Study of the reaction between conjugated azoalkenes and α-unsubstituted- or α-substituted-β-dicarboxylate derivatives: an improved preparation of unknown polyfunctionalized 1-amino-1*H*-pyrrol-2(3*H*)-ones[1]

ORAZIO A. ATTANASI, LUCIA DE CRESCENTINI, AND FRANCO SERRA-ZANETTI[2]

Istituto di Chimica Organica della Facoltà di Scienze, Università di Urbino, Piazza della Repubblica 13, 61029 Urbino, Italy

AND

ELISABETTA FORESTI

Dipartimento di Chimica "G. Ciamician," Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

Received October 27, 1993[3]

ORAZIO A. ATTANASI, LUCIA DE CRESCENTINI, FRANCO SERRA-ZANETTI, and ELISABETTA FORESTI. Can. J. Chem. **72**, 2305 (1994).

In the presence of sodium methoxide in catalytic amounts, conjugated azoalkenes easily react with α-unsubstituted-or α-substituted-β-dicarboxylate derivatives to give at first hydrazonic derivatives, by 1,4-conjugate addition, and, by increasing sodium methoxide up to stoichiometric amounts, new polyfunctionalized 1-amino-1*H*-pyrrol-2(3*H*)-ones.

ORAZIO A. ATTANASI, LUCIA DE CRESCENTINI, FRANCO SERRA-ZANETTI et ELISABETTA FORESTI. Can. J. Chem. **72**, 2305 (1994).

En présence de quantités catalytiques de méthylate de sodium, les azoalcènes conjugués réagissent avec les dérivés β-dicarboxylates, substitués ou non en α, pour donner en premier lieu des dérivés hydrazoniques, par addition-1,4 conjuguée. Lorsqu'on augmente les quantités de méthylate de sodium pour arriver à des proportions stoechiométrique, il y a formation de nouvelles 1-amino-1*H*-pyrrol-2(3*H*)-ones polyfonctionnalisées.

[Traduit par la rédaction]

Introduction

It is recognized that the synthesis of new heterocycles represents an important area of research of immense academic and industrial importance (1).

Conjugated azoalkenes have attracted increasing attention because of their potential use in the synthesis of heterocycles and a great deal of effort has been directed by our group towards the development of a convenient strategy for the synthesis of a variety of widely substituted new 1-aminopyrrole derivatives.

The reaction of conjugated azoalkenes with many compounds containing active methine and methylene groups gives polyfunctionalized 1-aminopyrrole derivatives via a preliminary 1,4-conjugate addition, followed by subsequent intramolecular cyclization of the hydrazonic intermediates first obtained (2).

In the course of our previous investigations, cyano or ketonic carbonyl groups had frequently been observed to be effective in the internal heterocyclization processes of the 1,4-adduct intermediates, but several other activating groups exhibited no efficiency in the ring-closure processes (3, 4). We also studied in detail the reactions, in different molar ratios, of conjugated azoalkenes with alkylcyanoacetates $RO_2C\text{-}CH_2\text{-}CN$, in which we always observed ring closure on the cyano group and never on the ester group (3).

It was noteworthy therefore, that in the reactions of conjugated azoalkenes with ethylphenylcyanoacetate Ph-CH(CN)-COOEt, the 1,4-adducts did not behave in the same way, and intramolecular heterocyclization was effective on the ester group with loss of an alcohol molecule to yield previously unknown 1-amino-3-cyano-3-phenyl-1*H*-pyrrol-2(3*H*)-ones in good to excellent yields (5). In this latter case, in fact, the ring closure on the ester group appeared to be favoured, probably because the final products 1-amino-1*H*-pyrrol-2(3*H*)-ones are more stable than the 2-iminopyrrolines arising from the heterocyclization on the cyano group.

This occurrence prompted us to turn our attention to a possible general procedure for the synthesis of new classes of pyrrolin-2-ones from the reaction between conjugated azoalkenes and β-dicarboxylate derivatives possessing one or two active hydrogen atoms (i.e., α-substituted- or α-unsubstituted-β-diesters).

We examined the possibility of carrying out a straightforward synthesis of pyrrolin-2-ones in a stable form in view of the biological activity associated with a variety of pyrrole derivatives (6, 7), especially as building blocks in the construction of antiviral and antitumour DNA antibiotics (8).

The ability to prepare the desired polyfunctionalized compounds by a simple and efficient procedure seemed to us particularly attractive.

Results and discussion

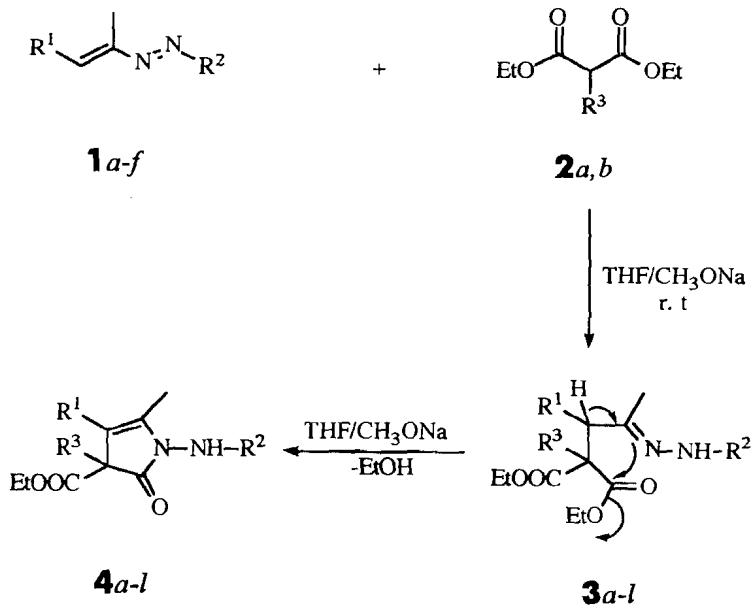
The reaction of conjugated azoalkenes **1***a–f* with an equimolecular amount of diethyl methylmalonate (**2***a*) or diethyl phenylmalonate (**2***b*) proceeded easily at room temperature and produced the pertinent hydrazonic derivatives **3***a–l* in the presence of sodium methoxide in catalytic amounts. These products can be isolated in good yields by chromatography on a silica gel column, crystallized, and characterized. When they were subsequently treated with a stoichiometric amount of sodium methoxide in tetrahydrofuran (THF), the related 1-amino-1*H*-pyrrol-2(3*H*)-ones (**4***a–l*) were isolated in good yields by column chromatography, crystallized, and characterized (Scheme 1).

More conveniently, the synthesis of 1-amino-1*H*-pyrrol-2(3*H*)-ones **4***a–l* may be directly achieved in one pot by treating conjugated azoalkenes **1***a–f* with diethyl methylmalonate (**2***a*) or diethyl phenylmalonate (**2***b*). At the beginning, the reaction can be carried out in the presence of a catalytic amount of sodium methoxide to afford hydrazonic intermediates **3***a–l* with complete disappearance of the azoalkene (monitored by TLC).

[1]Part XVII of the series on conjugated azoalkenes.

[2]Author to whom correspondence may be addressed. Telephone and Fax: 0722/2907.

[3]Revision received August 18, 1994.



SCHEME 1

TABLE 1. Yield of hydrazones (**3***a–l*) and 1-amino-1*H*-pyrrol-2(3*H*)-ones (**4***a–l*) from conjugated azoalkenes (**1***a–f*) and diethylmethylmalonate (**2***a*) or diethylphenylmalonate (**2***b*)[a]

Reactants					Products		Yields[b] (%)	
1	**2**	R^1	R^2	R^3	**3**	**4**	**3**	**4**
a	*a*	CO_2Me	$CONH_2$	Me	*a*	*a*	64	69
b	*a*	CO_2Et	$CONH_2$	Me	*b*	*b*	82	91
c	*a*	CO_2Me	CONHPh	Me	*c*	*c*	60	80
d	*a*	CO_2Et	CONHPh	Me	*d*	*d*	57	86
e	*a*	CO_2Me	CO_2Me	Me	*e*	*e*	87	67
f	*a*	CO_2Et	CO_2t-Bu	Me	*f*	*f*	72	89
a	*b*	CO_2Me	$CONH_2$	Ph	*g*	*g*	89	61
b	*b*	CO_2Et	$CONH_2$	Ph	*h*	*h*	89	82
c	*b*	CO_2Me	CONHPh	Ph	*i*	*i*	48	89
d	*b*	CO_2Et	CONHPh	Ph	*j*	*j*	54	75
e	*b*	CO_2Me	CO_2Me	Ph	*k*	*k*	87	77
f	*b*	CO_2Et	CO_2t-Bu	Ph	*l*	*l*	71	89

[a]All reaction times were 0.1 h.
[b]Yields of pure isolated products.

TABLE 2. Yield of hydrazones (**5***a–i*) and 1-amino-1*H*-pyrrol-2(3*H*)-ones (**6***a–i*) from conjugated azoalkenes (**1***a–f*) and dimethylmalonate (**2***c*) or dibenzylmalonate (**2***d*)[a]

Reactants					Products		Yields[b] (%)	
1	**2**	R^1	R^2	R^3	**5**	**6**	**5**	**6**
a	*c*	CO_2Me	$CONH_2$	Me	*a*	*a*	95	98
b	*c*	CO_2Et	$CONH_2$	Me	*b*	*b*	93	94
c	*c*	CO_2Me	CONHPh	Me	*c*	*c*	91	95
d	*c*	CO_2Et	CONHPh	Me	*d*	*d*	90	97
e	*c*	CO_2Me	CO_2Me	Me	*e*	*e*	94	64
f	*c*	CO_2Et	CO_2t-Bu	Me	*f*	*f*	89	74
a	*d*	CO_2Me	$CONH_2$	CH_2Ph	*g*	*g*	74	90
c	*d*	CO_2Me	CONHPh	CH_2Ph	*h*	*h*	93	98
e	*d*	CO_2Me	CO_2Me	CH_2Ph	*i*	*i*	83	99

[a]All reaction times were 0.1 h.
[b]Yields of pure isolated products.

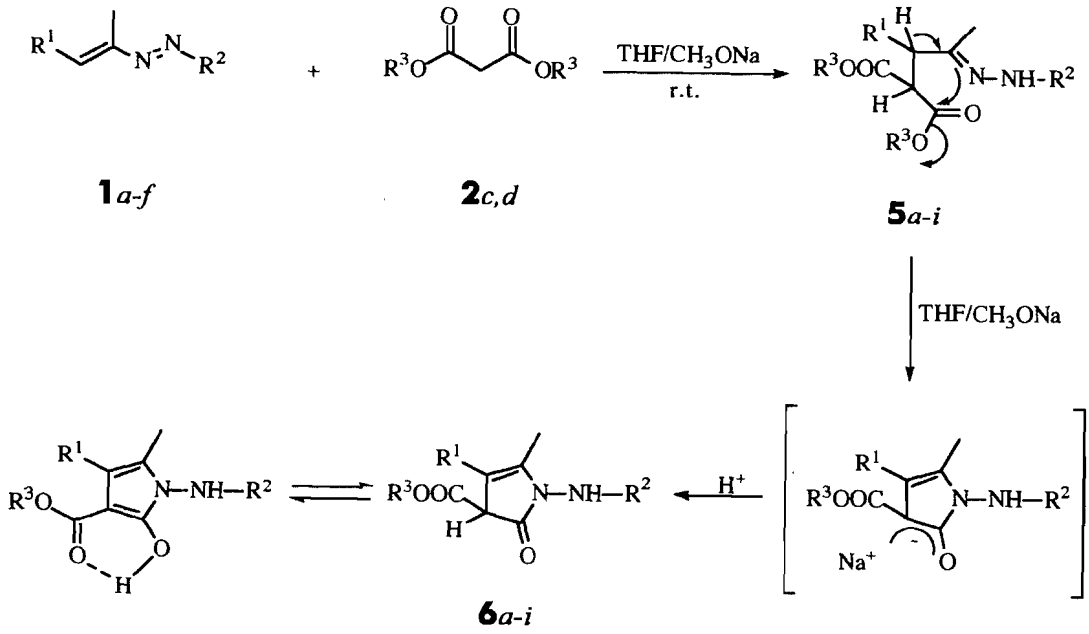
At this point, a further addition in situ of sodium methoxide, up to the stoichiometric amount, induces the ready cyclization of the hydrazonic intermediates **3***a–l* into 1-amino-1*H*-pyrrol-2(3*H*)-ones **4***a–l*. Yields of hydrazones **3***a–l* and 1-amino-1*H*-pyrrol-2(3*H*)-ones **4***a–l* are given in Table 1.

Presumably, the reaction takes place by a base-catalyzed nucleophilic attack from the active methine group of α-substituted-β-diesters containing one active hydrogen atom to the azo-ene system of conjugated azoalkene, resulting in the 1,4-addition (Michael-type) of the diester residue to the azoalkene molecule to provide the preliminary formation of the hydrazonic compound. In the presence of sodium methoxide in stoichiometric amounts, this compound undergoes ring closure by means of internal nucleophilic attack from the C=N nitrogen atom on the ester carboxyl group, with consequential loss of an alcohol molecule. Under these conditions, the reaction stops and gives 1-amino-1*H*-pyrrol-2(3*H*)-one.

Also the reactions of conjugated azoalkenes **1***a–f* (Scheme 2) at room temperature with an equimolecular amount of dimethyl malonate (**2***c*) or dibenzyl malonate (**2***d*) readily led to the related hydrazonic derivatives **5***a–i* in the presence of sodium methoxide in catalytic amounts. These products (**5***a–i*) were crystallized in good yield and utilized for the smooth preparation, by addition of the stoichiometric amount of sodium methoxide in THF and subsequent treatment by strongly acid cation exchanger, of pertinent 1-amino-1*H*-pyrrol-2(3*H*)-ones **6***a–i*, bearing a hydrogen atom in position 3 and probably susceptible to tautomeric equilibrium (Scheme 2) (6, 9, 10).

More conveniently, the synthesis of 1-amino-1*H*-pyrrol-2(3*H*)-ones **6***a–i* from conjugated azoalkenes **1***a–f* by treatment with dimethyl malonate (**2***c*) or dibenzyl malonate (**2***d*) may be directly achieved in one pot in the same way as broadly described above for the synthesis of products **4**. Yields of the hydrazones **5***a–i* and 1-amino-1*H*-pyrrol-2(3*H*)-ones **6***a–i* are listed in Table 2.

The first and the second step of this reaction follow the same pathway as previously discussed in detail. In this case, however, the 1,4-adducts contain, in position α to a carbonyl group,



1*a-f* **2***c,d* **5***a-i* **6***a-i*

SCHEME 2

a further hydrogen atom probably able to tautomerize (Scheme 2).

When conjugated azoalkenes **1***a–f* reacted with dibenzyl malonate (**2***d*) to produce related 1-amino-1*H*-pyrrol-2(3*H*) ones **6***g–i*, the loss of the alcohol molecule was demonstrated by isolation of benzyl alcohol in quantitative yield from the residual solution after filtration of solid reaction products. Benzyl alcohol was detected by TLC, isolated, and characterized by comparison with an authentic specimen. This result supports the reaction mechanism pictured in Scheme 2.

Furthermore, in early experiments, we studied the reactions between conjugated azoalkenes with nitriles containing active methylene groups (i.e., malononitrile, β-cyanoesters, β-cyanoamides) in the ratio 2:1. Double conjugated additions afforded bis-1,4 adducts that underwent double ring closure on the cyano group to give pyrrol[2,3-*b*]pyrroles (3, 4).

From these findings we went on to explore the reactions between conjugated azoalkenes **1***a–f* and dimethyl malonate (**2***c*) or dibenzyl malonate (**2***d*) in the ratio 2:1, but very poor yields of bis adducts were obtained, reactions did not go to completion, and reaction times were very slow.

To tentatively improve the yields of bis adducts, we also tried the 1,4-conjugate addition of the hydrazonic intermediates **5***a–i* to the heterodienic system of the azoalkenes **1***a–f* in the presence of sodium methoxide. All attempts were unsuccessful, because a preferential cyclization to the 1-amino-1*H*-pyrrol-2(3*H*)-ones prevented the conjugated addition to a further molecule of azoalkene.

In conclusion, this simple procedure really represents a useful entry to a new class of pyrrole derivatives not obtainable by other methods (11). In fact, all the pyrrole ring positions may be simultaneously functionalized with different substituents that are very difficult to introduce separately. These substituents may be selected in advance by varying the functionalization both on the starting conjugated azoalkenes (2) and β-diester derivatives. Moreover, some of these functional groups appear to be suitable for further structural modifications.

In former studies on the simple monocyclic pyrrolinones (or 2-hydroxypyrroles) as terminal rings of the bile pigments, Fischer and Plieninger formulated the products as 2-hydroxypyrroles (9), but more recently it was reported, based on NMR studies, that 2-hydroxypyrroles exist predominantly in the tautomeric pyrrolin-2-one form (10).[4] However, spectroscopic evidence indicates the considerable presence of the enol form, in solution. Further investigations are presently in progress to better clarify the nature of this tautomeric equilibrium.

Experimental section

General

Products **1***a–d*(12) and **1***e–f*(13) were prepared as described previously. Products **2***a–d* were commercial materials and were used without further purification. All melting points were recorded on a capillary melting point apparatus and are uncorrected. IR spectra were obtained as Nujol mulls, and ^{1}H NMR spectra were measured in DMSO-d_6 solution. Chemical shifts (δ) are reported in ppm, downfield from Me_4Si as internal standard. Machery–Nagel precoated silica gel SIL G-25 UV_{254} plates (0.25 mm) were employed for analytical thin-layer chromatography (TLC), Baker silica gel (0.063-0.200 mm) for column chromatography, and Merck I strongly acid cation exchanger for Na^+/H^+ exchange.

Preparation of hydrazones 3a–l and 5a–i

To a stirred solution of azoalkene (**1***a–f*) (1 mmol) in THF (3 mL) was added dropwise a solution of β-diester (**2***a–d*) (1 mmol) and sodium methoxide (0.1 mmol) in THF (3 mL). The mixture was magnetically stirred at room temperature (~5 min) until the reaction was completed (monitored by TLC). Products **3***a–l* were purified by chromatography on a silica gel column (elution with cyclohexane – ethyl acetate mixtures) and then crystallized from THF–*n*-pentane. Products **5***a–i* were crystallized by partial evaporation of the reaction solvent and by addition of *n*–pentane to this crude reaction.

[4]To unambiguously confirm the structure of these compounds, an X-ray diffraction study of methyl 4-benzyl-oxycarbonyl-2-methyl-5-oxo-1-(*N'*-phenylureido)-1,4-dihydropyrrole-3-carboxylate (**6***h*) was carried out. Structure determination confirmed that, in the solid state, the pyrrole derivatives reported here exist in the keto form, but a final unsatisfactory all-data agreement index $R = 0.3924$ prevented us from publishing these results in the text.

Ethyl 4-(carbamoylhydrazono)-2-(ethoxycarbonyl)-3-(methoxycarbonyl)-2-methylpentanoate (**3**a): mp 154–156°C; crystallized from THF–*n*-pentane; IR: 3460 (NH), 3300, 3220, 3170 (NH, NH_2 overlap), 1735 (C=O), 1690 (C=O), 1645 (C=O), and 1590 (C=O) cm^{-1}; ^1H NMR: 1.00–1.20 (6H, m, 2 × CO_2CH_2*Me*), 1.45 (3H, s, Me), 1.82 (3H, s, Me), 3.61 (3H, s, CO_2Me), 3.84 (1H, s, CH), 4.02–4.16 (4H, m, 2 × CO_2*CH_2*Me), 6.09 (2H, br s, NH_2, D_2O-exch.), and 9.33 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{14}H_{23}N_3O_7$: C 48.69, H 6.71, N 12.17; found: C 48.85, H 6.52, N 12.29.

Ethyl 4-(carbamoylhydrazono)-2,3-(diethoxycarbonyl)-2-(methylpentanoate) (**3**b): mp 110–112°C; crystallized from THF–*n*-pentane; IR: 3450 (NH), 3300, 3220, 3170 (NH, NH_2 overlap), 1740 (C=O), 1690 (C=O), 1650 (C=O), and 1585 (C=O) cm^{-1}; ^1H NMR: 1.09–1.19 (9H, m, 3 × CO_2CH_2*Me*), 1.44 (3H, s, Me), 1.81 (3H, s, Me), 4.03–4.09 (7H, m, CH and 3 × CO_2*CH_2*Me), 6.06 (2H, br, s, NH_2, D_2O-exch.), and 9.30 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{15}H_{25}N_3O_7$: C 50.13, H 7.01, N 11.69; found: C 50.29, H 6.81, N 11.87.

Ethyl 2-(ethoxycarbonyl)-3-(methoxycarbonyl)-2-(methyl-4-(N′-phenylcarbamoylhydrazono)pentanoate (**3**c): mp 119–122°C; crystallized from THF–*n*-pentane; IR: 3340 (NH), 3190 (NH), 3090 (NH, 1740 (C=O), 1710 (C=O), 1675 (C=O), and 1590 (C=O) cm^{-1}; ^1H NMR: 1.08–1.20 (6H, m, 2 × CO_2CH_2*Me*), 1.51 (3H, s, Me), 1.90 (3H, s, Me), 3.63 (3H, s, CO_2Me), 4.07–4.18 (5H, m, CH and 2 × CO_2*CH_2*Me), 7.00–7.63 (5H, m, Ph), 8.15 (1H, s, NH, D_2O-exch.), and 9.85 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{20}H_{27}N_3O_7$: C 57.0, H. 6.46, N 9.97; found: C 57.12, H 6.31, N 9.88.

Ethyl 2,3-(diethoxycarbonyl)-2-methyl-4-(N′-phenylcarbamoylhydrazono)pentanoate (**3**d): mp 128–130°C; crystallized from THF–*n*-pentane; IR: 3340 (NH), 3190 (NH), 3090 (NH), 1745 (C=O), 1730 (C=O), 1675 (C=O), and 1595 (C=O) cm^{-1}; ^1H NMR: 1.10–1.22 (9H, m, 3 × CO_2CH_2*Me*), 1.53 (3H, s, Me), 1.92 (3H, s, Me), 4.06–4.18 (7H, m, CH and 3 × CO_2*CH_2*Me), 7.00–7.65 (5H, m, Ph), 8.17 (1H, s, NH, D_2O-exch.), and 9.87 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{21}H_{29}N_3O_7$: C 57.92, H 6.71, N 9.65; found: C 58.02, H 6.61, N 9.81.

Ethyl 2-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-(methoxycarbonylhydrazono)-2-methylpentanoate (**3**e): mp 88–91°C; crystallized from THF–*n*-pentane; IR: 3250 (NH), 1740 (C=O), 1725 (C=O), 1690 (C=O), and 1630 (C=O) cm^{-1}; ^1H NMR: 1.11–1.19 (6H, m, 2 × CO_2CH_2*Me*), 1.44 (3H, s, Me), 1.79 (3H, s, Me), 360 (3H, s, CO_2Me), 3.63 (3H, s, CO_2Me), 4.04–4.11 (5H, m, CH and 2 × CO_2*CH_2*Me), and 9.97 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{15}H_{24}N_2O_8$: C 50.0, H 6.71, N 7.77; found: C 50.15, H 6.57, N 7.69.

Ethyl 4-(tert-*butoxycarbonylhydrazono)-2,3-(diethoxycarbonyl)-2-methylpentanoate* (**3**f): mp 60–62°C; crystallized from THF–*n*-pentane; IR: 3250 (NH), 1765 (C=O), 1730 (C=O), 1685 (C=O), and 1640 (C=O) cm^{-1}; ^1H NMR: 1.15 (9H, t, J = 7 Hz, 3 × CO_2CH_2*Me*), 1.43 (9H, s, *t*-Bu), 1.46 (3H, s, Me), 1.78 (3H, s, Me), 4.03–4.16 (7H, m, CH and 3 × CO_2*CH_2*Me), and 9.62 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{19}H_{32}N_2O_8$: C 54.8, H 7.74, N 6.73; found: C 54.61, H 7.63, N 6.64.

Ethyl 4-(carbamoylhydrazono)-2-(ethoxycarbonyl)-3-(methoxycarbonyl)-2-phenylpentanoate (**3**g): mp 153–160°C; crystallized from THF–*n*-pentane; IR: 3440 (NH), 3290, 3170 (NH, NH_2 overlap), 1735 (C=O), 1705 (C=O), 1695 (C=O), and 1590 (C=O) cm^{-1}; ^1H NMR: 1.10–1.22 (6H, m, 2 × CO_2*CH_2*Me), 1.96 (3H, s, Me), 3.67 (3H, s, CO_2Me), 4.08–4.18 (4H, m, 2 × CO_2*CH_2*Me), 4.69 (1H, s, CH), 5.43 and 6.25 (2H, 2 br s, NH_2, D_2O-exch.), 7.28–7.33 (5H, m, Ph), and 9.21 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{19}H_{25}N_3O_7$: C 56.01, H. 6.18, N 10.31; found: C 56.15, H 6.18, N 10.31.

Ethyl 4-(carbamoylhydrazono)-2,3-(diethoxycarbonyl)-2-(phenylpentanoate (**3**h): mp 161–164°C; crystallized from THF–*n*-pentane; IR: 3430 (NH), 3270, 3150 (NH, NH_2 overlap), 1720 (C=O), 1700 (C=O), 1685 (C=O), and 1585 (C=O) cm^{-1}; ^1H NMR: 1.02–1.16 (9H, m, 3 × CO_2CH_2*Me*), 1.89 (3H, s, Me), 4.02–4.12 (6H, m, 3 × CO_2*CH_2*Me), 4.60 (1H, s, CH), 5.34 and 6.16 (2H, 2 br s, NH_2, D_2O-exch.), 7.19–7.27 (5H, m, Ph), and 9.14 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{20}H_{27}N_3O_7$: C 57.0, H. 6.46, N 9.97; found: C 57.19, H 6.35, N 10.06.

Ethyl 2-(ethoxycarbonyl)-3-(methoxycarbonyl)-2-(phenyl-4-(N′-phenylcarbamoylhydrazono)pentanoate (**3**i): mp 178–180°C; crystallized from THF–*n*-pentane; IR: 3350 (NH), 3200 (NH), 3080 (NH), 1745 (C=O), 1725 (C=O), 1680 (C=O), and 1595 (C=O) cm^{-1}; ^1H NMR: 1.05–1.12 (6H, m, 2 × CO_2CH_2*Me*), 2.03 (3H, s, Me), 3.64 (3H, s, CO_2Me), 4.07–4.12 (4H, m, 2 × CO_2*CH_2*Me), 4.82 (1H, s, CH), 6.90–7.44 (10H, m, 2 × Ph), 7.70 (1H, s, NH, D_2O-exch.), and 9.74 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{25}H_{29}N_3O_7$: C 62.10, H 6.05, N 8.69; found: C 61.98, H 6.21, N 8.86.

Ethyl 2,3-(diethoxycarbonyl)-2-phenyl-4-(N′-phenylcarbamoylhydrazono)pentanoate (**3**j): mp 138–141°C; crystallized from THF–*n*-pentane; IR: 3340 (NH), 3190 (NH), 3060 (NH), 1750 (C=O), 1725 (C=O), 1675 (C=O), and 1590 (C=O) cm^{-1}; ^1H NMR: 1.03–1.16 (9H, m, 3 × CO_2CH_2*Me*), 2.03 (3H, s, Me), 4.02–4.14 (6H, m, 3 × CO_2*CH_2*Me), 4.80 (1H, s, CH), 6.93–7.48 (10H, m, 2 × Ph), 7.72 (1H, s, NH, D_2O-exch.), and 9.75 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{26}H_{31}N_3O_7$: C 62.76, H 6.28, N 8.45; found: C 62.67, H 6.39, N 8.36.

Ethyl 2-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-(methoxycarbonylhydrazono)-2-phenylpentanoate (**3**k): mp 139–141°C; crystallized from THF–*n*-pentane; IR: 3310 (NH), 1750 (C=O), 1730 (C=O), and 1695 (C=O) cm^{-1}; ^1H NMR: 1.08–1.17 (6H, m, 2 × CO_2CH_2*Me*), 1.67 (3H, s, Me), 3.58 (6H, s, 2 × CO_2Me), 4.10–4.21 (4H, m, 2 × CO_2*CH_2*Me), 4.49 (1H, s, CH), 7.27 (5H, s, Ph), and 9.79 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{20}H_{26}N_2O_8$: C 56.87, H. 6.20, N 6.63; found: C 57.06, H 6.11, N 6.81.

*Ethyl 4-*tert-*butoxycarbonylhydrazono)-2,3-(diethoxycarbonyl)-2-phenylpentanoate* (3l): mp 90–93°C; crystallized from THF–*n*-pentane; IR: 3250 (NH), 1780 (C=O), 1730 (C=O), and 1690 (C=O) cm^{-1}; ^1H NMR: 1.08–1.17 (9H, m, 3 × COX_2CH_2*Me*), 1.40 (9H, s, *t*-Bu), 1.61 (3H, s, Me), 4.00–4.21 (6H, m, 3 × CO_2*CH_2*Me), 4.44 (1H, s, CH), 7.27 (5H, s, Ph), and 9.38 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{24}H_{34}N_2O_8$: C 60.39, H. 7.16, N 5.85; found: C 60.39, H 7.33, N 5.74.

Methyl 4-carbamoylhydrazono)-2,3-(dimethoxycarbonyl)pentanoate (**5**a): mp 138–140°C; crystallized from THF–*n*-pentane; IR: 3450 (NH), 3440 (NH), 3300 (NH_2), 3190 (NH_2), 1730 (C=O), 1695 (C=O), 1665 (C=O), and 1640 (C=O) cm^{-1}; ^1H NMR: 1.86 (3H, s, Me), 3.60–3.65 (9H, m, 3 × CO_2*CH_2*Me), 3.91 (1H, d, J = 10 Hz, CH), 4.23 (1H, d, J = 10 Hz, CH), 6.25 (2H, br s, NH_2, D_2O-exch.), and 9.33 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{11}H_{17}N_3O_7$: C 43.57, H. 5.65, N 13.86; found: C 43.49, H 5.79, N 13.98.

Methyl 4-carbamoylhydrazono)-3-(ethoxycarbonyl)-2-(methoxycarbonyl)pentanoate (**5**b): mp 119–122°C; crystallized from THF–*n*-pentane; IR: 3530 (NH), 3400 (NH), 3200 (NH_2), 1750 (C=O), 1730 (C=O), 1690 (C=O), and 1640 (C=O) cm^{-1}; ^1H NMR: 1.16 (3H, t, J = 7 Hz, CO_2CH_2*Me*), 1.86 (3H, s, Me), 3.61 (3H, s, CO_2Me), 3.65 (3H, s, CO_2Me), 3.88 (1H, d, J = 10 Hz, CH), 4.10 (2H, q, J = 7 Hz, CO_2*CH_2*Me), 4.21 (1H, d, J = 10 Hz, CH), 6.20 (2H, br s, NH_2, D_2O-exch.), and 9.32 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{12}H_{19}N_3O_7$: C 45.42, H. 6.04, N 13.24; found: C 45.35, H 6.21, N 13.16.

Methyl 2,3-(dimethoxycarbonyl)-4-(N′-phenylcarbamoylhydrazono)pentanoate (**5**c): mp 145–147°C; crystallized from THF–*n*-pentane; IR: 3380 (NH), 3200 (NH), 3090 (NH), 1740 (C=O), 1720 (C=O), 1700 (C=O), and 1600 (C=O) cm^{-1}; ^1H NMR: 1.94 (3H, s, Me), 3.58 (3H, s, CO_2Me), 3.66 (6H, s, 2 × CO_2Me), 4.03 (1H, d, J = 10 Hz, CH), 4.48 (1H, d, J = 10 Hz, CH), 7.00–7.61 (5H, m, Ph), 8.48 (1H, s, NH, D_2O-exch.), and 9.86 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{17}H_{21}N_3O_7$: C 53.82, H 5.58, N 11.08; found: C 53.99, H 5.39, N 11.15.

Methyl 3-(ethoxycarbonyl)-2-(methoxycarbonyl)-4-(N′-phenylcarbamoylhydrazono)pentanoate (**5**d): mp 130–132°C; crystallized from THF–*n*-pentane; IR: 3370 (NH), 3210 (NH), 3100 (NH), 1745 (C=O), 1730 (C=O), 1700 (C=O), and 1605 (C=O) cm^{-1}; ^1H NMR: 1.18 (3H, t, J = 7 Hz, CO_2CH_2*Me*), 1.95 (3H, s, Me), 3.59 (3H, s, CO_2Me), 3.66 (3H, s, CO_2Me), 4.01 (1H, d, J = 10 Hz, CH), 4.13 (2H, q, J = 7 Hz, CO_2*CH_2*Me), 4.46 (1H, d, J = 10 Hz, CH), 7.00–7.61 (5H, m, Ph), 8.46 (1H, s, NH, D_2O-exch.), and 9.85 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{18}H_{23}N_3O_7$: C 54.96, H 5.89, N 10.68; found; C 55.13, H 5.75, N 10.74.

Methyl 2,3-(dimethoxycarbonyl)-4-(methoxycarbonylhydrazono)-pentanoate (5e): mp 127–129°C; crystallized from THF–*n*-pentane; IR: 3230 (NH), 3150 (NH), 1730, 1710 (C=O overlap), and 1640 (C=O) cm^{-1}; ^1H NMR: 1.87 (3H, s, Me), 3.61–3.66 (12H, m, 4 × CO_2Me), 3.88 (1H, d, J = 10 Hz, CH), 4.08 (1H, d, J = 10 Hz, CH), and 10.03 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{12}H_{18}N_2O_8$: C 45.28, H 5.70, N 8.80; found: C 45.16, H 5.82, N 8.96.

*Methyl 4-(*tert*-butoxycarbonylhydrazono)-3-(ethoxycarbonyl)-2-(methoxycarbonyl)pentanoate (5f)*: mp 90–93°C; crystallized from THF–*n*-pentane; IR: 3230 (NH), 3150 (NH), 1745, (C=O), 1730 (C=O), 1720 (C=O), 1690 (C=O), and 1640 (C=O) cm^{-1}; ^1H NMR: 1.15 (3H, t, J = 7 Hz, CO_2CH_2*Me*), 1.43 (9H, s, *t*-Bu), 1.86 (3H, s, Me), 3.61 (3H, s, CO_2Me), 3.66 (3H, s, CO_2Me), 3.84 (1H, d, J = 10 Hz, CH), 4.05–4.11 (3H, m, CH and CO_2CH_2Me), and 9.71 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{16}H_{26}N_2O_8$: C 51.33, H 7.0, N 7.48; found: C 51.21, H 7.17, N 7.39.

Benzyl 2-(benzyloxycarbonyl)-4-(carbamoylhydrazono)-3-(methoxycarbonyl)pentanoate (5g): mp 110–112°C; crystallized from THF–*n*-pentane; IR: 3520 (NH), 3400 (NH), 3180 (NH_2), 1745, (C=O), 1720 (C=O), 1685 (C=O), and 1630 (C=O) cm^{-1}; ^1H NMR: 1.85 (3H, s, Me), 3.56 (3H, s, CO_2Me), 3.94 (1H, d, J = 10 Hz, CH), 4.43 (1H, d, J = 10 Hz, CH), 5.04–5.20 (4H, m, 2 × CO_2CH_2Ph), 6.27 (2H, br s, NH_2, D_2O-exch.), 7.27–7.34 (10H, m, 2 × CO_2CH2*Ph*), and 9.33 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{23}H_{25}N_3O_7$: C 60.65, H 5.53, N 9.23; found: C 60.51, H 5.71, N 9.09.

Benzyl 2-(benzyloxycarbonyl)-3-(methoxycarbonyl)-4-(N′-phenylcarbamoylhydrazono)pentanoate (5h): mp 152–154°C; crystallized from THF–*n*-pentane; IR: 3360 (NH), 3190 (NH), 1755, (C=O), 1730 (C=O), 1680 (C=O), and 1640 (C=O) cm^{-1}; ^1H NMR: 1.91 (3H, s, Me), 3.57 (3H, s, CO_2Me), 4.07 (1H, d, J = 10 Hz, CH), 4.84 (1H, d, J = 10 Hz, CH), 5.14–5.20 (4H, m, 2 × CO_2CH_2Ph), 7.00–7.58 (15H, m, Ph and 2 × CO_2CH_2*Ph*), 8.47 (1H, s, NH, D_2O-exch.) and 9.80 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{29}H_{29}N_3O_7$: C 65.53, H. 5.50, N 7.90; found: C 65.39, H 5.41, N 7.75.

Benzyl 2-(benzyloxycarbonyl)-3-(methoxycarbonyl)-4-(methoxycarbonylhydrazono)pentanoate (5i): mp 118–120°C; crystallized from THF–*n*-pentane; IR: 3230 (NH), 1735, and 1700 (C=O overlap) cm^{-1}; ^1H NMR: 1.86 (3H, s, Me), 3.56 (3H, s, CO_2Me), 3.64 (3H, s, CO_2Me), 3.93 (1H, d, J = 10 Hz, CH), 4.24 (1H, d, J = 10 Hz, CH), 5.08–5.15 (4H, m, 2 × CO_2CH_2Ph), 7.31–7.34 (10H, m, 2 × CO_2CH_2*Ph*), and 10.07 (1H, s, NH, D_2O-exch.). Anal. calcd. for: $C_{24}H_{26}N_2O_8$: C 61.27, H 5.57, N 5.95; found: C 61.27, H 5.73, N 6.09.

Conversion of hydrazones **3**a–l *into 1-amino-1*H*-pyrrol-2(3*H*)-ones* **4**a–l

To a stirred solution of hydrazone (**3***a–l*) in THF (3 mL) was added a solution of sodium methoxide (1 mmol) in methanol (1 mL). The conversion to give products **4***a–l* occurred rapidly, under magnetic stirring at room temperature (~5 min), and was monitored by TLC. The reaction mixture was concentrated to a small volume under reduced pressure, the residue was dissolved in ethyl acetate, and the solution extracted with aqueous sulphuric acid (1%). The organic phase was separated, washed with water, dried with magnesium sulphate, and concentrated under reduced pressure. Products **4***a–l* were purified by chromatography on a silica gel column (elution with cyclohexane – ethyl acetate mixtures), and then crystallized from ethyl ether – light petroleum, bp 30–60°C, or dichloromethane – light petroleum, bp 30–60°C.

*Direct preparation of 1-amino-1*H*-pyrrol-2(3*H*)-ones* **4**a–l

To a stirred solution of azoalkene (**1***a–f*) (1 mmol) in THF (3 mL) was added dropwise a solution of β-diester (**2***a, b*) (1 mmol) and sodium methoxide (0.1 mmol) in THF (3 mL). When the reaction at room temperature was completed, affording hydrazones (**3***a–l*) (monitored by TLC), a solution of sodium methoxide (1 mmol) in methanol (1 mL) was added directly to the reaction. The conversion to afford products **4***a–l* occurred rapidly, under magnetic stirring at room temperature (~5 min), and was monitored by TLC. The reaction mixture was then treated as described in detail above for the isolation of the same products **4***a–l*.

Methyl 4-ethoxycarbonyl-2,4-dimethyl-5-oxo-1-ureido-1,4-dihydropyrrole-3-carboxylate (4a): mp 138–140°C; crystallized from dichloromethane – light petroleum, bp 30–60°C; IR: 3440 (NH), 3290, 3250, 3190 (NH, NH_2 overlap), 1750 (C=O), 1705 (C=O), 1645 (C=O), and 1615 (C=O) cm^{-1}; ^1H NMR: 1.07 (3H, t, J = 7 Hz, CO_2CH_2*Me*), 1.44 (3H, s, Me), 2.25 (3H, s, Me), 3.63 (3H, s, CO_2Me), 4.06 (2H, q, J = 7 Hz, CO_2CH_2Me), 6.33 and 6.39 (2H, 2 s, NH_2, D_2O-exch.), and 8.65 and 8.96 (1H, 2 s, NH, D_2O-exch.), Anal. calcd. for: $C_{12}H_{17}N_3O_6$: C 48.16, H 5.73, N 14.04; found: C 48.05, H 5.65, N 14.15.

Ethyl 4-ethoxycarbonyl-2,4-dimethyl-5-oxo-1-ureido-1,4-dihydropyrrole-3-carboxylate (4b): mp 102–106°C; crystallized from dichloromethane – light petroleum, bp 30–60°C; IR: 3435 (NH), 3290, 3250, 3190 (NH, NH_2 overlap), 1745 (C=O), 1705 (C=O), 1640 (C=O), and 1615 (C=O) cm^{-1}; ^1H NMR: 1.05–1.21 (6H, m, 2 × CO_2CH_2*Me*), 1.45 (3H, s, Me), 2.26 (3H, s, Me), 4.00–4.15 (4H, m, 2 × CO_2CH_2Me), 6.29 and 6.36 (2H, 2 s, NH_2, D_2O-exch.), and 8.62 and 8.93 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{13}H_{19}N_3O_6$: C 49.84, H 6.11, N 13.41; found: C 49.75, H 6.26, N 13.32.

Methyl 4-ethoxycarbonyl-2,4-dimethyl-5-oxo-1-(N′-phenylureido-1,4-dihydropyrrole-3-carboxylate (4c): mp 149–151°C; crystallized from ethyl ether – light petroleum, bp 30–60°C; IR: 3300 (NH), 3210 (NH), 1760 (C=O), 1710 (C=O), 1650 (C=O), and 1605 (C=O) cm^{-1}; ^1H NMR: 1.10 (3H, t, J = 7 Hz, CO_2CH_2Me), 1.49 (3H, s, Me), 2.31 (3H, s, Me), 3.66 (3H, s, CO_2Me), 4.10 (2H, q, J = 7 Hz, CO_2CH_2Me), 6.95–7.46 (5H, m, Ph), 9.19 (1H, s, NH, D_2O-exch.), and 9.37 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{18}H_{21}N_3O_6$: C 57.59, H 5.64, N 11.19; found: C 57.44, H 5.73, N 11.38.

Ethyl 4-ethoxycarbonyl-2,4-dimethyl-5-oxo-1-(N′-phenylureido-1,4-dihydropyrrole-3-carboxylate (4d): mp 236–239°C; crystallized from ethyl ether – light petroleum, bp 30–60°C; IR: 3310 (NH), 3200 (NH), 1760 (C=O), 1720 (C=O), 1675 (C=O), and 1615 (C=O) cm^{-1}; ^1H NMR: 1.08–1.23 (6H, m, 2 × CO_2CH_2*Me*), 1.51 (3H, s, Me), 2.32 (3H, s, Me), 4.05–4.18 (4H, m, 2 × CO_2CH_2Me), 6.96–7.48 (5H, m, Ph), 8.19 (1H, s, NH, D_2O-exch.), and 9.59 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{19}H_{23}N_3O_6$: C 58.60, H 5.95, N 10.79; found: C 58.78, H 5.81, N 10.93.

Methyl 4-ethoxycarbonyl-1-(methoxycarbonylamino)-2,4-dimethyl-5-oxo-1,4-dihydro-pyrrole-3-carboxylate (4e): mp 109–111°C; crystallized from ethyl ether – light petroleum, bp 30–60°C; IR: 3240 (NH), 1770 (C=O), 1750 (C=O), 1730 (C=O), 1675 (C=O), and 1635 (C=O) cm^{-1}; ^1H NMR: 1.08 (3H, t, J = 7 Hz, CO_2CH_2*Me*), 1.45 (3H, s, Me), 2.28 (3H, s, Me), 3.67 (3H, s, CO_2Me), 3.88 (3H, s, CO_2Me), 4.05 (2H, q, J = 7 Hz, CO_2CH_2Me), and 10.35 (1H, br s, NH, D_2O-exch.). Anal. calcd. for $C_{13}H_{18}N_2O_7$: C 49.68, H 5.77, N 8.91; found: C 49.53, H 5.95, N 8.83.

*Ethyl 1-(*tert*-butoxycarbonylamino)-4-ethoxycarbonyl-2,4-dimethyl-5-oxo-1,4-dihydropyrrole-3-carboxylate (4f)*: mp 72–75°C; crystallized from ethyl ether – light petroleum, bp 30–60°C; IR: 3245 (NH), 1765 (C=O), 1740 (C=O). 1730 (C=O), 1680 (C=O), and 1635 (C=O) cm^{-1}; ^1H NMR: 1.05–1.21 (6H, m, 2 × CO_2CH_2*Me*), 1.42 (9H, s, *t*-Bu), 1.45 (3H, s, Me), 2.26 (3H, s, Me), 3.97–4.18 (4H, m, 2 × CO_2CH_2Me), and 10.01 (1H, br s, NH, D_2O-exch.). Anal. calcd. for $C_{17}H_{26}N_2O_7$: C 55.13, H 7.08, N 7.56; found: C 55.02, H 7.22, N 7.47.

Methyl 4-ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1-ureido-1,4-dihydropyrrole-3-carboxylate (4g): mp 207–209°C; crystallized from dichloromethane – light petroleum, bp 30–60°C; IR: 3400 (NH), 3320, 3250, 3180 (NH, NH_2 overlap), 1760 (C=O), 1735 (C=O), 1670 (C=O), and 1635 (C=O) cm^{-1}; ^1H NMR: 1.09–1.16 (3H, m, CO_2CH_2*Me*), 2.33 and 2.35 (3H, 2 s, Me), 3.57 and 3.60 (3H, 2 s, CO_2Me), 4.10–4.16 (2H, m, CO_2CH_2Me), 6.35 (2H, s, NH_2, D_2O-exch.), 7.28–7.43 (5H, m, Ph), and 8.76 and 9.06 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{17}H_{19}N_3O_6$: C 56.51, H 5.30, N 11.63; found: C 56.65, H 5.21, N 11.77.

Ethyl 4-ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1-ureido-1,4-dihydropyrrole-3-carboxylate (4h): mp 214–216°C; crystallized from dichloromethane – light petroleum, bp 30–60°C; IR: 3420 (NH), 3320, 3260, 3210 (NH, NH_2 overlap), 1765 (C=O), 1740 (C=O), 1675 (C=O), and 1640 (C=O) cm^{-1}; ^1H NMR: 1.07–1.17 (6H, m, 2 ×

CO_2CH_2*Me*), 2.35 and 2.37 (3H, 2 s, Me), 4.02–4.15 (4H, m, 2 × CO_2CH_2Me), 6.34 (2H, s, NH_2, D_2O-exch.), 7.29–7.45 (5H, m, Ph), and 8.75 and 9.05 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{18}H_{21}N_3O_6$: C 57.59, H 5.64, N 11.19; found: C 57.54, H 5.53, N 11.37.

*Methyl 4-ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1-(*N′*-phenylureido-1,4-dihydropyrrole-3-carboxylate (***4i***)*: mp 162–164°C; crystallized from dichloromethane – light petroleum, bp 30–60°C; IR: 3340 (NH), 3300 (NH), 1725 (C=O), 1710 (C=O), 1650 (C=O), and 1600 (C=O) cm^{-1}; ^1H NMR: 1.12–1.19 (3H, m, CO_2CH_2*Me*), 2.40 (3H, s, Me), 3.60 and 3.62 (3H, 2 s, CO_2Me), 4.12–4.18 (2H, m, CO_2CH_2Me), 6.98–7.48 (10H, m, 2 × Ph), 8.96 and 9.33 (1H, 2 s, NH, D_2O-exch.), and 9.36 and 9.43 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{23}H_{23}N_3O_6$: C 63.15, H 5.30, N 9.61; found: C 63.31, H 5.24, N 9.72.

*Ethyl 4-ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1-(*N′*-phenylureido)-1,4-dihydropyrrole-3-carboxylate (***4j***)*: mp 169–173°C; crystallized from dichloromethane – light petroleum, bp 30–60°C; IR: 3360 (NH), 3290 (NH), 1755 (C=O), 1715 (C=O), 1695 (C=O), and 1650 (C=O) cm^{-1}; ^1H NMR: 1.08–1.20 (6H, m, 2 × CO_2CH_2*Me*), 2.39 (3H, s, Me), 4.04–4.26 (4H, m, 2 × CO_2CH_2Me), 6.98–7.48 (10H, m, 2 × Ph), 8.93 and 9.28 (1H, 2 s, NH, D_2O-exch.), and 9.39 and 9.43 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{24}H_{25}N_3O_6$: C 63.85, H 5.58, N 9.31; found: C 63.78, H 5.74, N 9.42.

*Methyl 4-ethoxycarbonyl-1-(methoxycarbonylamino)-2-methyl-5-oxo-4-phenyl-1,4-dihydropyrrole-3-carboxylate (***4k***)*: mp 143–146°C; crystallized from ethyl ether – light petroleum, bp 30–60°C; IR: 3320 (NH), 1765 (C=O), 1725 (C=O), 1690 (C=O), and 1635 (C=O) cm^{-1}; ^1H NMR: 1.09–1.24 (3H, m, CO_2CH_2*Me*), 2.36 (3H, s, Me), 3.60 and 3.62 (3H, 2 s, CO_2Me), 3.67 and 3.70 (3H, 2 s, CO_2Me), 4.04–4.24 (2H, m, CO_2CH_2Me), 7.32–7.43 (5H, m, Ph), and 10.13 and 10.46 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{18}H_{20}N_2O_7$: C 57.44, H 5.36, N 7.44; found: C 57.64, H 5.45, N 7.28.

*Ethyl 1-(*tert*-butoxycarbonylamino)-4-ethoxycarbonyl-2-methyl-5-oxo-4-phenyl-1,4-dihydropyrrole-3-carboxylate (***4l***)*: mp 120–125°C; crystallized from ethyl ether – light petroleum, bp 30–60°C; IR: 3280 (NH), 1765 (C=O), 1735 (C=O), 1710 (C=O), 1675 (C=O), and 1640 (C=O) cm^{-1}; ^1H NMR: 1.06–1.65 (6H, m, 2 × CO_2CH_2*Me*), 1.41 and 1.44 (9H, 2 s, *t*-Bu), 2.35 (3H, s, Me), 4.04–4.25 (4H, m, 2 × CO_2CH_2Me), 7.32–7.37 (5H, m, Ph), and 10.12 and 10.45 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{22}H_{28}N_2O_7$: C 61.10, H 6.53, N 6.48; found: C 60.95, H 6.36, N 6.66.

Conversion of hydrazones **5**a–i *into 1-amino-1*H*-pyrrol-2(3*H*)-ones* **6**a–i

To a stirred solution of hydrazone (**5***a–i*) (1 mmol) in THF (3 mL) was added a solution of sodium methoxide (1 mmol) in methanol (1 mL). The conversion to give products **6***a–i* occurred rapidly, under magnetic stirring at room temperature (~5 min), and was monitored by TLC. Products **6***a–i*, after partial evaporation of the reaction solvent, were crystallized by addition of ethyl ether to the crude reaction, dissolved in water and treated by the strongly acid cation exchanger. The aqueous solution was extracted with ethyl acetate and the organic phase was separated, dried with magnesium sulphate, and concentrated under reduced pressure. After this treatment, products **6** crystallized as follows: **6***a*, **6***b* from tetrahydrofuran – *n*-pentane, **6***c*, **6***d*, and **6***h* from ethyl acetate, **6***g* from dichloromethane – light petroleum, bp 30–60°C, while products **6***e*, **6***f*, and **6***i* are oils.

*Direct preparation of 1-amino-1*H*-pyrrol-2(3*H*)-ones* **6**a–i

To a stirred solution of azoalkene (**1***a–f*) (1 mmol) in THF (3 mL) was added dropwise a solution of β-diester (**2***c*, *d*) (1 mmol) and sodium methoxide (0.1 mmol) in THF (3 mL). When the reaction was completed, affording hydrazones **5***a–i* (monitored by TLC), a solution of sodium methoxide (1 mmol) in methanol (1 mL) was added directly to the reaction. The conversion to afford products **6***a–i* occurred rapidly, under magnetic stirring at room temperature (~5 min), and was monitored by TLC. The reaction mixture was then treated as described in detail above for the isolation of the same products **6***a–i*.

*Methyl 4-methoxycarbonyl-2-methyl-5-oxo-1-ureido-1,4-dihydropyrrole-3-carboxylate (***6a***)*: mp 166–168°C; crystallized from tetrahydrofuran – *n*-pentane; IR: 3440 (NH), 3330, 3190 (NH_2 overlap), 1760, 1680, 1640, and 1610 (C=O overlap) cm^{-1}; ^1H NMR: 2.26 (3H, s, Me), 3.65 (6H, s, 2 × CO_2Me), 4.37 and 4.44 (1H, 2 s, CH, D_2O-exch.), 6.28 and 6.40 (2H, 2 s, NH_2, D_2O-exch.), and 8.68 and 8.76 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{10}H_{13}N_3O_6$: C 44.14, H 4.83, N 15.49; found: C 44.14, H 4.74, N 15.35.

*Ethyl 4-methoxycarbonyl-2-methyl-5-oxo-1-ureido-1,4-dihydropyrrole-3-carboxylate (***6b***)*: mp 80–82°C; crystallized from tetrahydrofuran – *n*-pentane; IR: 3440 (NH), 3330, 3190 (NH_2 overlap), 1760, 1690, 1645, and 1600 (C=O overlap) cm^{-1}; ^1H NMR: 1.17 (3H, t, J = 7 Hz, CO_2CH_2*Me*), 2.26 (3H, s, Me), 3.66 (3H, s, CO_2Me), 4.14 (2H, q, J = 7 Hz, CO_2CH_2Me), 4.36 and 4.43 (1H, 2 s, CH, D_2O-exch.). 6.30 and 6.42 (2H, 2 s, NH_2, D_2O-exch.), and 8.70 and 8.77 (1H, 2 s, NH, D_2O-exch.), Anal. calcd. for $C_{11}H_{15}N_3O_6$: C 46.32, H 5.30, N 14.73; found: C 46.46, H 5.21, N 14.91.

*Methyl 4-methoxycarbonyl-2-methyl-5-oxo-1-(*N′*-phenylureido)-1,4-dihydropyrrole-3-carboxylate (***6c***)*: mp 174–177°C; crystallized from ethyl acetate; IR: 3340 (NH), 3200, 3140 (NH overlap), 1760 (C=O), 1715 (C=O), 1690 (C=O), 1650 (C=O), and 1600 (C=O) cm^{-1}; ^1H NMR: 2.31 (3H, s, Me) 3.67 (3H, s, CO_2Me), 3.68 (3H, s, CO_2Me), 4.51 (1H, s, CH, D_2O-exch.), 6.99–7.46 (5H, m, Ph), 8.89 and 9.06 (1H, 2 s, NH, D_2O-exch.), and 9.30 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{16}H_{17}N_3O_6$: C 55.33, H 4.93, N 12.10; found: C 55.21, H 5.01, N 12.27.

*Ethyl 4-methoxycarbonyl-2-methyl-5-oxo-1-(*N′*-phenylureido)-1,4-dihydropyrrole-3-carboxylate (***6d***)*: mp 188–190°C; crystallized from ethyl acetate; IR: 3340 (NH), 3190, 3120 (NH overlap), 1760 (C=O), 1710 (C=O), 1680 (C=O, 1650 (C=O), and 1600 (C=O) cm^{-1}; ^1H NMR: 1.19 (3H, t, J = 7 Hz, CO_2CH_2*Me*) 2.31 (3H, s, Me), 3.68 (3H, s, CO_2Me), 4.12 (2H, q, J = 7 Hz, CO_2CH_2Me), 4.48 (1H, s, CH, D_2O-exch.), 6.99–7.46 (5H, m, Ph), 8.87 and 9.04 (1H, 2 s, NH, D_2O-exch.), and 9.28 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{17}H_{19}N_3O_6$: C 56.51, H 5.22, N 11.63; found: C 56.71, H 5.22, N 11.77.

*Methyl 2-methyl-4-methoxycarbonyl-1-(methoxycarbonylamino)-5-oxo-1,4-dihydropyrrole-3-carboxylate (***6e***)*: oil; IR: 3480, 3280 (NH overlap), 1770, 1730, 1710 (C=O overlap), and 1640 (C=O) cm^{-1}; ^1H NMR: 2.27 (3H, s, Me), 3.66 (9H, s, 3 × CO_2Me), 4.58 (1H, s, CH, D_2O-exch.), and 10.19 and 10.25 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{11}H_{14}N_2O_7$: C 46.16, H 4.93, N 9.79; found: C 46.31, H 4.77, N 9.88.

*Ethyl 1-(*tert*-butoxycarbonylamino)-4-(methoxycarbonyl-2-methyl-5-oxo-1,4-dihydropyrrole-3-carboxylate (***6f***)*: oil; IR: 3480, 3290 (NH overlap), 1765, 1735, 1710 (C=O overlap), and 1645 (C=O) cm^{-1}; ^1H NMR: 1.20 (3H, q, J = 7 Hz, CO_2CH_2*Me*), 1.43 (9H, s, t-Bu), 2.30 (3H, s, Me), 4.18 (2H, t, J = 7 Hz, CO_2CH_2Me), 4.58 (1H, s, CH, D_2O-exch.), and 9.91 and 9.93 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{15}H_{22}N_2O_7$: C 52.63, H 6.48, N 8.18; found: C 52.78, H 6.59, N 8.03.

*Methyl 4-benzyloxycarbonyl-2-methyl-5-oxo-1-ureido-1,4-dihydropyrrole-3-carboxylate (***6g***)*: mp 88–92°C; crystallized from dichloromethane – light petroleum, bp 30–60°C; IR: 3440 (NH), 3330, 3180 (NH_2 overlap), 1760, 1710, 1680, 1640, and 1610 (C=O overlap) cm^{-1}; ^1H NMR: 2.25 (3H, s, Me), 3.55 (3H, s, CO_2Me), 4.43 and 4.49 (1H, 2 s, CH, D_2O-exch.), 5.17 (2H, s, CO_2CH_2Ph), 6.29 and 6.39 (2H, 2 s, NH_2, D_2O-exch.), 7.35 (5H, s, CO_2CH_2*Ph*), and 8.69 and 8.76 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{16}H_{17}N_3O_6$: C 55.33, H 4.93, N 12.10; found: C 55.27, H 5.07, N 11.96.

*Methyl 4-benzyloxycarbonyl-2-methyl-5-oxo-1-(*N′*-phenylureido)-1,4-dihydropyrrole-3-carboxylate (***6h***)*: mp 118–120°C; crystallized from ethyl acetate; IR: 3320 (NH), 3210, 3140 (NH overlap), 1750 (C=O), 1690 (C=O overlap), 1640 (C=O), and 1600 (C=O) cm^{-1}; ^1H NMR: 2.32 (3H, s, Me), 3.57 (3H, s, CO_2Me), 4.58 (1H, s, CH, D_2O-exch.), 5.21 (2H, s, CO_2CH_2Ph), 8.96–7.48 (10H, m, Ph and CO_2CH_2*Ph*), 8.92 and 9.09 (1H, 2 s, NH, D_2O-exch.), and 9.34 (1H, s, NH, D_2O-exch.). Anal. calcd. for $C_{22}H_{21}N_3O_6$: C 62.41, H 5.0, N 9.92; found: C 62.53, H 4.86, N 10.05.

*Methyl 4-benzyloxycarbonyl-1-(methoxycarbonylamino)-2-methyl-5-oxo-1,4-dihydropyrrole-3-carboxylate (***6i***)*: oil; IR: 3490, 3280 (NH

overlap), 1760, 1740, 1710 (C=O overlap), 1640 (C=O) cm^{-1}; ^1H NMR: 2.28 (3H, s, Me), 3.65 (6H, s, 2 × CO_2Me), 4.58 (1H, s, CH, D_2O-exch.), 5.19 (2H, s, CO_2CH_2Ph), 7.36 (5H, s, CO_2CH_2Ph), and 10.06 and 10.10 (1H, 2 s, NH, D_2O-exch.). Anal. calcd. for $C_{17}H_{18}N_2O_7$: C 56.35, H 5.01, N 7.73; found: C 56.49, H 5.15, N 7.65.

Acknowledgement

This work was supported by financial assistance from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST-Roma) and the Consiglio Nazionale delle Ricerche (CNR-Roma).

1. A.R. Katritzky. Chem. Heterocycl. Compd. (Engl. Transl.), **28**, 291 (1992).
2. O. Attanasi and L. Caglioti. Org. Prep. Proced. Int. **18**, 299 (1986).
3. O. Attanasi, S. Santeusanio, F. Serra-Zanetti, E. Foresti, and A. McKillop. J. Chem. Soc. Perkin Trans. 1, 1669 (1990).
4. O. Attanasi, L. De Crescentini, S. Santeusanio, F. Serra-Zanetti, A. McKillop, and Z. Liao. J. Chem. Soc. Perkin Trans. 1, 1009 (1992).
5. O. Attanasi, L. De Crescentini, A. McKillop, S. Santeusanio, and F. Serra-Zanetti. J. Chem. Soc. Perkin Trans. 1, 3099 (1992).
6. J.H. Atkinson, R.S. Atkinson, and A.W. Johnson, J. Chem. Soc. 5999 (1964).
7. R. Di Santo, S. Massa, and M. Artico. Farmaco, **48**, 209 (1993).
8. J. Parrick and M. Porssa. Tetrahedron Lett. **34**, 5011 (1993); F. Arcamone. Farmaco, **48**, 143 (1993).
9. H. Fischer and H. Plieninger. Z. Physiol. Chem **274**, 231 (1949).
10. H. Plieninger, H. Bauer, and A.R. Katritzky. Justus Liebigs Ann. Chem. **654**, 165 (1962).
11. H. Suschitzky and O. Meth-Cohn (*Editors*). Heterocyclic chemistry. Vols. 1–4. Royal Society of Chemistry, London. 1978–1985; H. Suschitzky and E.F.V. Scriven (*Editors*). Progress in heterocyclic chemistry. Vols. 1–4. Pergamon Press, Oxford. 1985–1991; E.A.A. Hafez, N.N. Abed, M. Rifaat, H. Elmoghayer, and A.G.A. El-Agamey. Heterocycles, **22**, 1821 (1984). A.R. Katritzky and C.W. Rees (*Editors*). Comprehensive heterocyclic chemistry. Pergamon Press, Oxford. 1984; R.A. Jones and G.P. Bean. The chemistry of pyrroles. Academic Press, New York. 1977; J.M. Patterson. Synthesis, 281 (1976); A. Gossauer. Die Chemie der Pyrrole. Springer Verlag, Berlin. 1974.
12. O.A. Attanasi, P. Filippone, A. Mei, and S. Santeusanio. Synthesis, 873 (1984).
13. O.A. Attanasi, P. Filippone, A. Mei, and S. Santeusanio. Synthesis, 671 (1984).