acid to afford the product as fawn needles (82% yield), mp 195–197°C (ethanol) (lit.[11] 188–189°C). δ_H ($CDCl_3$/CF_3COOH 10/1) 4.09 (2H, s, CH_2), 7.41 (2H, d, *J* 8.7, 2ArH), 7.63 (2H, d, *J* 8.7, 2ArH), 7.90 (1H, s, =CH), 10.75 (1H, br s, NH).

N-*(4-Chlorophenyl)malonamic Acid Ethyl Ester* ***1p***

Colourless needles from ethanol (47% yield), mp 96–97°C (lit.[12] 97°C).

2-Cyano-N-*[2-(3,4-dimethoxyphenyl)ethyl]acetamide* ***1q***

Fawn needles from isopropyl alcohol, mp 114–115°C (64% yield) (lit.[13] 115°C). δ_H ($CDCl_3$) 2.79 (2H, t, *J* 10, $ArCH_2$), 3.30 (2H, s, CH_2CN), 3.75 (2H, overlapping t, *J* 10, CH_2NH), 3.85, 3.87 (3H, 3H, each s, 2OMe), 6.32 (1H, br s, NH), 7.72–8.86 (3H, m, 3ArH).

2-Cyano-N-*phenethylacetamide* ***1r***

From aqueous ethanol to give colourless plates (77% yield), mp 87–89°C (lit.[14] 93–95°C). δ_H ($CDCl_3$) 2.76 (2H, t, *J* 10, $PhCH_2$), 3.23 (2H, s, 3.50, overlapping t, *J* 10, CH_2NH), 6.4 (1H, br, NH), 7.1–7.4 (5H, m, Ph).

2-Cyano-N-*(3,4-dimethoxybenzyl)acetamide* ***1s***

The cyanoacetamide (67%) was obtained as colourless needles from isopropyl alcohol, mp 134–135°C (lit.[15] 133°C). δ_H ($CDCl_3$) 3.31 (1H, s, CH_2CN), 3.82, 3.83 (3H, 3H, each s, 2OMe), 4.43 (2H, d, *J* 10, CH_2NH), 6.7–7.1 (4H, m, 3ArH & NH).

General Method for the Preparation of γ-Hydroxy γ-Lactams ***3***

A solution of the cyanoacetamide (10 mmol) in *N*,*N*-dimethylformamide (6 mL) containing the 1,2-diketone (11 mmol) was treated with three drops of morpholine or piperidine and the mixture was left to stand at room until thin layer chromatography (TLC) showed consumption of the cyanoacetamide to be complete (1–5 days). The mixture was stirred into water (100 mL) and the product collected as a crystalline precipitate or extracted with dichloromethane and purified by chromatography over silica gel. In some instances such as **3c**, **3g**, and **3f** the crude residue remaining after removal of the dichloromethane was treated with an acid and converted directly into the corresponding methylene lactam without attempt isolate the intermediate hydroxy lactam **3**.

*1-(4-Chlorophenyl)-4,5-dimethyl-5-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3b***

Butane-2,3-dione (1.62 g, 20 mmol) was added to a solution of 4-chlorophenyl cyanoacetamide (**1b**, 3.9 g, 20 mmol) in DMF (12 mL) and stirred for 10 min without noticeable change. Addition of two drops of morpholine initiated a rapid rise in the temperature of the solution, which was moderated by external cooling with tap water. The next day the solution was diluted by the addition of water (25 mL) to precipitate an oil that solidified upon stirring. Following the addition of aqueous ethanol (30 mL, 50%) the mixture was stirred at 80°C for 30 min, cooled to room temperature, and stirred for a further 2 h. The product was collected by filtration, washed on the filter with 80% aqueous ethanol, and dried to give the hydroxy compound as a powder (4.8 g, 91%), mp 189–192°C. A portion was recrystallized from aqueous isopropyl alcohol to afford colourless prisms, mp 196–197°C. (Found: C 59.6, H 4.2, N 10.7. $C_{13}H_{11}ClN_2O_2$ requires C 59.4, H 4.2, N 10.7%). ν_{max} (KBr)/cm^{-1} 3299, 2923, 2856, 2236, 1693, 1675. δ_H ($CDCl_3$/$(CD_3)_2SO$ 10/1) 1.25 (3H, s, C(OH)Me), 2.15 (3H, s, MeC=C), 3.8–4.2 (1H, br, OH), 7.20 (2H, d, *J* 8.9, 2ArH), 7.33 (2H, d, *J* 8.9, 2ArH). δ_C ($CDCl_3$/$(CD_3)_2SO$) 12.8, 21.9, 91.5, 108.1, 112.5, 127.4, 128.9. 132.4, 133.6, 133.7, 134.5, 163.2, 174.5. *m*/*z* $APCI^+$ 283, 247, 245, 236, 211, 202, 174, 156, 127, 117, 110.

*1-(4-Chlorophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4b***

The hydroxy compound **3b** (1.4 g, 6 mmol) was suspended in formic acid (9 mL, 98%). The mixture was heated at 80°C for 4 h, during which the solid dissolved and was gradually replaced by a new precipitate. Aqueous isopropyl alcohol (8 mL, 50%) was added to the hot mixture that was stirred as it cooled. Filtration followed by a wash on the filter with aqueous isopropyl alcohol gave the methylene lactam **4b** as

an off-yellow powder (1.1 g, 85%), mp 182–184°C. The same product was obtained in a comparable yield when the reaction was carried out in the presence of one molar equivalent amount of either imidazole or triazole. Recrystallization from acetic acid (with filtration of the warm solution to remove a small amount of insoluble material) gave pale yellow plates, mp 184–186°C. (Found: C 64.0, H 3.8, N 11.5. $C_{13}H_9ClN_2O$ requires C 63.8, H 3.7, N 11.5%). ν_{max} (KBr)/cm^{-1} 2933, 2858, 2227, 1705, 1632, 1612. δ_H ($CDCl_3$) 2.46 (3H, s, Me), 5.01 (1H, d, *J* 2.6, =C(H)H), 5.27 (1H, d, *J* 2.6, =C(H)H), 7.24 (2H, d, *J* 8.8, 2ArH), 7.5 (2H, d, *J* 8.8, 2ArH). δ_C ($CDCl_3$) 12.5, 100.6, 107.2, 112.3, 128.8, 129.9, 131.9, 134.9, 145.1, 157.4, 164.4. *m/z* APCI$^+$ 245, 211, 136, 117, 99.

*1-Cyclohexyl-5-hydroxy-4-methyl-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3d*** *and*
*1-Cyclohexyl-5-methylene-2-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4c***

Piperidine (3 drops) was added to a mixture of phenylpropane-1,2-dione (0.74 g, 5 mmol) and the cyanoacetamide (0.83 g, 5 mmol) in DMF (4 mL), and the solution left to stand at room temperature for 7 days. Addition of water (20 mL) caused separation of a tarry material which was extracted into dichloromethane (15 mL). The organic extract was separated, washed with water (3 × 50 mL), and the solvent removed under reduced pressure to leave a residue that was dissolved in formic acid (8 mL) and then warmed to 80°C for 90 min. The solution was cooled, stirred into ether (60 mL), shaken with water (100 mL), and the whole left to stand for 3 h. The mixture was filtered to remove some suspended solid, and the ether layer was separated and evaporated to give an oil which soon solidified. Radial chromatography over silica gave the methylene lactam **4c** as the more mobile component (0.66 g, 47%); recrystallization from light petroleum gave colourless rods, mp 162–163°C. (Found: C 77.6, H 6.7, N 10.0. $C_{18}H_{18}N_2O$ requires C 77.7, H 6.5, N 10.1%). δ_H ($CDCl_3$) 1.05–2.18 (10H, m, cyclohex), 3.84 (1H, m, cyclohex), 5.17 (1H, d, *J* 2.7, =C(H)H), 5.22 (1H, d, *J* 2.7, =C(H)H), 7.45 (5H, br s, ArH). δ_C ($CDCl_3$) 25.1, 26.1, 29.8, 53.5, 103.8, 106.4, 112.5, 128.9, 129.0, 129.1, 131.1, 143.2, 157.6, 163.6. *m/z* APCI$^+$ 279 (M + 1).

Continued elution gave the hydroxy lactam **3d** (0.51 g, 36%), which was recrystallized from light petroleum to give colourless needles, mp 178–180°C. (Found: C 72.9, H 6.8, N 9.4. $C_{18}H_{20}N_2O_2$ requires C 73.0, H 6.8, N 9.5%). δ_H ($CDCl_3$) 0.77–2.05 (10H, m, cyclohexyl), 1.86 (3H, s, Me), 3.1 (1H, m, cyclohexyl), 5.0 (1H, br s, OH), 7.2–7.4 (5H, m, Ph). δ_C ($CDCl_3$) 12.98, 25.04, 26.02, 29.55, 30.78, 53.80, 93.52, 111.78, 126.07, 128.75, 129.25, 135.02, 163.48, 174.93.

*1-(2,6-Diethylphenyl)-4,5-dimethyl-5-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3e***

Obtained as colourless needles from ethanol, mp 207–208°C (66% yield). (Found: C 71.7, H 7.1, N 9.8. $C_{17}H_{20}N_2O_2$ requires C 71.8, H 7.1, N 9.9%). δ_H ($CDCl_3$) 1.03–1.14 (6H, overlapping t, *J* 7.5, 2 × CH_2Me), 1.35 (3H, s, C(OH)Me), 2.30 (3H, s, MeC=C), 2.2–2.7 (4H, m, 2 × CH_2Me), 7.20–7.38 (3H, m, 3ArH). δ_C ($CDCl_3$) 18.4, 20.2, 20.5, 26.9, 97.2, 111.8, 117.7, 131.5, 131.9, 133.9, 135.7, 149.0, 150.3, 167.8, 181.5.

*1-(2,6-Diethylphenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4e***

A solution of the hydroxy compound (**3e**, 0.57 g, 2 mmol) in dichloromethane (5 mL) was treated with trifluoroacetic acid (0.5 mL), left to stand for 24 h, evaporated to dryness, and the residue recrystallized from cyclohexane to give the product (0.38 g, 81%) as colourless needles, mp 83–84°C. (Found: C 76.5, H 6.6, N 10.6. $C_{17}H_{18}N_2O$ requires C 76.7, H 6.8, N 10.5%). δ_H ($CDCl_3$) 1.18 (6H, t, *J* 7.5, 2 × CH_2Me), 2.30–2.47 (4H, dq, *J* 2.0, 7.4, 2 × CH_2Me), 2.46 (3H, s, Me), 4.65 (1H, d, *J* 2.3, HHC=C), 5.17 (1H, d, *J* 2.3, HHC=C), 7.1–7.35 (3H, m, 3ArH). δ_C ($CDCl_3$) 14.5, 17.7, 24.2, 100.0, 126.9, 128.7, 129.7, 133.2, 137.8, 143.7, 144.8, 157.6, 163.5.

*1-[(2-Chloro-6-methyl)phenyl]-4-ethyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4f***

Obtained without purification of the crude hydroxy compound by dehydration in dichloromethane/trifluoroacetic acid (10/1) overnight, colourless needles, mp 152–153°C (from ethyl acetate, 68% yield overall). (Found: C 66.3, H 4.7, N 10.6. $C_{15}H_{13}N_2ClO$ requires C 66.1, H 4.8, N 10.3%). δ_H ($CDCl_3$) 1.07 (3H, t, *J* 7.6, CH_2Me), 2.32 (3H, s, ArMe), 2.68 (2H, q, *J* 7.6, CH_2Me), 4.67 and 5.30 (1H, H, each d, *J* 2.6, =CH_2), 7.20–7.42 (3H, m, ArH). δ_C ($CDCl_3$) 14.2, 18.1, 20.5, 99.8, 107.1, 112.5, 128.0, 129.5, 129.5, 130.5, 134.7, 140.1, 143.4, 163.1, 163.9.

*4-Butyl-1-(2-chloro-6-methylphenyl)-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4g***

Obtained without purification of the crude hydroxy compound by dehydration in dichloromethane/trifluoroacetic acid (10/1) overnight, mp 101–102°C (prisms from ether/light petroleum, 42% overall yield). (Found: C 67.8, H 5.6, N 9.5. $C_{17}H_{17}ClN_2O$ requires C 67.9, H 5.7, N 9.3%). δ_H ($CDCl_3$) 1.0 (3H, t, *J* 7, CH_2Me), 1.37–1.55 (2H, m, CH_2Me), 1.68–1.83 (2H, m, CH_2CH_2Me), 2.15 (3H, s, ArMe), 2.81 (2H, t, *J* 7, $CH_2CH_2CH_2$Me), 4.64 (1H, d, *J* 2.5, HHC=), 5.23 (1H, d, *J* 2.5, HHC=), 7.2–7.4 (3H, m, 3ArH). δ_C ($CDCl_3$) 13.7, 18.1, 22.6, 26.9, 32.0, 99.9, 107.6, 111.8, 128.0, 129.5, 129.8, 130.5, 134.1, 140.1, 143.0, 162.3, 162.6.

*1-(2-Methyl-6-isopropyl)phenyl-5-methylene-2-oxo-4- isopropyl-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4h***

Obtained without isolation of the crude hydroxy compound by dehydration in dichloromethane/trifluoroacetic acid (10/1) overnight, mp 149–152°C (needles from isopropyl alcohol, 61% overall yield). (Found: C 77.3, H 7.7, N 9.6. $C_{19}H_{22}N_2O$ requires C 77.5, H 7.5, N 9.5%). δ_H ($CDCl_3$) 1.12, 1.15 (3H, 3H, each d, *J* 7, $CHMe_2$), 1.49, 1.52 (3H, 3H, each d, *J* 7, $CHMe_2$), 2.2 (3H, s, ArMe), 2.59 (1H, sept., *J* 7, $CHMe_2$), 3.16 (1H, sept., *J* 7, 1H, $CHMe_2$), 4.65, 5.26 (1H, 1H, each d, *J* 2, =CH_2), 7.03–7.40 (3H, m, ArH). δ_C ($CDCl_3$) 17.8, 21.8, 22.0, 23.6, 24.3, 27.5, 28.6, 99.9, 124.4, 128.5, 129.3, 129.9, 130.4, 144.2, 148.0, 167.2.

*1-(4-Cyanophenyl)-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3i***

Obtained from the reaction between the cyanoacetamide **1i** and butanedione to afford the hydroxy compound mp 222–224°C (72%) as colourless prisms from ethanol. (Found: C 66.4, H 4.1, N 16.6. $C_{14}H_{11}N_3O_2$ requires C 66.4, H 4.4, N 16.6%). ν_{max} (KBr)/cm^{-1} 3329, 2923, 2856, 2233, 1699, 1686, 1600. δ_H ($(CD_3)_2SO$) 1.42 (3H, s, C(OH)Me), 2.30 (3H, s, Me–C=), 7.80, 7.84 (2H, 2H, each d, *J* 9.0, 4ArH). *m/z* APCI$^+$ 254, 227, 210, 156, 119, 117.

When a solution containing D_2O was left 24 h and the spectrum rerun, the peak at δ 2.30 had decreased by 40% relative to the other absorptions which were unchanged. After 4 days most of this peak had vanished.

*1-(4-Cyanophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4i***

By elimination of water from the crude hydroxy compound **3i** in dichloromethane/trifluoroacetic acid (10/1) overnight, pale yellow needles were isolated, mp 239–240°C from dichloromethane/methanol (81%). (Found: C 71.5, H 3.7, N 18.0. $C_{14}H_9N_3O$ requires C 71.5, H 3.9, N 17.9%). ν_{max} (KBr)/cm^{-1} 2930, 2856, 2227, 1708, 1633, 1606. δ_H ($(CD_3)_2SO$) 2.52 (3H, s, Me), 5.26, 5.70 (1H, 1H, each d, *J* 3.1, =CH_2), 7.58, 8.10 (2H, 2H, each d, *J* 8.7, 4ArH) (no change during 4 days in DMSO/D_2O).

*1-Cyclohexyl-4,5-dimethyl-5-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3j***

A solution of the cyanoacetamide (3.32 g, 20 mmol) in DMF (10 mL) was treated with butane-2,3-dione (1.72 g, 20 mmol) followed by morpholine (two drops). The next day the mixture containing a substantial precipitate of colourless plates was diluted with aqueous ethanol (10 mL,

50%), digested at 75°C for 10 min, cooled, filtered off, and washed on the filter with aqueous ethanol (70%). Drying gave the crude hydroxy compound as pink-tinted plates (4.1 g, 95%), mp 200–202°C. Recrystallization from aqueous isopropyl alcohol gave the product as colourless plates, mp 201–203°C. (Found: C 66.5, H 7.6, N 11.9. $C_{13}H_{18}N_2O_2$ requires C 66.6, H 7.7, N 11.9%). ν_{max} (KBr)/cm^{-1} 3344, 2925, 2855, 2235, 1679. *m/z* APCI$^+$ 235, 218, 217, 208, 153. δ_H ($CDCl_3$/$(CD_3)_2SO$ 10/1) 1.05–1.23 (4H, m, cyclohexyl), 1.33 (3H, s, C(OH)Me), 1.4–1.88 (4H, m, cyclohexyl), 1.95–2.1 (2H, m, cyclohexyl), 2.17 (3H, s, Me) (reduction by 80% of this peak with D_2O in DMSO over 4 days at RT), 3.1–3.3 (1H, m, N–CH), 4.6–5.0 (1H, br, OH). δ_C ($CDCl_3$/$(CD_3)_2SO$ 1/1) 12.6, 22.1, 25.0, 26.1, 30.1, 32.4, 90.4, 108.4, 113.5, 162.8, 173.3.

*1-Cyclohexyl-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4j***

A suspension of the hydroxy compound (1.0 g) in formic acid (4.6 g, 98%) was stirred for 2 h and the resulting solution was left to stand overnight. The next day the solution was diluted with water (5 mL), stirred for 2 h, and the precipitate collected by filtration to afford the lactam (0.85 g, 92%), mp 140–142°C. A portion was recrystallized from methanol to give colourless plates, mp 143–145°C. (Found: C 72.1, H 7.4, N 12.9. $C_{13}H_{16}N_2O$ requires C 72.2, H 7.5, N 13.0%). δ_H ($CDCl_3$) 1.05–2.10 (10H, m, cyclohexyl), 2.33 (3H, s, Me) (no exchange observed as a solution in DMSO over 4 days with D_2O), 3.75–3.95 (1H, m, N–CH), 5.18 (1H, d, *J* 2.8, =C(H)H), 5.24 (1H, d, *J* 2.8, =C(H)H). δ_C ($CDCl_3$) 12.4, 25.3, 26.2, 29.9, 53.2, 99.4, 108.1, 112.1, 144.3, 157.5, 163.9.

*1-(1-(4-Chloronaphthyl)-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3k***

The cyanoacetamide **1k** and butane-2,3-dione gave colourless plates, mp 207–209°C (from benzene, 62%). (Found: C 65.1, H 4.0, N 9.0. $C_{17}H_{13}N_2O_2Cl$ requires C 65.3, H 4.2, N 9.0%). δ_H (mixture of diastereomers approx. 2:1, $CDCl_3$) 1.28, 1.57 (3H, s, s (2:1), C(OH)Me), 2.35, 2.36 (3H, s, s (2:1), Me), 6.97, 7.09 (1H, s, s (1:2), C(OH)Me, exchanges with D_2O), 7.49, 7.56 (1H, d, d (1:2), *J* 7.9, ArH), 7.65 (1H, m, ArH), 7.73 (1H, m, ArH), 7.82 (2H, m, 2ArH), 8.26 (1H, m, ArH).

*1-(1-(4-Chloronaphthyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4k***

Formed by dehydration of the hydroxy compound **3k** with trifluoroacetic acid overnight, mp 189–191°C (recrystallized from isopropyl alcohol, 65%). (Found: C 69.1, H 3.4, N 9.6. $C_{17}H_{11}N_2OCl$ requires C 69.3, H 3.8, N 9.5%). δ_H ($CDCl_3$) 2.53 (3H, s, Me), 4.69, 5.24 (1H, 1H, each d, *J* 2.7, C=CH_2), 7.34 (1H, d, *J* 7.8, ArH), 7.4–7.75 (4H, m, 4ArH), 8.36 (1H, d, *J* 7.8, ArH). δ_C ($(CD_3)_2SO$) 12.6, 101.4, 107.7, 112.3, 122.9, 125.4, 125.9, 127.4, 127.9, 128.2, 129.6, 132.4, 133.5, 134.5, 145.9, 158.1, 164.5. ν_{max} (KBr)/cm^{-1} 3418, 2238, 1713, 1633.

*1-[2-(5-Chloropyridyl)]-4,5-dimethyl-5-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3l***

Condensation overnight of the cyanoacetamide **1l** with butane-2,3-dione gave prisms, mp 167–168°C (55% yield) from ethanol. (Found: C 54.7, H 3.8, N 16.0, Cl 13.3. $C_{12}H_{10}ClN_3O_2$ requires C 54.7, H 3.8, N 15.9, Cl 13.5%). *m/z* APCI$^+$ 249, 248, 246, 131, 129. ν_{max} (Nujol)/cm^{-1} 3390, 2927, 2856, 2238, 1715. δ_H ($(CD_3)_2SO$) 1.73, 2.27 (3H, 3H, each s, 2Me), 7.8–8.5 (3H, m, pyridyl). δ_C ($(CD_3)_2SO$) 12.8, 22.9, 92.3, 106.9, 111.9. 118.9, 127.5, 138.0, 146.3, 148.2, 162.3, 176.6.

*1-[2-(5-Chloropyridyl)]-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4l***

Colourless needles from methanol, mp 175–177°C (dehydration with trifluoroacetic acid for 48 h, 51% yield). (Found: C 58.8, H 3.3, N 17.1, Cl 14.3. $C_{12}H_8ClN_3O$ requires C 58.7, H 3.3, N 17.1, Cl 14.4%). δ_H ($CDCl_3$) 2.55 (3H, s, Me), 5.50, 6.08 (1H, 1H, each d, *J* 2.1, =CH_2), 7.69, 7.83, & 8.47 (3H, m, 3 pyridylH). δ_C ($CDCl_3$) 12.4, 105.1, 107.2, 111.4, 120.8, 130.1, 138.2, 142.6, 146.6, 147.2, 159.2, 163.2.

*5-Hydroxy-4,5-dimethyl-1-(5-methyl[1,3,4]thiadiazol-2-yl)-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3m***

From butane-2,3-dione and **1l**, 61%, mp 216–218°C (ethanol). (Found: C 48.0, H 4.0, N 22.4, S 12.8. $C_{10}H_{10}N_4O_2S$ requires C 47.9, H 4.0, N 22.4, S 12.8%). ν_{max} (Nujol)/cm^{-1} 2926, 2856, 2238, 1723, 1651. δ_H ($(CD_3)_2SO$) 1.91 (3H, s, C(OH)Me), 2.34 (3H, s, MeC=), 2.66 (3H, s, ArMe), 7.56 (1H, s, OH (exch. D_2O)). After 24 h in the presence of D_2O, the peak at δ 2.34 had diminished by 50% and after 7 days it had exchanged completely. δ_C ($(CD_3)_2SO$) 13.0, 14.7, 21.2, 93.4, 105.9, 111.4, 154.8, 180.0, 161.1, 178.2.

*Formation of 4-Methyl-5-methylene-1-(5-methyl[1,3,4]thiadiazol-2-yl)-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4m***

A solution of the hydroxy compound **3m** showed little change by TLC after standing at room temperature for 24 h in trifluoroacetic acid; trifluoromethane sulfonic acid effected elimination but the product obtained by precipitation with water gradually decomposed during attempted recrystallization. δ_H ($CDCl_3$) 2.51, 2.76 (3H, 3H, each s, 2Me), 5.87, 7.37 (1H, 1H, each d, *J* 2.2, =CH_2).

*1-[(4-Chlorobenzylidene)amino]-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3n***

Yellow plates from chloroform/methanol, mp 165–166°C (41%). (Found: C 58.1, H 4.2, N 14.5, Cl 12.1. $C_{14}H_{12}ClN_3O_2$ requires C 58.0, H 4.2, N 14.5, Cl 12.2%). *m/z* APCI$^+$ 290, 275, 274, 272, 263, 157, 155, 140, 138, 99. ν_{max} (KBr)/cm^{-1} 3378, 2922, 2858, 2239, 1709, 1693. δ_H ($CDCl_3$) 1.71, 2.38 (3H, 3H, each s, 2 × Me), 4.19 (1H, br s, OH), 7.29, 7.60 (2H, 2H, each d, *J* 8.4, ArH), 9.44 (1H, s, =CH). After 24 h in the presence of D_2O, the signal at δ 2.38 had diminished by 30%. δ_C ($CDCl_3$) 13.3, 22.1, 90.8, 108.5, 110.8, 128.6, 128.8, 132.6, 136.7, 151.3, 159.5, 172.9.

This material failed to give a stable product following treatment with trifluoroacetic acid.

*4,5-Dimethyl-1-ethoxycarbonyl-5-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3o***

From ethyl *N*-cyanoacetylcarbamate and butane-2,3-dione to afford colourless prisms from isopropyl alcohol (68%), mp 136–138°C. (Found: C 53.4, H 5.2, N 12.2. $C_{10}H_{12}N_2O_4$ requires C 53.6, H 5.4, N 12.5%). δ_H ($CDCl_3$) 1.41 (3H, t, *J* 7.1, CH_2Me), 1.82 (3H, s, C(OH)Me), 2.35 (s, Me–C=), 4.45 (q, *J* 7.1, CH_2Me), 4.51 (s, OH (exch. D_2O)).

This material failed to give a stable product upon attempted dehydration.

*Ethyl 1-(4-Chlorophenyl)-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate* ***3p***

Obtained as colourless needles (light petroleum, 61%), mp 130–131°C. (Found: C 58.1, H 5.0, N 4.6. $C_{15}H_{16}ClNO_4$ requires C 58.2, H 5.2, N 4.5%). δ_H ($CDCl_3$) 1.33 (3H, s, C(OH)Me), 1.40 (3H, t, *J* 7.0, CH_2Me), 2.48 (3H, s, MeC=), 4.28 (2H, dq, *J* 7, CH_2Me), 7.11, 7.29 (2H, 2H, each d, *J* 6.7, 4ArH). ν_{max} (KBr)/cm^{-1} 3423, 1742, 1725(sh). Weak signals due to the methylene lactam were observed in the spectrum after 15 min, apparently as a result of elimination initiated by traces of deuterium chloride; after 4 days at room temperature approx. 30% had been converted.

*Ethyl 1-(4-Chlorophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate* ***4p***

The hydroxy lactam (0.5 g) was dissolved in trifluoroacetic acid (3 mL). After 10 min at room temperature the mixture was diluted with benzene (20 mL) washed with water (2 × 20 mL) and then with aqueous 5% sodium citrate. The organic phase was collected and evaporated to yield a white solid which was recrystallized from isopropyl alcohol to afford colourless needles (271 mg, 58%), mp 114–116°C. (Found: C 61.5, H 4.8, N 4.8. $C_{15}H_{14}ClNO_3$ requires 61.8, H 4.8, N 4.8%). ν_{max} (KBr)/cm^{-1} 3001, 1710, 1620, 1492, 1386, 1344. δ_H ($CDCl_3$) 1.34 (3H, t, *J* 7.1, CH_2Me), 2.54 (3H, s, Me), 4.35 (2H, q, *J* 7.1, CH_2Me),

4.97, 5.18 (1H, 1H, d, d, each *J* 2.4, $=CH_2$), 7.20 & 7.42 (2H, 2H, each d, *J* 8.8, 4 ArH). δ_C ($CDCl_3$) 11.5, 14.2, 61.1, 98.1, 122.2, 129.0, 129.5, 132.7, 133.6, 145.9, 153.5, 163.1, 175.1.

*1-(2-(3,4-Dimethoxyphenyl)ethyl)-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3q***

Recrystallized from isopropyl alcohol to give the hydroxy compound (44% yield) as colourless needles, mp 146–148°C. (Found: C 64.6, H 6.2, N 8.8. $C_{17}H_{20}N_2O_4$ requires C 64.5, H 6.4, N 8.9%). δ_H ($CDCl_3$) 1.38, 2.22 (3H, 3H, each s, 2Me), 2.83 (2H, m, $ArCH_2$), 3.47 (2H, m, NCH_2), 3.77 (6H, s, 2OMe), 6.71 (3H, br s, 3ArH). δ_C ($CDCl_3$) 12.8, 21.6, 34.1, 41.2, 55.0 (overlapping signals), 90.3, 108.4, 111.53, 111.56, 112.2, 120.8, 131.2, 147.6, 148.9, 163.3, 174.5.

*8,9-Dimethoxy-1,10*b*-dimethyl-3-oxo-3,5,6,10*b*-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-carbonitrile* ***6***

The hydroxy compound **3q** (0.63 g) was dissolved in formic acid (3 mL, 95%), the solution left to stand for 6 h, and then diluted with water (10 mL). The precipitate was collected by filtration and purified by chromatography over silica gel. The material obtained by eluting with light petroleum/ethyl acetate (25/75) was recrystallized from ethyl acetate/light petroleum to give the product as colourless needles (0.36 g, 61%), mp 194–195°C. (Found: C 68.5, H 6.0, N 9.5. $C_{17}H_{18}N_2O_3$ requires C 68.4, H 6.1, N 9.4%). δ_H ($CDCl_3$) 1.68, 2.73 (3H, 3H, each s, 2 × Me), 2.5–2.7 (1H, m, –CHHCH$_2$–), 2.8–3.2 (2H, m, –NCHHCH$_2$–), 3.81, 3.88 (6H, each s, 2 × OMe), 4.4–4.5 (1H, m, –NCHHCH$_2$–), 6.60, 7.79 (1H, 1H, each s, 2ArH). δ_C ($CDCl_3$) 15.3, 26.7, 29.8, 36.3, 55.9, 56.3, 67.3, 109.1, 109.8, 111.9, 112.3, 126.2, 126.5, 147.1, 148.8, 164.8, 176.8.

*5-Hydroxy-4,5-dimethyl-2-oxo-1-(2-(phenyl)ethyl)-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3r***

The hydroxy compound (37%) crystallized from ethyl acetate/light petroleum as woolly needles, mp 135–136°C. (Found: C 70.2, H 6.1, N 10.6. $C_{15}H_{16}N_2O_2$ requires C 70.3, H 6.3, N 10.9%). δ_H ($CDCl_3$) 1.37, 2.21 (3H, 3H, each s, 2Me), 2.8–3.2 (2H, m, $PhCH_2$), 3.4–3.8 (2H, m, NCH_2), 7.2 (5H, m, Ph). δ_C ($CDCl_3$) 12.9, 21.5, 34.6, 41.3, 90.3, 108.5, 111.6, 126.7, 128.7, 128.8, 138.6, 163.4, 174.5.

*4-Methyl-5-methylene-2-oxo-1-(2-phenylethyl)-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4r***

The action of formic acid on **3r** over 48 h gave the methylene lactam (56%), mp 130–131°C (aqueous ethanol). (Found: C 75.4, H 6.0, N 11.6. $C_{15}H_{14}N_2O$ requires C 75.6, H 5.9, N 11.8%). δ_H ($CDCl_3$) 2.35 (3H, s, Me), 2.87 (2H, t, *J* 10, $PhCH_2$), 3.86 (2H, t, *J* 10, CH_2N), 4.96, 5.14 (1H, 1H, each d, *J* 2, $=CH_2$), 7.1–7.4 (5H, m, Ph). δ_C ($CDCl_3$) 12.2, 34.5, 41.6, 98.5, 108.0, 111.8, 126.8, 128.67, 128.72, 137.9, 144.5, 157.5, 163.7.

*4,5-Dimethyl-5-hydroxy-2-oxo-1-(3,4-dimethoxyphenylmethyl)-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***3s***

Condensation of the cyanoacetamide **1s** and butane-2,3-dione in the usual way gave the hydroxy compound (52%), mp 138–139°C (ethanol). (Found: C 63.4, H 65.7, N 9.1. $C_{16}H_{18}N_2O_4$ requires C 63.6, H 6.0, N 9.3%). δ_H ($CDCl_3$) 1.31, 2.19 (3H, 3H, each s, 2Me), 3.78, 4.06 (3H, 3H, each s, 2OMe), 4.38 (1H, br s, OH), 4.46, 4.61 (1H, 1H, each d, *J* 16, CH_2), 6.7–7.0 (3H, m, 3ArH). δ_C ($CDCl_3$) 12.7, 22.3, 42.1, 55.8, 55.9, 90.6, 108.1, 111.1, 111.4, 111.5, 120.5, 130.0, 148.3, 148.8, 163.5, 175.1.

*1-(3,4-Dimethoxyphenyl)methyl-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4s***

A solution of the hydroxy compound (0.45 g) in trifluoroacetic acid (2 mL) was diluted with water (3 mL) after 16 h, the precipitate was filtered off, washed with water, and recrystallized from isopropyl alcohol to give the methylene lactam **4s** (0.33 g, 79%), mp 116–117°C. (Found: C 67.5, H 5.4, N 9.8. $C_{16}H_{16}N_2O_3$ requires C 67.6, H 5.7, N 9.9%). δ_H ($CDCl_3$) 2.33 (3H, s, Me), 3.87, 3.89 (3H, 3H, each s, 2OMe), 4.86 (2H, s, CH_2), 5.12, 5.21 (1H, 1H, each d, *J* 2, $=CH_2$), 6.6–7.0 (3H, m, 3ArH). δ_C ($CDCl_3$) 12.1, 43.4, 55.75, 55.82, 100.0, 107.5, 110.5, 111.0, 111.8, 119.5, 128.3, 144.1, 148.6, 149.2, 157.9, 163.9.

*1-Cyclohexyl-2-oxo-2,4,5,6-tetrahydro-1*H*-indole-3-carbonitrile* ***5***

Obtained from the reaction between cyclohexane-2,3-dione and **1j**, followed by extraction of the crude hydroxy compound with dichloromethane and dehydration overnight as a solution in formic acid, mp 131–132°C (67%, colourless prisms from ethanol). (Found: C 74.2, H 7.4, N 11.3. $C_{15}H_{18}N_2O$ requires C 74.4, H 7.5, N 11.6%). δ_H ($CDCl_3$) 1.08–1.46 (3H, m), 1.61–2.3 (9H, m), 2.44 (2H, dd, *J* 5.8), 2.81 (2H, m), 3.8–4.1 (1H, m, N–CH), 6.11 (1H, t, *J* 4.8, CH_2–CH=). δ_C ($CDCl_3$) 22.2, 24.3, 24.8, 25.2, 26.0, 30.3, 52.3, 102.0, 112.3, 118.4, 137.3, 157.1, 164.2.

*Reversible Sulfinate Addition to 1-(4-Chlorophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile* ***4b***

Sodium 4-toluenesulfinate (200 mg) was added to a suspension of **4b** (100 mg) in formic acid (1.5 mL). The mixture was warmed to 90°C for 5 min, cooled to room temperature, and the precipitate was filtered off to yield the crude adduct (116 mg). δ_H ($CDCl_3$/CF_3COOH 10/1) 2.44, 2.53 (3H, 3H, s, 2Me), 3.66 (2H, d, *J* 3.7, CH_2CH), 5.24 (1H, t, *J* 3.7, CH_2CH), 7.03 (2H, d, *J* 8.6, 2ArH), 7.35 (2H, d, *J* 8.6, 2ArH), 7.49 (2H, d, *J* 8.2, 2ArH), 7.72 (2H, d, *J* 8.2, 2ArH), peaks characteristic of the methylene lactam starting material were evident in the spectrum at 5.27 (1H, d, *J* 2.7, =C(H)H) and 5.60 (1H, d, *J* 2.7, =C(H)H), which integrated for 15–20% of the total material. Chromatography of a solution of this crude adduct (80 mg) in dichloromethane over silica gel resulted in elution of **4b** (30 mg, 61%).

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