Conjugated Azoalkenes. Part 13.[1] Facile and High-yield Synthesis of New 1-Amino-3-cyano-2,3-dihydropyrrol-2-ols and 1-Amino-3-cyano-1*H*-pyrrol-2(3*H*)-ones

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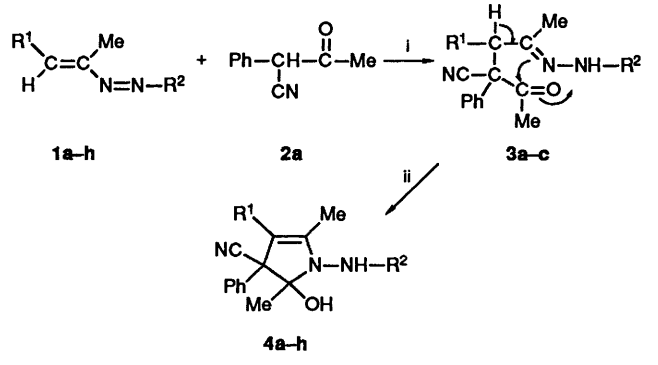
Cyano derivatives containing active methine hydrogen readily underwent 1,4-conjugate addition to conjugated azoalkenes, to give initially hydrazones which cyclised to 1-amino-3-cyano-2,3-dihydropyrrol-2-ols and 1-amino-3-cyano-1*H*-pyrrole-2(3*H*)-ones. Both processes took place in high yield and under mild reaction conditions.

Recently we reported that reaction of conjugated azoalkenes with β-cyano ketones gives 1-aminopyrrole-3-carbonitriles or 1,3a,6,6a-tetrahydropyrrolo[2,3-*b*]pyrroles depending on the molar ratios of the reagents.[1] In both cases reaction proceeds by initial 1,4-conjugate addition of the β-cyano ketones to the azo-ene system, and heterocyclisation at this stage gives the 1-aminopyrrole-3-carbonitriles. Alternatively, further addition of the intermediate 1,4-adduct to an excess of the azoalkene leads to a bis-adduct, double ring closure of which gives the 1,3a,6,6a-tetrahydropyrrolo[2,3-*b*]pyrroles. We have also shown that the related condensations of β-cyano esters with the azoalkenes resulted in two successive 1,4-conjugate additions followed by double ring closure to the cyano groups to give, *via* a postulated iminopyrroline intermediate, pyrrolo[2,3-*b*]-pyrroles as the exclusive products.[2] Finally, some years ago we described the preparation of 2,3-dihydropyrrol-2-ols by reaction of conjugated azoalkenes with β-dicarbonyl compounds.[3a] These various reactions, which generally proceed in excellent yield and under very mild reaction conditions, are simple and flexible methods for the preparation of a wide range of highly substituted mono- and bi-cyclic five-membered heterocyclic compounds. In continuation of our work in this area we now describe the reactions of conjugated azoalkenes with cyano derivatives containing active methine hydrogen.

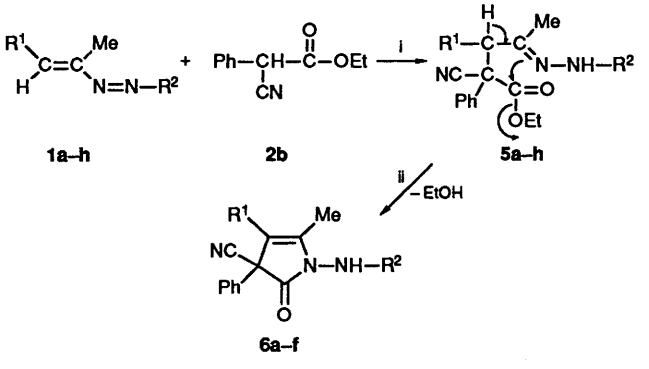
Results and Discussion

The conjugated azoalkenes **1a–h** undergo smooth reaction with α-acetylphenylacetonitrile **2a** in the presence of a catalytic amount of sodium methoxide to give, in high yield and *via* the 1,4-addition adducts **3**, the 1-amino-2-hydroxy-2,3-dihydropyrrole-3-carbonitriles **4a–h** (Scheme 1). When tetrahydrofuran (THF) was used as solvent with azoalkenes **1a–h**, at room temperature, the red colour of the conjugated azoalkene was not discharged until after *ca.* 10 min. TLC examination of the mixture at this stage revealed that both the hyrazone intermediates **3** and the dihydropyrroles **4a–h** were present in the mixtures in varying amounts. Attempts to isolate the pure intermediates **3** in the cases of the reactions with the azoalkenes **1a–h** under the same conditions were unsuccessful, and only the dihydropyrroles **4a–d** could be directly isolated, even after only a few minutes. In the cases of the azoalkenes **1e–h**, the reactions in THF at room temperature did not proceed to completion. They were carried through to completion by heating the mixture under reflux for a further 8–17 h, and the dihydropyrroles **4e–h** were obtained in high yield. In the case of azoalkenes **1e–g**, reaction with **2a** in methanol at 0–5 °C resulted in the separation of colourless powders from solution. These could be isolated and characterised as the hydrazono derivatives **3a–c**. Even at 0–5 °C, however, monitoring of the mixtures by TLC revealed that both the intermediates **3a–c** and the cyclised products **4e–g** were present in solution. Attempts to isolate the pure intermediates **3** under the same conditions were unsuccessful in the other cases. Yields and reaction times for preparation of the intermediates **3a–c** and the 1-amino-2-hydroxy-2,3-dihydropyrrole-3-carbonitriles **4a–h** are given in Table 1.

We have also studied the base-catalysed reactions of the conjugated azoalkenes **1a–h** with ethyl phenylcyanoacetate **2b** in THF (Scheme 2). Use of sodium methoxide as base at room temperature results in rapid, high yield formation of the hydrazone intermediates **5a–h**, but attempted cyclisation of these with preformed methoxide as base led to the formation of



Scheme 1 *Reagents and conditions:* i, THF–MeONa, room temp.; ii, room temp. or heat



Scheme 2 *Reagents and conditions:* i, THF–MeONa, room temp.; ii, THF–MeOH, NaH, room temp

Table 1 Yields and reaction times for the synthesis of intermediates **3a–c** and pyrroles **4a–h** from conjugated azoalkenes **1a–h** and α-acetylphenylacetonitrile **2a**

1	2	R^1	R^2	t/h 3	t/h 4	Product 3	Product 4	Yield[a] (%) 4
a	**a**	CO_2Me	CO_2Me	*b*	0.2[d]	*a*	**a**	91
b	**a**	CO_2Et	CO_2Me	*b*	0.2[d]	*a*	**b**	93
c	**a**	CO_2Me	CO_2Bu^t	*b*	0.2[d]	*a*	**c**	98
d	**a**	CO_2Et	CO_2Bu^t	*b*	0.2[d]	*a*	**d**	94
e	**a**	CO_2Me	$CONH_2$	2.0[c]	0.2/08.0[e]	**a**	**e**	80
f	**a**	CO_2Et	$CONH_2$	1.0[c]	0.2/10.0[e]	**b**	**f**	81
g	**a**	CO_2Me	CONHPh	0.5[c]	0.2/17.0[e]	**c**	**g**	83
h	**a**	CO_2Et	CONHPh	*b*	0.2/12.0[e]	*a*	**h**	88

[a] Yield of pure isolated product. [b] The reaction directly provided pyrroles **4a–d** and **4h**, without the possibility to isolate the intermediates **3**. [c] Reaction time for the formation of the intermediates **3a–c**. [c] Reaction time for the formation of the intermediates **3a–c** in methanol at 0–5 °C. [d] Reaction time for the direct conversion at room temperature of the starting materials **1a–d** and **2a** into pyrroles **4a–d**. [e] The first reaction time indicates the time at room temperature for the disappearance of conjugated azoalkenes **1e–h**, and the second reaction time refers to the additional time under reflux for the complete formation of pyrroles **4e–h**.

Table 2 Yield data for the synthesis of hydrazones **5a–h** and pyrroles **6a–f** from conjugated azoalkenes **1a–h** and ethyl phenylcyanoacetate **2b**[a]

1	2	R^1	R^2	Product 5	Product 6	Yield[b] (%) 5	Yield[b] (%) 6
a	**b**	CO_2Me	CO_2Me	**a**	**a**	90	68
b	**b**	CO_2Et	CO_2Me	**b**	**b**	95	68
c	**b**	CO_2Me	CO_2Bu^t	**c**	**c**	97	70
d	**b**	CO_2Et	CO_2Bu^t	**d**	**d**	97	78
e	**b**	CO_2Me	$CONH_2$	**e**	**e**	95	87
f	**b**	CO_2Et	$CONH_2$	**f**	**f**	97	86
g	**b**	CO_2Me	CONHPh	**g**	*c*	78	*c*
h	**b**	CO_2Et	CONHPh	**h**	*c*	99	*c*

[a] All reaction times were 0.1 h. [b] Yield of pure isolated product. [c] The conversion of hydrazones **5g** and **5h** into pertinent pyrroles **6** produced intricate reaction mixtures.

complex mixtures of products. By contrast, the one-pot conversion of a mixture of **1a–h** and **2b** to the previously unknown 1-amino-3-cyano-1*H*-pyrrol-2(3*H*)-ones **6a–f** could be effected easily by brief treatment first with sodium methoxide to give the hydrazone intermediates **5a–h**, followed by addition of sodium hydride to induce cyclisation to **6a–f**. Each reaction only required a few minutes to go to completion, and yields of the dihydropyrroles **6a–f** were good to excellent. Yields and reaction times for the synthesis of the hydrazone intermediates **5a–h** and the 1-amino-3-cyano-1*H*-pyrrol-2(3*H*)-ones are listed in Table 2.

The overall reactivity patterns outlined in Scheme 1 are in good agreement with our previous findings that reactions of conjugated azoalkenes with β-dicarbonyl compounds gave 2,3-dihydropyrrol-2-ols, structure confirmation of which has been provided by an X-ray diffraction study.[3b] In the case of the sodium hydride induced cyclisation of the hydrazone intermediates **5a–f** to the dihydropyrroles **6a–f**, however, cyclisation rather unexpectedly involves the ester group rather than the cyano group. As far as we are aware, with the exception of one particular case[4] where electronic and mesomeric effects seem to play a determining role, this represents the first general case where heterocyclisation involves the ester group and leads to pyrrol-2-ones.[2,3,5]

Experimental

Alkoxycarbonylazoalkenes[6] **1a–d** and aminocarbonylazoalkenes[7] **1e–h** were prepared as previously reported. α-Acetylphenylacetonitrile **2a** and ethyl phenylcyanoacetate **2b** were commercial materials (Aldrich) and were used without further purification. M.p.s were determined in capillary tubes with a Buchi apparatus, and are uncorrected. Frequently, the range of m.p. is large because the products are mixtures of isomeric forms, and the products often decompose at the m.p. Yields are of isolated products. IR spectra were obtained for Nujol mull or in solution (CCl_4) with a Perkin-Elmer 298 spectrophotometer. All ^1H NMR spectra at 200 MHz were recorded with a Bruker AC-200 spectrometer in [$^2H_6$]-DMSO solution. Chemical shifts (δ) are reported downfield from Me_4Si as internal standard. The abbreviations used are as follows: s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet; br, broad; D_2O-exch., D_2O exchange. Macherey–Nagel precoated silica gel SIL G-25 UV_{254} plates (0.25 mm) were employed for analytical thin layer chromatography (TLC), and Baker silica gel (0.063–0.200 mm) for column chromatography. All compounds prepared gave satisfactory elemental analyses (C ± 0.4; H ± 0.4; N ± 0.3%).

Typical Procedure for the Synthesis of 1-*Amino*-2-*hydroxy*-2,3-*dihydropyrrole*-3-*carbonitriles* **4a–h**.—To a stirred solution of the azoalkene **1a–h** (1 mmol) in THF (3 cm^3) was added dropwise a solution of α-acetylphenylacetonitrile **2a** (1 mmol) and sodium methoxide (0.1 mmol) in THF (3 cm^3). The mixture was magnetically stirred at room temperature until the orange–red colour of the azoalkene disappeared and checked by TLC. In the case of azoalkenes **1a–d** the reaction directly afforded the products **4** in *ca.* 10 min, while in the case of the azoalkenes **1a–h** a TLC check revealed as major components two spots corresponding to the intermediate **3** and product **4** in different ratio. In this last case the reaction was completed by heating under reflux for an additional 8–17 h, until the intermediate **3** was completely converted into relevant product **4**. In all cases, THF was evaporated under reduced pressure and the crude pyrroles **4a–h** were purified by chromatography on a silica gel column (cyclohexane–ethyl acetate). Further purification was effected by crystallization from dichloromethane–pentane (or light petroleum 30–60 °C). For the isolation of the 1,4-adduct intermediate **3a–c** the reaction was carried out at 0–5 °C (ice-bath) using methanol as solvent. The white solid which formed was collected by filtration.

Typical Procedure for the Synthesis of 1-*Amino*-3-*cyano*-1H-*pyrrole*-2(3H)-*ones* **6a–f**.—To a stirred solution of the azoalkene **1a–h** (1 mmol) in THF (3 cm^3) was added dropwise a solution of ethyl phenylcyanoacetate **2b** (1 mmol) and sodium methoxide

(0.1 mmol) in THF (3 cm^3). The mixture was magnetically stirred at room temperature (~5 min) until the reaction was complete (TLC: two spots as major components). The products were purified by chromatography on a silica gel column (cyclohexane–ethyl acetate) and identified as mixtures of isomers of the 1,4-adduct intermediates **5a–h**. To a stirred solution of the adduct **5a–h** (1 mmol) in THF–CH_3OH (1:1, 6 cm^3) was added a catalytic amount of NaH. The conversion occurred rapidly (*ca.* 5 min) and was monitored by TLC. Alternatively, the two above-described reactions may be carried out in one-flask. The first mixture was allowed to stand in THF at room temperature with sodium methoxide under magnetic stirring until conjugated azoalkenes disappeared (monitoring by TLC). Then freshly prepared sodium methoxide, from sodium hydride and methanol, was added to the reaction mixture. Finally, the reaction mixture was concentrated to a small volume under reduced pressure, and the residue was dissolved in ethyl acetate and the solution extracted with aqueous sulfuric acid (1%). The organic phase was separated, washed with water, dried (magnesium sulfate), and concentrated under reduced pressure to give the pyrroles **6a–f**. The products **6** were purified by chromatography on a silica gel column (cyclohexane–ethyl acetate). Further purification was effected by crystallization from THF–pentane or dichloromethane–light petroleum, b.p. 30–60 °C.

Intermediates **3**.—*Methyl* 4-*cyano*-2-(*methoxycarbonylhydrazono*)-5-*oxo*-4-*phenylhexane*-3-*carboxylate* **3a**. M.p. 179–183 °C; ν_{max}/cm^{-1} 3460, 3340, 3280, 3220, 2240, 1740, 1720, 1695 and 1585; δ_H 1.62 (3 H, s, COMe), 2.32 (3 H, s, Me), 3.71 (3 H, s, CO_2Me), 4.73 (1 H, s, CH), 6.30 (2 H, br s, NH_2, D_2O-exch.), 7.40–7.54 (5 H, m, Ph) and 9.26 (1 H, s, NH, D_2O-exch.) (Found: C, 58.3; H, 5.6; N, 17.2. $C_{16}H_{18}N_4O_4$ requires C, 58.2; H, 5.5; N, 17.0%).

Ethyl 4-*cyano*-2-(*methoxycarbonylhydrazono*)-5-*oxo*-4-*phenylhexane*-3-*carboxylate* **3b**. M.p. 157–160 °C; ν_{max}/cm^{-1} 3460, 3340, 3290, 3220, 2240, 1740, 1720, 1700 and 1580; δ_H 1.19 (3 H, t, *J* 7, CO_2CH_2*Me*), 1.63 (3 H, s, COMe), 2.32 (3 H, s, Me), 4.13–4.23 (2 H, q, *J* 7, CO_2*CH*$_2$Me), 4.72 (1 H, s, CH), 6.30 (2 H, br s, NH_2, D_2O-exch.), 7.40–7.54 (5 H, m, Ph) and 9.29 (1 H, s, NH, D_2O-exch.) (Found: C, 59.5; H, 5.6; N, 16.4. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.8; N, 16.3%).

Methyl 2-(tert-*butoxycarbonylhydrazono*)-4-*cyano*-5-*oxo*-4-*phenylhexane*-3-*carboxylate* **3c**. M.p. 164–168 °C; ν_{max}/cm^{-1} 3365, 3200, 3095, 2240, 1745, 1730, 1680 and 1590; δ_H 1.73 (3 H, s, COMe), 2.35 (3 H, s, Me), 3.72 (3 H, s, CO_2Me), 4.91 (1 H, s, CH), 7.00–7.57 (10 H, m, 2 × Ph), 8.39 (1 H, s, NH, D_2O-exch.) and 9.84 (1 H, s, NH, D_2O-exch.) (Found: C, 64.8; H, 5.6; N, 14.0. $C_{22}H_{22}N_4O_4$ requires C, 65.0; H, 5.5; N, 13.8%).

Pyrroles **4**.—*Methyl* 4-*cyano*-5-*hydroxy*-1-(*methoxycarbonylamino*)-5-*methyl*-4-*phenyl*-4,5-*dihydropyrrole*-3-*carboxylate* **4a**. M.p. 77–82 °C; ν_{max}/cm^{-1} 3290, 2240, 1735, 1690 and 1530; δ_H 0.80 and 1.52 (3 H, 2 s, Me), 2.22 and 2.24 (3 H, 2 s, Me), 3.43 and 3.48 (3 H, 2 s, CO_2Me), 3.60 and 3.66 (3 H, 2 s, CO_2Me), 6.40 and 7.30 (1 H, 2 s, OH, D_2O-exch.), 7.33 and 7.36 (5 H, 2 s, Ph) and 9.50 and 9.60 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 59.3; H, 5.6; N, 12.3. $C_{17}H_{19}N_3O_5$ requires C, 59.1; H, 5.5; N, 12.2%).

Ethyl 4-*cyano*-5-*hydroxy*-1-(*methoxycarbonylamino*)-5-*methyl*-4-*phenyl*-4,5-*dihydropyrrole*-3-*carboxylate* **4b**. M.p. 58–65 °C; ν_{max}/cm^{-1} 3440, 3380, 3280, 2270, 1740, 1690 and 1535; δ_H 0.83 and 1.52 (3 H, 2 s, Me), 0.86 and 0.97 (3 H, 2 t, *J* 7, CO_2CH_2*Me*), 2.22 and 2.24 (3 H, 2 s, Me), 3.61 and 3.66 (3 H, 2 s, CO_2Me), 3.88–3.98 (2 H, m, CO_2*CH*$_2$Me), 6.40 and 7.30 (1 H, 2 s, OH, D_2O-exch.), 7.33 and 7.36 (5 H, 2 s, Ph) and 9.50 and 9.60 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 59.9; H, 5.7; N, 12.0. $C_{18}H_{21}N_3O_3$ requires C, 60.2; H, 5.9; N, 11.7%).

Methyl 1-(tert-*butoxycarbonylamino*)-4-*cyano*-5-*hydroxy*-5-*methyl*-4-*phenyl*-4,5-*dihydropyrrole*-3-*carboxylate* **4c**. M.p. 77–88 °C; ν_{max}/cm^{-1} 3390, 3230, 2240, 1700, 1680 and 1625; δ_H 0.83 and 1.52 (3 H, 2 s, Me), 1.40 and 1.43 (9 H, 2 s, Bu^t), 2.21 and 2.24 (3 H, 2 s, Me), 3.42 and 3.47 (3 H, 2 s, CO_2Me), 6.30 and 7.21 (1 H, 2 s, OH, D_2O-exch.), 7.30 and 7.34 (5 H, 2 s, Ph) and 8.70 and 9.50 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 61.8; H, 6.7; N, 10.6. $C_{20}H_{25}N_3O_5$ requires C, 62.0; H, 6.5; N, 10.8%).

Ethyl 1-(tert-*butoxycarbonylamino*)-4-*cyano*-5-*hydroxy*-5-*methyl*-4-*phenyl*-4,5-*dihydropyrrole*-3-*carboxylate* **4d**. M.p. 56–62 °C; ν_{max}/cm^{-1} 3435, 3385, 3280, 2280, 1740, 1720, 1690 and 1540; δ_H 0.83 and 1.52 (3 H, 2 s, Me), 0.89 and 1.00 (3 H, 2 t, *J* 7, CO_2CH_2*Me*), 1.39 and 1.43 (9 H, 2 s, Bu^t), 2.21 and 2.23 (3 H, 2 s, Me), 3.67–3.94 (2 H, m, CO_2*CH*$_2$Me), 6.30 and 7.20 (1 H, 2 s, OH, D_2O-exch.), 7.32 and 7.34 (5 H, 2 s, Ph) and 8.70 and 9.40 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 63.1; H, 6.8; N, 10.3. $C_{21}H_{27}N_3O_5$ requires C, 62.8; H, 6.8; N, 10.5%).

Methyl 4-*cyano*-5-*hydroxy*-5-*methyl*-4-*phenyl*-1-*ureido*-4,5-*dihydropyrrole*-3-*carboxylate* **4e**. M.p. 147–154 °C; ν_{max}/cm^{-1} 3500, 3400, 3360, 3260, 3220, 2240, 1700, 1680, 1630 and 1580; δ_H 0.80 and 1.53 (3 H, 2 s, Me), 2.23 and 2.26 (3 H, 2 s, Me), 3.44 and 3.48 (3 H, 2 s, CO_2Me), 6.00 (2 H, br s, NH_2, D_2O-exch.), 6.18 and 7.22 (1 H, 2 s, OH, D_2O-exch.), 7.30 and 7.37 (5 H, 2 s, Ph) and 8.00 and 8.54 (1 H, 2 br s, NH, D_2O-exch.) (Found: C, 58.2; H, 5.7; N, 16.8. $C_{16}H_{18}N_4O_4$ requires C, 58.2; H, 5.5; N, 17.0%).

Ethyl 4-*cyano*-5-*hydroxy*-5-*methyl*-4-*phenyl*-1-*ureido*-4,5-*dihydropyrrole*-3-*carboxylate* **4f**. M.p. 147–153 °C; ν_{max}/cm^{-1} 3480, 3350, 3300, 3210, 2250, 1695, 1680, 1625 and 1580; δ_H 0.81 and 1.53 (3 H, 2 s, Me), 0.88 and 1.00 (3 H, 2 t, *J* 7, CO_2CH_2*Me*), 2.23 and 2.26 (3 H, 2 s, Me), 3.88–3.99 (2 H, m, CO_2*CH*$_2$Me), 6.01 (2 H, br s, NH_2, D_2O-exch.), 6.38 and 7.32 (1 H, s, OH, D_2O-exch.), 7.33 and 7.37 (5 H, 2 s, Ph) and 8.10 and 8.58 (1 H, 2 br s, NH, D_2O-exch.) (Found: C, 59.4; H, 5.7; N, 16.5. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.8; N, 16.3%).

Methyl 4-*cyano*-5-*hydroxy*-5-*methyl*-4-*phenyl*-1-(N′-*phenylureido*)-4,5-*dihydropyrrole*-3-*carboxylate* **4g**. M.p. 129–135 °C; ν_{max}/cm^{-1} 3310, 2240, 1675, 1620, 1590 and 1530; δ_H 0.83 and 1.55 (3 H, 2 s, Me), 2.29 (3 H, s, Me), 3.47 and 3.60 (3 H, 2 s, CO_2Me), 6.27 and 7.31 (1 H, 2 s, OH, D_2O-exch.), 6.70–7.35 (10 H, m, 2 × Ph), 8.18 (1 H, s, NH, D_2O-exch.) and 8.95 (1 H, s, NH, D_2O-exch.) (Found: C, 65.2; H, 5.6; N, 13.6. $C_{22}H_{22}N_4O_4$ requires C, 65.0; H, 5.5; N, 13.8%).

Ethyl 4-*cyano*-5-*hydroxy*-5-*methyl*-4-*phenyl*-1-(N′-*phenylureido*)-4,5-*dihydropyrrole*-3-*carboxylate* **4h**. M.p. 125–132 °C; ν_{max}/cm^{-1} 3340, 3280, 3240, 2240, 1685, 1665, 1630 and 1595; δ_H 0.86 and 1.55 (3 H, 2 s, Me), 0.93 (3 H, t, *J* 7, CO_2CH_2*Me*), 2.29 (3 H, s, Me), 3.88–3.95 (2 H, m, CO_2*CH*$_2$Me), 6.30 and 7.31 (1 H, 2 s, OH, D_2O-exch.), 6.75–7.45 (10 H, m, 2 × Ph), 8.19 (1 H, s, NH, D_2O-exch.) and 9.00 (1 H, s, NH, D_2O-exch.) (Found: C, 65.8; H, 5.6; N, 13.2. $C_{23}H_{24}N_4O_4$ requires C, 65.7; H, 5.7; N, 13.3%).

Intermediates **5**.—*Ethyl* 2-*cyano*-3-(*methoxycarbonyl*)-4-(*methoxycarbonylhydrazono*)-2-*phenylpentanoate* **5a**. M.p. 136–139 °C; ν_{max}/cm^{-1} 3280, 3180, 2250, 1755, 1740, 1710 and 1490; δ_H 1.12 (3 H, t, *J* 7, CO_2CH_2*Me*), 1.50 and 1.85 (3 H, 2 s, Me), 3.38 and 3.58 (3 H, 2 s, CO_2Me), 3.66 and 3.69 (3 H, 2 s, CO_2Me), 4.05–4.25 (2 H, m, CO_2*CH*$_2$Me), 4.50 and 4.57 (1 H, 2 s, CH), 7.41–7.55 (5 H, m, Ph) and 9.80 and 10.25 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 57.7; H, 5.9; N, 11.0. $C_{18}H_{21}N_3O_6$ requires C, 57.6; H, 5.6; N, 11.2%).

Ethyl 2-*cyano*-3-(*ethoxycarbonyl*)-4-(*methoxycarbonylhydrazono*)-2-*phenylpentanoate* **5b**. M.p. 122–127 °C; ν_{max}/cm^{-1} 3330, 3200, 2240, 1755, 1740, 1720 and 1520; δ_H 0.84 (3 H, t, *J* 7, CO_2CH_2*Me*), 1.11–1.24 (3 H, m, CO_2CH_2*Me*), 1.54 and 1.87 (3 H, s, Me), 3.60 and 3.69 (3 H, 2 s, CO_2Me), 3.87 (2 H, q, *J* 7, CO_2*CH*$_2$Me), 4.13–4.21 (2 H, m, CO_2*CH*$_2$Me), 4.49 and 4.56

(1 H, 2 s, CH), 7.40–7.54 (5 H, m, Ph) and 9.89 and 10.20 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 58.3; H, 5.7; N, 10.9. $C_{19}H_{23}N_3O_6$ requires C, 58.6; H, 5.9; N, 10.8%).

Ethyl 4-(tert-*butoxycarbonylhydrazono*)-2-*cyano*-3-(*methoxycarbonyl*)-2-*phenylpentanoate* **5c**. M.p. 140–144 °C; ν_{max}/cm^{-1} 3215, 3150, 3115, 2250, 1755, 1740, 1735, 1690 and 1490; δ_H 1.08–1.14 (3 H, m, CO_2CH_2Me), 1.39 and 1.45 (9 H, 2 s, Bu^t), 1.50 and 1.85 (3 H, 2 s, Me), 3.39 and 3.70 (3 H, 2 s, CO_2Me), 4.10–4.23 (2 H, m, CO_2CH_2Me), 4.47 and 4.57 (1 H, 2 s, CH), 7.42–7.54 (5 H, m, Ph) and 9.53 and 9.83 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 60.6; H, 6.3; N, 10.2. $C_{21}H_{27}N_3O_6$ requires C, 60.4; H, 6.5; N, 10.0%).

Ethyl 4-(tert-*butoxycarbonylhydrazono*)-2-*cyano*-3-(*ethoxycarbonyl*)-2-*phenylpentanoate* **5d**. M.p. 121–125 °C; ν_{max}/cm^{-1} 3220, 3150, 3110, 2250, 1745, 1735, 1690 and 1490; δ_H 0.81 (3 H, t, *J* 7, CO_2CH_2Me), 1.07–1.15 (3 H, m, CO_2CH_2Me), 1.39 and 1.45 (9 H, 2 s, Bu^t), 1.51 and 1.83 (3 H, 2 s, Me), 3.84 (2 H, q, *J* 7, CO_2CH_2Me), 3.98–4.15 (2 H, m, CO_2CH_2Me), 4.42 and 4.52 (1 H, 2 s, CH), 7.41–7.58 (5 H, m, Ph) and 9.45 and 9.71 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 61.5; H, 6.7; N, 9.9. $C_{22}H_{29}N_3O_6$ requires C, 61.2; H, 6.8; N, 9.7%).

Ethyl 4-(*carbamoylhydrazono*)-2-*cyano*-3-(*methoxycarbonyl*)-2-*phenylpentanoate* **5e**. M.p. 138–142 °C; ν_{max}/cm^{-1} 3460, 3280, 3220, 3160, 2250, 1745, 1740, 1700, 1595 and 1490; δ_H 1.07–1.19 (3 H, m, CO_2CH_2Me), 1.60 and 1.92 (3 H, 2 s, Me), 3.44 and 3.72 (3 H, 2 s, CO_2Me), 4.06–4.20 (2 H, m, CO_2CH_2Me), 4.59 and 4.72 (1 H, 2 s, CH), 6.01 and 6.70 (2 H, 2 s, NH_2, D_2O-exch.), 7.35–7.60 (5 H, m, Ph) and 9.28 and 6.93 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 56.7; H, 5.6; N, 15.5. $C_{17}H_{20}N_4O_5$ requires C, 56.6; H, 5.9; N, 15.4%).

Ethyl 4-(*carbamoylhydrazono*)-2-*cyano*-3-(*ethoxycarbonyl*)-2-*phenylpentanoate* **5f**. M.p. 150–154 °C; ν_{max}/cm^{-1} 3460, 3280, 3230, 3160, 2240, 1755, 1740, 1705, 1595 and 1490; δ_H 0.85 (3 H, t, *J* 7, CO_2CH_2Me), 1.08–1.22 (3 H, m, CO_2CH_2Me), 1.61 and 1.91 (3 H, 2 s, Me), 3.90 (2 H, q, *J* 7, CO_2CH_2Me), 4.10–4.21 (2 H, m, CO_2CH_2Me), 4.55 and 4.75 (1 H, 2 s, CH), 6.00 and 6.80 (2 H, 2 s, NH_2, D_2O-exch.), 7.45–7.60 (5 H, m, Ph) and 9.35 and 9.81 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 57.7; H, 5.9; N, 15.0. $C_{18}H_{22}N_4O_5$ requires C, 57.9; H, 7.1; N, 14.8%).

Ethyl 2-*cyano*-3-(*methoxycarbonyl*)-2-*phenyl*-4-(N′-*phenylcarbamoylhydrazono*)*pentanoate* **5g**. M.p. 163–165 °C; ν_{max}/cm^{-1} 3360, 3200, 3090, 3060, 2250, 1740, 1735, 1690, 1680, 1595 and 1490; δ_H 0.99 and 1.15 (3 H, 2 t, *J* 7, CO_2CH_2Me), 1.75 and 2.04 (3 H, 2 s, Me), 3.49 and 3.76 (3 H, 2 s, Me), 4.08–4.22 (2 H, m, CO_2CH_2Me), 4.77 and 4.93 (1 H, 2 s, CH), 7.03–7.67 (10 H, m, 2 × Ph), 8.42 and 8.47 (1 H, 2 s, NH, D_2O-exch.) and 9.90 and 10.24 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 63.3; H, 5.5; N, 12.8. $C_{23}H_{24}N_4O_5$ requires C, 63.5; H, 5.4; N, 13.1%).

Ethyl 2-*cyano*-3-(*ethoxycarbonyl*)-2-*phenyl*-4-(N′-*phenylcarbamoylhydrazono*)*pentanoate* **5h**. M.p. 157–160 °C; ν_{max}/cm^{-1} 3360, 3190, 3090, 3060, 2240, 1740, 1730, 1690, 1680, 1595 and 1475; δ_H 0.86–1.22 (6 H, m, 2 × CO_2CH_2Me), 1.74 and 2.02 (3 H, 2 s, Me), 3.90–4.22 (4 H, m, 2 × CO_2CH_2Me), 4.70 and 4.89 (1 H, 2 s, CH), 7.28–7.70 (10 H, m, 2 × Ph), 8.40 and 8.47 (1 H, 2 s, NH, D_2O-exch.) and 9.85 and 10.25 (1 H, 2 s, NH, D_2O-exch.) (Found: C, 63.8; H, 5.9; N, 12.8. $C_{24}H_{26}N_4O_5$ requires C, 64.0; H, 5.8; N, 12.4%).

Pyrroles **6**.—*Methyl* 4-*cyano*-1-(*methoxycarbonylamino*)-2-*methyl*-5-*oxo*-4-*phenyl*-1,4-*dihydropyrrole*-3-*carboxylate* **6a**. M.p. 71–78 °C; ν_{max}/cm^{-1} 3280, 2250, 1775, 1750, 1710 and 1645; δ_H 2.49 (3 H, s, Me), 3.67 (3 H, s, CO_2Me), 3.75 (3 H, s, CO_2Me), 7.39–7.49 (5 H, m, Ph) and 10.52 (1 H, s, NH, D_2O-exch.) (Found: C, 58.2; H, 4.9; N, 12.6. $C_{16}H_{15}N_3O_5$ requires C, 58.4; H, 4.6; N, 12.8%).

Ethyl 4-*cyano*-1-(*methoxycarbonylamino*)-2-*methyl*-5-*oxo*-4-*phenyl*-1,4-*dihydropyrrole*-3-*carboxylate* **6b**. M.p. 69–75 °C; ν_{max}/cm^{-1} 3280, 2240, 1770, 1750, 1705 and 1640; δ_H 1.06 (3 H, t, *J* 7, CO_2CH_2Me), 2.44 (3 H, s, Me), 3.72 (3 H, s, CO_2Me), 4.06 (2 H, q, *J* 7, CO_2CH_2Me), 7.31–7.45 (5 H, m, Ph) and 10.50 (1 H, s, NH, D_2O-exch.) (Found: C, 59.8; H, 4.9; N, 12.6. $C_{17}H_{17}N_3O_5$ requires C, 59.5; H, 5.0; N, 12.2%).

Methyl 1-(tert-*butoxycarbonylamino*)-4-*cyano*-2-*methyl*-5-*oxo*-4-*phenyl*-1,4-*dihydropyrrole*-3-*carboxylate* **6c**. M.p. 95–100 °C; ν_{max}/cm^{-1} 3290, 2240, 1775, 1740, 1710 and 1640; δ_H 1.43 (9 H, s, Bu^t), 2.47 (3 H, s, Me), 3.61 (3 H, s, CO_2Me), 7.34–7.49 (5 H, m, Ph) and 10.20 (1 H, s, NH, D_2O-exch.) (Found: C, 61.3; H, 6.0; N, 11.5. $C_{19}H_{21}N_3O_5$ requires C, 61.4; H, 5.7; N, 11.3%).

Ethyl 1-(tert-*butoxycarbonylamino*)-4-*cyano*-2-*methyl*-5-*oxo*-4-*phenyl*-1,4-*dihydropyrrole*-3-*carboxylate* **6d**.—M.p. 69–75 °C; ν_{max}/cm^{-1} 3280, 2240, 1770, 1735, 1710 and 1640; δ_H 1.14 (3 H, t, *J* 7, CO_2CH_2Me), 1.45 (9 H, s, Bu^t), 2.48 (3 H, s, Me), 4.12 (2 H, q, *J* 7, CO_2CH_2Me), 7.42–7.54 (5 H, m, Ph) and 10.25 (1 H, s, NH, D_2O-exch.) (Found: C, 62.5; H, 6.3; N, 11.1. $C_{20}H_{23}N_3O_5$ requires C, 62.3; H, 6.0; N, 11.0%).

Methyl 4-*cyano*-2-*methyl*-5-*oxo*-4-*phenyl*-1-*ureido*-1,4-*dihydropyrrole*-3-*carboxylate* **6e**. M.p. 120–122 °C; ν_{max}/cm^{-1} 3440, 3240, 3190, 2240, 1770, 1715, 1690, 1675, 1660, 1590 and 1535; δ_H 2.40 (3 H, s, Me), 3.58 (3 H, s, CO_2Me), 6.55 (2 H, s, NH_2, D_2O-exch.), 7.30–7.46 (5 H, m, Ph), and 8.86 (1 H, s, NH, D_2O-exch.) (Found: C, 57.4; H, 4.7; N, 17.6. $C_{15}H_{14}N_4O_4$ requires C, 57.3; H, 4.5; N, 17.8%).

Ethyl 4-*cyano*-2-*methyl*-5-*oxo*-4-*phenyl*-1-*ureido*-1,4-*dihydropyrrole*-3-*carboxylate* **6f**. M.p. 94–100 °C; ν_{max}/cm^{-1} 3440, 3250, 3190, 2240, 1770, 1710, 1695, 1680, 1655, 1600 and 1535; δ_H 1.05 (3 H, t, *J* 7, CO_2CH_2Me), 2.38 (3 H, s, Me), 4.04 (2 H, q, *J* 7, CO_2CH_2Me), 6.58 (2 H, s, NH_2, D_2O-exch.), 7.31–7.40 (5 H, m, Ph) and 8.92 (1 H, s, NH, D_2O-exch.) (Found: C, 58.6; H, 5.2; N, 17.1. $C_{16}H_{16}N_4O_4$ requires C, 58.5; H, 4.9; N, 17.1%).

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References

1 Part 12; O. A. Attanasi, L. De Crescentini, S. Santeusanio, F. Serra-Zanetti, A. McKillop and Z. Liao, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1009.
2 O. A. Attanasi, S. Santeusanio, F. Serra-Zanetti, E. Foresti and A. McKillop, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1669.
3 (*a*) O. A. Attanasi, S. Santeusanio and F. Serra-Zanetti, *Gazz. Chim. Ital.*, 1989, **119**, 631; (*b*) O. A. Attanasi, M. Grossi, F. Serra-Zanetti and E. Foresti, *Tetrahedron*, 1987, **43**, 4249.
4 O. A. Attanasi, P. Filippone, A. Mei, A. Bongini and E. Foresti, *Tetrahedron*, 1990, **46**, 5685.
5 O. A. Attanasi and L. Caglioti, *Org. Prep. Proced. Int.*, 1986, **18**, 299 and references cited therein.
6 O. A. Attanasi, P. Filippone, A. Mei and S. Santeusanio, *Synthesis*, 1984, 873.
7 O. A. Attanasi, P. Filippone, A. Mei and S. Santeusanio, *Synthesis*, 1984, 671.

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