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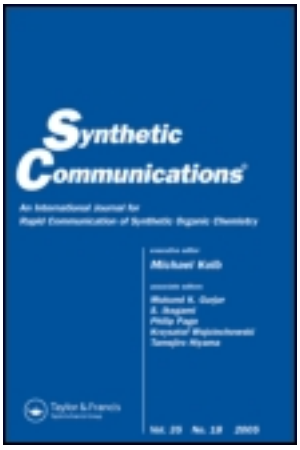

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of New N-(5-Oxo-2,5-dihydro)pyrrol-3-yl Glycines and N-(5-Oxo-2,5-dihydro)pyrrol-3-yl Glycines Esters

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Published online: 18 Aug 2006.

To cite this article: Fabrice Jourdan , Jens T. Kaiser & David J. Lowe (2005) Synthesis of New N-(5-Oxo-2,5-dihydro)pyrrol-3-yl Glycines and N-(5-Oxo-2,5-dihydro)pyrrol-3-yl Glycines Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:18, 2453-2466

To link to this article: http://dx.doi.org/10.1080/00397910500191219

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Synthetic Communications®, 35: 2453–2466, 2005
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ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500191219

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Synthesis of New N-(5-Oxo-2,5-dihydro)pyrrol-3-yl Glycines and N-(5-Oxo-2,5-dihydro)pyrrol-3-yl Glycines Esters

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Abstract: Following our efforts towards the synthesis of new potential inhibitors of Xanthine Dehydrogenase (XDH), we describe here a general method for the preparation of N-(5-oxo-2,5-dihydro)pyrrol-3-yl glycines and N-(5-oxo-2,5-dihydro)pyrrol-3-yl glycine esters from glycine ethyl ester hydrochloride and various 4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylic acid esters and carbonitriles.

Keywords: Xanthine dehydrogenase, amino acid, 5-oxopyrrol-3-ylglycine

INTRODUCTION

Xanthine dehydrogenase (XDH) is a 290-kDa homodimeric enzyme that catalyses the oxidation of hypoxanthine to xanthine and xanthine to uric

Received in the U.K. January 22, 2005
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acid.[1,2] Its crystal structure displays three major domains:[3] a 20-kDa N-terminal domain containing two Fe-S clusters, a central 40-kDa FAD domain, and a C-terminal 85-kDa molybdopterin-binding domain. XDH is a target of drugs against gout and hyperuricemia.[4] The conversion of the enzyme to its oxydase form xanthine oxidase (XO) has also been implicated in diseases characterized by oxygen radical–induced tissue damage such as postischemic reperfusion injury.[5] It has also been suggested that XO might be associated with blood-pressure regulation.[6]

During the past decades, a number of inhibitors such as anthraquinones,[7] flavonoids,[8,9] xanthones,[10] caffeic esters,[11] pteridines,[12–14] and purines[15–18] have been synthesized or isolated from plant sources. However, allopurinol remains to date the only drug available for the treatment of gout and hyperuricemia. As a consequence, the search for new inhibitors of XDH remains a very important goal. Within this context, we describe herein the results of our preliminary efforts toward the synthesis of new 3-hydroxy-6-oxo-1,4,5,6-tetrahydro pyrrolo[3,4-*b*]pyrrole-2-carboxylic acids (**II**, Figure 1). In particular, we describe a general procedure to access new N-(5-oxo-2,5-dihydro)pyrrol-3-yl glycines and N-(5-oxo-2,5-dihydro)-pyrrol-3-yl glycine esters from glycine ethyl ester hydrochloride and various 4-hydroxy-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid esters and carbonitriles.

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RESULT AND DISCUSSION

To design new XDH/XO inhibitors, we have taken advantage of the recent elucidation of bovine milk's XDH/XO crystal structure. Our study, which will be discussed elsewhere, led to a general model (**I**) described in Figure 1. It is composed of two fused five-membered heterocyclic rings (pyrrole, furan or thiophene rings). It was established that H-bond donor (HBD) and acceptor (HBA) substituents are crucial, in particular those at

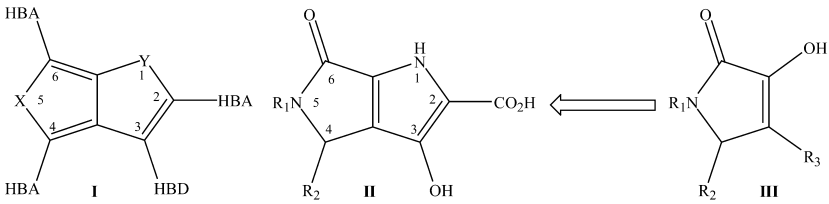

Figure 1. Design of XDH inhibitors. General model **I** and target molecules **II** and its precursor **III**.

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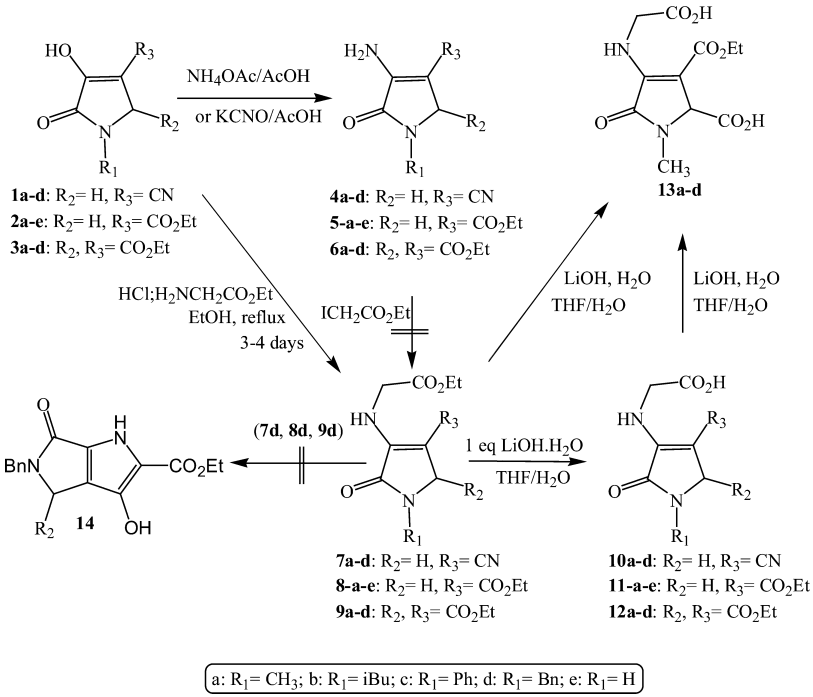
positions 2 and 3. They interact in the binding site of XDH with the guanidiium group of an arginine (Arg880), the carboxylate group of a glutamate (Glu1261), and the hydroxyl group of a threonine (Thr1010). Although some two- or three-heteroatom-containing rings were found to display good interactions with the active site of the enzyme, they were usually less promising. This was in general due to the fact that an increasing number of heteroatoms in the heterocyclic backbone implicitly decreases the number of H-bond donor/acceptor groups on the heterocyclic backbone. Our study also showed that a phenylalanine (Phe914) interacts by π-stacking with the aromatic ring of the substrate (e.g., salicylate in the crystal structure).

Among the various possibilities of structures fitting our model **I**, we decided to focus our attention on the synthesis of the 3-hydroxy-6-oxo-1,4,5,6-tetrahydro pyrrolo[3,4-*b*]pyrrole-2-carboxylic acids **II** via the intermediate 4-amino-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carbonitriles or -3-carboxylic acid esters **III**, the preparation of which are described in the literature.

The synthesis of the different 4-hydroxy-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid esters and carbonitriles **1a–d**, **2a–e**, and **3a–d** (Scheme 1) was achieved following different methods previously described



Scheme 1. Synthesis of the N-pyrrol-3-yl glycines **10–13**.

in the literature.[19–22] Their corresponding enamines **4a–d**, **5a–e**, and **6a–d** were obtained by treatment with ammonium acetate or potassium cyanate.[23] Unfortunately, these enamines proved unreactive and could not be alkylated with iodoacetic acid ethyl ester. On the other hand, the enols **1a–d**, **2a–e**, and **3a–d** proved to react with glycine ethyl ester hydrochloride in refluxing ethanol, although this nucleophilic substitution was found to be slow and refluxing times of 3 to 4 days were required to obtain the target N-pyrrolyl glycine esters **7a–d**, **8a–e** and **9a–d** in good yields (65–85%). Various attempts to obtain the target 3-hydroxy-6-oxo-1,4,5,6-tetrahydro pyrrolo[3,4-*b*]pyrrole-2-carboxylic acid esters **14** from the (1-benzyl-4-cyano-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid ethyl ester (**7d**) and (1-benzyl-4-ethoxycarbonyl-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid ethyl esters (**8d**, **9d**) failed. No reaction occurred by direct action of these starting materials with bases (NaOH, NaH, BuLi) in dry THF. In parallel, we tried to protect **8d** with various protecting groups to subsequently carry out the intramolecular cyclization. Unfortunately the enamine could not be protected and access to **14** following this route was abandoned.

Conversely, hydrolysis of the different ester groups was found to take place selectively with good to excellent yields upon careful hydrolysis of **7–9** with lithium hydroxide monohydrate. As expected, **7a–d** were deprotected in THF and water with at least 1 equivalent of base, leading to the (4-cyano-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid **10a–d**. Compounds **8a–e** afforded, following the same method, the monoacids **11a–e**. Interestingly, in the case of the triesters **9a–d**, selective hydrolyses of the glycine ester occurred when strictly one equivalent of LiOH, H_2O was used. Two or more equivalents of the base directly led to the 4-(carboxymethyl-amino)-5-oxo-2,5-dihydro-*1H*-pyrrole-2,3-dicarboxylic acid 3-ethyl ester **13a–d**. The latter were also obtained by further hydrolyses of the monoesters **12a–d** with an excess of lithium hydroxide. Furthermore, no hydrolysis of the 3-carboxylic acid ester of the di- and triesters **8a–e** and **9a–d** and their corresponding acids **11a–e**, **12a–d**, and **13a–d** was found to be occur with LiOH as well as with NaOH or KOH at room temperature. These selective deprotections of the carboxylic acids can be used to functionalize the N-pyrrolyl glycine at specific positions. This strategy is currently used in our laboratory with the aim of preparing new peptidic structures analogous to the antibiotic Microcin B17, a DNA gyrase inhibitor containing the unnatural amino acids 2-aminomethyloxazol-4-carboxylic acids and 2-aminomethylthiazol-4-carboxylic acids.

In conclusion, despite failing to obtain the target 3-hydroxy-6-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrole-2-carboxylic acids as potential inhibitors of XDH via **7a–d** through **9a–d**, we describe here a general method to access new N-pyrrolyl glycines and glycine esters **7a–d** through **13a–d**. Moreover, the selective deprotection of **9a–d** to its monoacids **12a–d** has proved very useful. Indeed, these monoacids are currently used in our laboratory with the aim of preparing new peptidomimetics.

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EXPERIMENTAL

Yields expressed are for isolated pure compounds (flash chromatography). Their characterization was obtained by a combination of IR, NMR, MS, and microanalysis. Infrared spectra were recorded on a FTIR-8300 Shimadzu spectrometer in KBr with absorptions in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM LA-400 spectrometer. Mass spectra were recorded on a Kratos MS25 spectrometer.

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General Method for the Synthesis of the N-Pyrrolyl Glycine Esters 7a–d, 8a–e, 9a–d

A solution of 4-hydroxy-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid esters and carbonitriles **1a–d**, **2a–e** or **3a–d** (1 mmol) and glycine ethyl ester hydrochloride (5 mmol, 0.70 g) in 30 ml of ethanol was heated to 80°C and the reaction monitored by TLC. When the reaction was complete (3–4 days), the solution was cooled to room temperature, ethanol evaporated under reduced pressure, and the residual solid was dissolved in ethyl acetate (50 ml) and water (20 ml). The aqueous layer was extracted with another 30 ml of ethyl acetate, and the combined organic layers were washed with successively with water and brine, dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The residual oil/solid was purified by column chromatography (hexane/ethyl acetate) to afford **7a–d, 8a–e** or **9a–d**.

(4-Cyano-1-methyl-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid ethyl ester **7a**: White crystals; 175 mg (78%); mp = 120–121°C; IR: 3307 (NH), 2198 (CN), 1749, and 1661 (C=O); ^1H NMR ($CDCl_3$) δ: 5.97 (t, $J_{H\text{-}H} = 5.9$ Hz, 1H, NH), 4.28 (d, $J_{H\text{-}H} = 5.9$ Hz, 2H, $NC\underline{H}_2CO_2Et$), 4.27 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, OCH_2), 3.96 (s, 2H, CH_2), 3.08 (s, 3H, CH_3N), 1.32 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 168.6 (CO), 163.8 (CO), 146.3 (C3), 116.1 (CN), 74.6 (C4), 61.9 (CH_2O), 50.5 (CH_2), 44.4 (CH_2), 29.8 (CH_3N), 14.4 (CH_3), 14.0 (CH_3). Anal. calcd. for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.72; H, 5.88; N, 18.78.

(4-Cyano-1-isobutyl-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid ethyl ester **7b**: White crystals; 210 mg (79%); mp = 82–83°C; IR: 3310 (NH), 2197 (CN), 1748, and 1659 (C=O); ^1H NMR ($CDCl_3$) δ: 5.89 (t, $J_{H\text{-}H} = 5.9$ Hz, 1H, NH), 4.30 (d, $J_{H\text{-}H} = 5.9$ Hz, 2H, $NC\underline{H}_2CO_2Et$), 4.29 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, OCH_2), 3.96 (s, 2H, CH_2), 3.28 (d $J_{H\text{-}H} = 7.8$ Hz, 2H, NCH_2), 1.96 (m, 1H, CH), 1.32 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3), 0.91 (d, $J_{H\text{-}H} = 6.6$ Hz, 6H, $2 \times rCH_3$); ^{13}C NMR ($CDCl_3$) δ: 168.6 (CO), 164.0 (CO), 146.2 (C3), 116.2 (CN), 74.8 (C4), 62.0 (CH_2O), 50.7 (CH_2), 49.3(CH_2), 44.5 (CH_2), 27.6 (CH), 19.9 ($2 \times CH_3$), 14.1 (CH_3). Anal. calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.63; H, 7.01; N, 15.59.

(4-Cyano-2-oxo-1-phenyl-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid ethyl ester **7c**: White crystals; 210 mg (74%); mp = 177–178°C; IR: 3322

(NH), 2203 (CN), 1747, and 1660 (C═O); ^{1}H NMR ($CDCl_3$) δ: 7.68 (m, 2H, Ph), 7.41 (m, 2H, Ph), 7.22 (m, 1H, Ph), 6.00 (t, $J_{H\text{-}H} = 5.9$ Hz, 1H, NH), 4.41 (s, 2H, CH2), 4.33 (d, $J_{H\text{-}H} = 5.9$ Hz, 2H, $NC\underline{H}_2CO_2Et$), 4.30 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, OCH_2), 1.33 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 168.6 (CO), 163.8 (CO), 146.3 (C3), 137.8, 129.3, 125.6 and 119.1 (Ph), 115.8 (CN), 74.9 (C4), 62.1 (CH_2O), 49.0 (CH_2), 44.4 (CH_2), 14.1 (CH_3). Anal. calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.97; H, 5.33; N, 14.72.

(1-Benzyl-4-Cyano-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid ethyl ester **7d**: White crystals; 230 mg (77%); mp = 78–79°C; IR: 3332 (NH), 2195 (CN), 1749, and 1660 (C═O); ^{1}H NMR ($CDCl_3$) δ: 7.30 (m, 3H, Ph), 7.22 (m, 2H, Ph), 6.07 (t, $J_{H\text{-}H} = 5.8$ Hz, 1H, NH), 4.29 (d, $J_{H\text{-}H} = 5.8$ Hz, 2H, $NC\underline{H}_2CO_2Et$), 4.27 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, OCH_2), 3.84 (s, 2H, CH_2), 1.31 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 168.6 (CO), 163.7 (CO), 146.0 (C3), 135.4, 128.9 and 128.0 (Ph), 116.0 (CN), 75.1 (C4), 62.0 (CH_2O), 48.1 (CH_2), 47.0 (CH_2), 44.4 (CH_2), 14.0 (CH_3); Anal. calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.18; H, 5.61; N, 13.86.

4-(Ethoxycarbonylmethyl-amino)-1-methyl-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **8a**: White crystals; 225 mg (83%); mp = 69°C; IR: 3347 (NH), 1750, 1702 and 1669 (C═O); ^{1}H NMR ($CDCl_3$) δ: 6.83 (br, 1H, NH), 4.50 (d, $J_{H\text{-}H} = 6.3$ Hz, 2H, $NC\underline{H}_2CO_2Et$), 4.14 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, OCH_2), 4.12 (q, $J_{H\text{-}H} = 7.3$ Hz, 2H, OCH_2), 3.86 (s, 2H, CH_2), 2.94 (s, 3H, CH_3N), 1.21 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3), 1.18 (t, $J_{H\text{-}H} = 7.3$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.4 (CO), 165.1 (CO), 164.6 (CO), 145.9 (C4), 98.9 (C3), 60.6 (CH_2O), 59.2 (CH_2O), 49.0 (CH_2), 43.7 (CH_2), 29.1 (CH_3N), 13.9 (CH_3), 13.7 (CH_3); Anal. calcd. for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.31; H, 6.66; N, 10.27.

4-(Ethoxycarbonylmethyl-amino)-1-isobutyl-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **8b**: Yellow crystals; 230 mg (72%); mp = 48°C; IR: 3328 (NH), 1748, 1698 and 1662 (C═O); ^{1}H NMR ($CDCl_3$) δ: 6.81 (br, 1H, NH), 4.52 (d, $J_{H\text{-}H} = 6.3$ Hz, 2H, $NC\underline{H}_2CO_2Et$), 4.15 (q, $J_{H\text{-}H} = 7.3$ Hz, 2H, OCH_2), 4.12 (q, $J_{H\text{-}H} = 7.3$ Hz, 2H, OCH_2), 3.89 (s, 2H, CH_2), 3.16 (d, $J_{H\text{-}H} = 7.5$ Hz, 2H, CH_2), 1.90 (m, 1H, CH), 1.23 (t, $J_{H\text{-}H} = 7.3$ Hz, 3H, CH_3), 1.19 (t, $J_{H\text{-}H} = 7.3$ Hz, 3H, CH_3), 0.83 (d, $J_{H\text{-}H} = 6.6$ Hz, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.6 (CO), 165.6 (CO), 164.9 (CO), 146.0 (C4), 99.3 (C3), 61.0 (CH_2O), 59.6 (CH_2), 50.1 (CH_2), 48.0 (CH_2), 44.7 (CH_2), 27.4 (CH), 19.8 (2 × CH_3), 14.2 (CH_3), 13.9 (CH_3). Anal. calcd. for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.43; H, 7.67; N, 9.01.

4-(Ethoxycarbonylmethyl-amino)-5-oxo-1-phenyl-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **8c**: White crystals; 275 mg (83%); mp = 104°C; IR: 3341 (NH), 1747, 1695 and 1665 (C═O); ^{1}H NMR ($CDCl_3$) δ: 7.72 (m, 2H, ArH), 7.38 (m, 2H, ArH), 7.15 (m, 1H, ArH), 6.88 (br, 1H, NH), 4,62 (d, $J_{H\text{-}H} = 6.2$ Hz, 2H, $NC\underline{H}_2CO_2Et$), 4.42 (s, 2H, CH_2), 4.26 (q, $J_{H\text{-}H} =$

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7.1 Hz, 2H, OCH_2), 4.23 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H, OCH_2), 1.34 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 1.29 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.6 (CO), 164.9 (CO), 164.5 (CO), 145.7 (C4), 138.6, 129.0, 125.0 and 119.3 (Ph), 99.4 (C3), 61.3 (CH_2O), 60.0 (CH_2), 48.0 (CH_2), 44.5 (CH_2), 14.4 (CH_3), 14.1 (CH_3). Anal. calcd. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.21; H, 5.98; N, 8.42.

1-Benzyl-4-(Ethoxycarbonylmethyl-amino)-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **8d**: White crystals; 280 mg (81%); mp = 77°C; IR: 3339 (NH), 1748, 1692 and 1669 (C=O); ^{1}H NMR ($CDCl_3$) δ: 7.35–7.22 (m, 5H, ArH), 6.91 (br, 1H, NH), 4.63 (d, $J_{H\text{-}H}$ = 6.5 Hz, 2H, $NC\underline{H}_2CO_2Et$), 4.61 (s, 2H, CH_2Ph), 4.23 (q, $J_{H\text{-}H}$ = 7.3 Hz, 2H, OCH_2), 4.18 (q, $J_{H\text{-}H}$ =7.3 Hz, 2H, OCH_2), 3.86 (s, 2H, CH_2), 1.28 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H, CH_3), 1.25 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.7 (CO), 165.4 (CO), 164.5 (CO), 145.9 (C4), 136.3, 128.7, 128.0 and 127.6 (Ph), 99.8 (C3), 61.1 (CH_2O), 59.6 (CH_2), 47.7 (CH_2), 46.5 (CH_2), 44.5 (CH_2), 14.3 (CH_3), 14.0 (CH_3). Anal. calcd. for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.46; H, 6.31; N, 8.05.

4-(Ethoxycarbonylmethyl-amino)-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **8e**: White crystals; 180 mg (70%); mp = 138°C; IR: 3351, 3188 (NH), 1753, 1699 and 1669 (C=O); ^{1}H NMR (CD_3COCD_3) δ: 7.62 (br, 1H, NH), 6.90 (br, 1H, NH), 4.47 (s, 2H, $NC\underline{H}_2CO_2Et$), 4.06 (q, $J_{H\text{-}H}$ = 7.3 Hz, 2H, OCH_2), 4.02 (q, $J_{H\text{-}H}$ = 7.3 Hz, 2H, OCH_2), 3.81 (s, 2H, CH_2), 1.13 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H, CH_3), 1.10 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H, CH_3); ^{13}C NMR (CD_3COCD_3) δ: 171.5 (CO), 168.5 (CO), 165.8 (CO), 147.4 (C4), 102.0 (C3), 61.3 (CH_2O), 60.0 (CH_2O), 44.5 (CH_2), 43.0 (CH_2), 14.7 (CH_3), 14.5 (CH_3). Anal. calcd. for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.43; H, 6.17; N, 10.83.

4-(Ethoxycarbonylmethyl-amino)-1-methyl-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylic acid diethyl ester **9a**: White crystals; 245 mg (71%); mp = 96°C; IR: 3320 (NH), 1748, 1726, 1698 and 1659 (C=O); ^{1}H NMR ($CDCl_3$) δ: 7.19 (br, 1H, NH), 4.74 (m, 1H, $NC\underline{H}_2CO_2Et$), 4.64 (s, 1H, CH), 4.47 (m, 1H, $NC\underline{H}_2CO_2Et$), 4.26–4.17 (m, 6H, 3 × OCH_2), 2.95 (s, 3H, CH_3N), 1.29 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 1.28 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 1.26 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.2 (CO), 168.7 (CO), 165.5 (CO), 164.5 (CO), 147.2 (C4), 99.4 (C3), 62.2 (CH), 61.7 (CH_2O), 61.3 (CH_2O), 59.9 (CH_2O), 43.8 (CH_2), 28.2 (CH_3N), 14.3 (CH_3), 14.1 (2 × CH_3). Anal. calcd. for $C_{15}H_{22}N_2O_7$: C, 52.63; H, 6.48; N, 8.18. Found: C, 52.61; H, 6.37; N, 8.16.

4-(Ethoxycarbonylmethyl-amino)-1-isobutyl-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylic acid diethyl ester **9b**: Yellow oil; 290 mg (75%); IR: 3332 (NH), 1750, 1722, 1700 and 1661 (C=O); ^{1}H NMR ($CDCl_3$) δ: 6.12 (br, 1H, NH), 4.61 (s, 1H, CH), 4.55 (m, 1H, $NC\underline{H}_2CO_2Et$), 4.44 (m, 1H, $NC\underline{H}_2CO_2Et$), 4.16–4.04 (m, 6H, 3 × OCH_2), 3.40 [dd, $J_{H\text{-}H}$ = 13.8 and 9.0 Hz, 1H, $(CH_3)_2CHC\underline{H}_2N$], 2.70 [dd, $J_{H\text{-}H}$ = 13.8 and 6.3 Hz, 1H, $(CH_3)_2CHC\underline{H}_2N$], 1.85 (m, 1H, $(CH_3)_2C\underline{H}CH_2N$), 1.20–1.12 (m, 9H,

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3 × CH_3), 0.82 (d, $J_{H\text{-}H}$ = 6.6 Hz, 3H, CH_3), 0.74 (d, $J_{H\text{-}H}$ = 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.7 (CO), 169.4 (CO), 166.1 (CO), 165.8 (CO), 147.8 (C4), 99.9 (C3), 62.1 (CH_2O), 61.6 (CH_2O), 61.4 (CH), 60.3 (CH_2O), 49.3 (CH_2), 44.3 (CH_2), 27.6 (CH), 20.2 (2 × CH_3), 14.5 (CH_3), 14.3 (CH_3) 14.2 (CH_3). Anal. calcd. for $C_{18}H_{28}N_2O_7$: C, 56.24; H, 7.34; N, 7.29. Found: C, 56.01; H, 7.32; N, 7.14.

4-(Ethoxycarbonylmethyl-amino)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2,3-dicarboxylic acid diethyl ester **9c**: White solid; 330 mg (82%); mp = 92°C; IR: 3328 (NH), 1750, 1720, 1697 and 1658 (C═O); ^{1}H NMR ($CDCl_3$) δ: 7.47 (m, 2H, ArH), 7.27 (m, 2H, ArH), 7.11 (m, 1H, ArH), 6.72 (br, 1H, NH), 5.26 (s, 1H, CH), 4.65 (m, 1H, NC$\underline{H}_2CO_2Et$), 4.43 (m, 1H, NC$\underline{H}_2CO_2Et$), 4.14 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H, OCH_2), 4.12 (q, $J_{H\text{-}H}$ = 7.2 Hz, 2H, OCH_2), 3.97 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H, OCH_2), 1.21 (t, $J_{H\text{-}H}$ = 7.2 Hz, 3H, CH_3), 1.18 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 0.98 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.0 (CO), 168.3 (CO), 164.4 (CO), 164.2 (CO), 146.7 (C4), 136.2, 128.8, 126.0 and 121.7 (Ph), 99.2 (C3), 61.5 (CH_2O), 61.3 (CH), 61.1 (CH_2O), 59.9 (CH_2O), 43.9 (CH_2), 14.0 (CH_3), 13.9 (CH_3) 13.6 (CH_3). Anal. calcd. for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.12; H, 5.93; N, 6.78.

1-Benzyl-4-(Ethoxycarbonylmethyl-amino)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylic acid diethyl ester **9d**: Yellow oil; 310 mg (74%); IR: 3339 (NH), 1748, 1723, 1698 and 1660 (C═O); ^{1}H NMR ($CDCl_3$) δ: 7.25–7.12 (m, 5H, ArH), 6.89 (br, 1H, NH), 4.81 (d, $J_{H\text{-}H}$ = 15.2 Hz, 1H, C$\underline{H}_2$Ph), 4.57 (m, 1H, NC$\underline{H}_2CO_2Et$), 4.46 (m, 1H, NC$\underline{H}_2CO_2Et$), 4.44 (s, 1H, CH), 4.15–3.90 (m, 7H, 3 × OCH_2 and C$\underline{H}_2$Ph), 1.18 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 1.12 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 1.10 (t, $J_{H\text{-}H}$ = 7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 171.1 (CO), 170.7 (CO), 166.0 (CO), 165.8 (CO), 147.3 (C4), 136.2, 129.0, 128.7 and 128.2 (Ph), 99.6 (C3), 62.1 (CH_2O), 61.7 (CH_2O), 60.5 (CH), 60.3 (CH_2O), 45.7 (CH_2), 44.9 CH_2), 14.4 (CH_3), 14.3 (CH_3) 14.2 (CH_3). Anal. calcd. for $C_{21}H_{26}N_2O_7$: C, 60.28; H, 6.26; N, 6.69. Found: C, 60.04; H, 6.12; N, 6.72.

General Method for the Hydrolysis of the N-Pyrrolyl Glycine Esters 7a–d, 8a–e, 9a–d

A solution of **7a–d**, **8a–e**, or **9a–d** (0.5 mmol) in 10 ml of THF and 10 ml of water was stirred at room temperature with 1 equivalents of lithium hydroxide monohydrate (0.50 mmol, 21 mg) and the reaction monitored by TLC. When the reaction was complete (30 min to 1 h), the solution extracted with ethyl acetate (50 ml). The aqueous layer was then made acidic with a ~1M aqueous solution of NH_4Cl and extracted with ethyl acetate (3 × 20 ml), and the combined organic layers were successively washed with water and brine, dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The residual oil/solid was purified by column chromatography

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(hexane/ethyl acetate) and/or recrystallized to afford **10a–d, 11a–e**, or **12a–d**.

Compounds **13a–d** were obtained directly from **9a–d** or from **12a–d** using 3 to 5 equivalents of LiOH; H_2O and following the method described previously. They were purified by column chromatography (hexane/ethyl acetate/methanol) and/or recrystallized (hexane/ethyl acetate).

(4-Cyano-1-methyl-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid **10a**: White crystals; 85 mg (87%); mp = 131–132°C; IR: 3410–3035 (OH, NH), 2198 (CN), 1733, and 1661 (C=O); ^{1}H NMR (CD_3COCD_3) δ: 6.42 (t, $J_{H\text{-}H}$ = 6.4 Hz, 1H, NH), 5.47 (br, 1H, OH), 4.30 (d, $J_{H\text{-}H}$ = 6.4 Hz, 2H, NCH_2CO_2H), 4.00 (s, 2H, CH_2), 3.01 (s, 3H, CH_3N); ^{13}C NMR (CD_3COCD_3) δ: 170.7 (CO), 164.5 (CO), 147.6 (C3), 116.9 (CN), 75.1 (C4), 50.9 (CH_2), 44.5 (CH_2), 29.7 (CH_3N). Anal. calcd. for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.02; H, 4.38; N, 21.46.

(4-Cyano-1-isobutyl-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid **10b**: White crystals; 110 mg (93%); mp = 192–193°C; IR: 3405–3040 (OH, NH), 2196 (CN), 1738, and 1660 (C=O); ^{1}H NMR (CD_3COCD_3) δ: 6.38 (t, $J_{H\text{-}H}$ = 6.4 Hz, 1H, NH), 5.09 (br, 1H, OH), 4.25 (d, $J_{H\text{-}H}$ = 6.4 Hz, 2H, NCH_2CO_2H), 4.00 (s, 2H, CH_2), 3.23 (d, $J_{H\text{-}H}$ = 7.5 Hz, 2H, CH_3N), 1.96 (m, 1H, CH), 0.84 (d, $J_{H\text{-}H}$ = 6.8 Hz, 6H, 2 × CH_3); ^{13}C NMR (CD_3COCD_3) δ: 170.8 (CO), 164.8 (CO), 147.4 (C3), 117.0 (CN), 75.2 (C4), 51.0 (CH_2), 49.7 (CH_2), 44.6 (CH_2), 28.2 (CH), 20.2 (2 × CH_3). Anal. calcd. for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.57; H, 6.24; N, 17.71.

(4-Cyano-2-oxo-1-phenyl-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid **10c**: White crystals; 115 mg (89%); mp = 219–220°C; IR: 3435–3050 (OH, NH), 2202 (CN), 1734, and 1658 (C=O); ^{1}H NMR (CD_3COCD_3) δ: 7.82 (m, 2H, Ph), 7.42 (m, 2H, Ph), 7.20 (m, 1H, Ph), 6.59 (t, $J_{H\text{-}H}$ = 6.3 Hz, 1H, NH), 5.51 (br, 1H, OH), 4.55 (s, 2H, CH_2), 4.36 (d, $J_{H\text{-}H}$ = 6.3 Hz, 2H, NCH_2CO_2H); ^{13}C NMR (CD_3COCD_3) δ: 170.6 (CO), 163.6 (CO), 147.1 (C3), 139.5, 129.9, 125.9 and 119.9 (Ph), 116.6 (CN), 75.7 (C4), 49.5 (CH_2), 44.4 (CH_2). Anal. calcd. for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.52; H, 4.13; N, 16.16.

(1-Benzyl-4-cyano-2-oxo-2,5-dihydro-*1H*-pyrrol-3-ylamino)-acetic acid **10d**: White crystals; 118 mg (87%); mp = 186–187°C; IR: 3430–3060 (OH, NH), 2195 (CN), 1736, and 1659 (C=O); ^{1}H NMR (CD_3COCD_3) δ: 7.33 (m, 3H, Ph), 7.24 (m, 2H, Ph), 6.47 (t, $J_{H\text{-}H}$ = 6.4 Hz, 1H, NH), 5.19 (br, 1H, OH), 4.38 (s, 2H, CH_2), 4.18 (d, $J_{H\text{-}H}$ = 6.4 Hz, 2H, NCH_2CO_2H), 3.92 (s, 2H, CH_2); ^{13}C NMR (CD_3COCD_3) δ: 170.7 (CO), 163.7 (CO), 146.9 (C3), 136.5, 128.8, 127.8 and 127.7 (Ph), 116.7 (CN), 73.3 (C4), 47.9 (CH_2), 46.1 (CH_2), 44.0 (CH_2); Anal. calcd. for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.97; H, 4.86; N, 15.31.

4-(Carboxymethyl-amino)-1-methyl-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **11a**: White crystals; 105 mg (87%); mp = 91–92°C; IR: 3390–3055 (OH, NH), 1738, 1701 and 1670 (C=O); ^{1}H NMR

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(DMSO-*d6*) δ: 8.96 (br, 1H, OH), 6.95 (br, 1H, NH), 4.48 (s, 2H, NCH_2CO_2H), 4.19 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, CH_2O), 3.97 (s, 2H, CH_2), 3.00 (s, 3H, CH_3N), 1.28 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-*d6*) δ: 174.4 (CO), 167.4 (CO), 166.4 (CO), 148.3 (C4), 100.2 (C3), 60.9 (CH_2O), 50.7 (CH_2), 45.1 (CH_2), 29.9 (CH_3N), 14.3 (CH_3); Anal. calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.26; H, 5.61; N, 11.23.

4-(Carboxymethyl-amino)-1-isobutyl-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **11b**: White crystals; 120 mg (84%); mp = 93–94°C; IR: 3395–3045 (OH, NH), 1742, 1700 and 1665 (C=O); ^1H NMR ($CDCl_3$) δ: 8.59 (br, 1H, OH), 6.75 (br, 1H, NH), 4.49 (d, $J_{H\text{-}H} = 6.4$ Hz, 2H, NCH_2CO_2H), 4.12 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, CH_2O), 3.90 (s, 2H, CH_2), 3.15 (d, $J_{H\text{-}H} = 7.5$ Hz, 2H, CH_2N), 1.88 (m, 1H, CH), 1.20 (t, $J_{H\text{-}H} =$ 7.1 Hz, 3H, CH_3), 0.81 (d, $J_{H\text{-}H} = 6.6$ Hz, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$) δ: 174.4 (CO), 166.4 (CO), 165.5 (CO), 146.2 (C4), 100.2 (C3), 60.3 (CH_2O), 50.8 (CH_2), 48.8 (CH_2), 44.7 (CH_2), 28.0 (CH), 20.1 ($2 \times CH_3$), 14.5 (CH_3). Anal. calcd. for $C_{13}H_{20}N_2O_5$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.75; H, 6.78; N, 9.81.

4-(Carboxymethyl-amino)-5-oxo-1-phenyl-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **11c**: White crystals; 130 mg (85%); mp = 158–159°C; IR: 3400–3050 (OH, NH), 1741, 1698 and 1665 (C=O); ^1H NMR ($CDCl_3$) δ: 8.76 (br, 1H, OH), 7.72 (m, 2H, Ph), 7.38 (m, 2H, Ph), 7.18 (m, 1H, Ph), 6.78 (br, 1H, NH), 4.52 (d, $J_{H\text{-}H} = 6.3$ Hz, 2H, NCH_2CO_2H), 4.44 (s, 2H, CH_2), 4.23 (q, $J_{H\text{-}H} = 7.3$ Hz, 2H, CH_2O), 1.28 (t, $J_{H\text{-}H} =$ 7.3 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 173.9 (CO), 166.1 (CO), 165.4 (CO), 145.9 (C4), 138.6, 128.9, 125.0 and 119.2 (Ph), 100.3 (C3), 60.8 (CH_2O), 48.3 (CH_2), 46.4 (CH_2), 14.4 (CH_3). Anal. calcd. for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.03; H, 5.07; N, 9.18.

1-Benzyl-4-(carboxymethyl-amino)-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **11d**: White crystals; 125 mg (79%); mp = 119–120°C; IR: 3410–3070 (OH, NH), 1739, 1697 and 1668 (C=O); ^1H NMR ($CDCl_3$) δ: 9.36 (br, 1H, OH), 7.28–7.14 (m, 5H, Ph), 6.82 (br, 1H, NH), 4.58 (d, $J_{H\text{-}H} = 6.4$ Hz, 2H, NCH_2CO_2H), 4.54 (s, 2H, CH_2Ph), 4.10 (q, $J_{H\text{-}H} =$ 7.1 Hz, 2H, CH_2O), 3.80 (s, 2H, CH_2), 1.18 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 174.9 (CO), 165.7 (CO), 165.2 (CO), 146.0 (C4), 136.1, 128.8, 128.1 and 127.8 (Ph), 100.2 (C3), 59.9 (CH_2O), 47.2 (CH_2), 46.7 (CH_2), 44.1 (CH_2), 14.3 (CH_3). Anal. calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.16; H, 5.49; N, 8.74.

4-(Carboxymethyl-amino)-5-oxo-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid ethyl ester **11e**: White crystals; 85 mg (74%); mp = 152–153°C; IR: 3375–3050 (OH, NH), 1743, 1700 and 1668 (C=O); ^1H NMR (DMSO-*d6*) δ: 8.65 (br, 1H, OH), 6.97 (br, 1H, NH), 4.34 (d, $J_{H\text{-}H} = 6.9$ Hz, 2H, NCH_2CO_2H), 4.13 (q, $J_{H\text{-}H} = 7.3$ Hz, 2H, CH_2O), 3.80 (s, 2H, CH_2), 1.18 (t, $J_{H\text{-}H} = 7.3$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-*d6*) δ: 172.5 (CO), 167.4 (CO), 165.0 (CO), 150.2 (C4), 100.1 (C3), 60.5 (CH_2O), 44.0 (CH_2), 42.7

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(CH_2), 14.7 (CH_3). Anal. calcd. for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.41; H, 5.25; N, 12.20.

4-(Carboxymethyl-amino)-1-methyl-5-oxo-2,5-dihydro-*1H*-pyrrole-2,3-dicarboxylic acid diethyl ester **12a**: White crystals; 125 mg (80%); mp = 103–104°C; IR: 3370–3110 (NH, OH), 1742, 1725, 1698 and 1658 (C═O); ^{1}H NMR ($CDCl_3$) δ: 9.92 (br, 1H, OH), 6.79 (br, 1H, NH), 4.66 (m, 1H, NC$\underline{H}_2CO_2H$), 4.61 (s, 1H, CH), 4.51 (m, 1H, NC$\underline{H}_2CO_2H$), 4.21 (q, $J_{H\text{-}H}$ = 7.3 Hz, 2H, CH_2O), 4.18 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H, CH_2O), 2.87 (s, 3H, CH_3N), 1.29 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 1.27 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 174.0 (CO), 168.7 (CO), 165.8 (CO), 164.6 (CO), 146.8 (C4), 99.3 (C3), 61.8 (CH_2O), 61.5 (CH), 60.2 (CH_2O), 44.0 (CH_2), 28.2 (CH_3N), 14.2 (CH_3), 14.1 (CH_3). Anal. calcd. for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.77; N, 8.91. Found: C, 49.66; H, 5.78; N, 8.85.

4-(Carboxymethyl-amino)-1-isobutyl-5-oxo-2,5-dihydro-*1H*-pyrrole-2,3-dicarboxylic acid diethyl ester **12b**: White crystals; 135 mg (76%); mp = 77–78°C; IR: 3360–3100 (NH, OH), 1745, 1722, 1699 and 1661 (C═O); ^{1}H NMR ($CDCl_3$) δ: 9.79 (br, 1H, OH), 7.12 (br, 1H, NH), 4.76 (m, 1H, NC$\underline{H}_2CO_2H$), 4.73 (s, 1H, CH), 4.57 (m, 1H, NC$\underline{H}_2CO_2H$), 4.22 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H, CH_2O), 4.20 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H, CH_2O), 3.53 (dd, $J_{H\text{-}H}$ = 13.9 and 8.7 Hz, 1H, CH_2N), 2.82 (dd, $J_{H\text{-}H}$ = 13.9 and 6.3 Hz 1H, CH_2N), 1.95 (m, 1H, CH), 1.28 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 1.26 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 0.93 (d, $J_{H\text{-}H}$ = 6.6 Hz 3H, CH_3), 0.84 (d, $J_{H\text{-}H}$ = 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 174.4 (CO), 168.9 (CO), 166.0 (CO), 164.4 (CO), 146.4 (C4), 99.1 (C3), 61.8 (CH_2O), 61.2 (CH), 60.0 (CH_2O), 49.1 (CH_2), 43.8 (CH_2), 27.1 (CH), 20.0 (CH_3), 19.6 (CH_3), 14.1 (CH_3), 14.0 (CH_3). Anal. calcd. for $C_{16}H_{24}N_2O_7$: C, 53.92; H, 6.79; N, 7.86. Found: C, 53.75; H, 6.51; N, 7.80.

4-(Carboxymethyl-amino)-5-oxo-1-phenyl-2,5-dihydro-*1H*-pyrrole-2,3-dicarboxylic acid diethyl ester **12c**: White crystals; 155 mg (82%); mp = 144–145°C; IR: 3350–3105 (NH, OH), 1743, 1720, 1700 and 1660 (C═O); ^{1}H NMR ($CDCl_3$) δ: 10.20 (br, 1H, OH), 8.55 (br, 1H, NH), 7.46 (m, 2H, Ph), 7.25 (m, 2H, Ph), 7.12 (m, 1H, Ph), 5.28 (s, 1H, CH), 4.69 (m, 1H, NC$\underline{H}_2CO_2H$), 4.48 (m, 1H, NC$\underline{H}_2CO_2H$), 4.15 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H, CH_2O), 3.97 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H, CH_2O), 1.21 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3), 0.99 (t, $J_{H\text{-}H}$ = 7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 174.7 (CO), 168.5 (CO), 168.0 (CO), 164.4 (CO), 146.4 (C4), 136.1, 129.0, 126.3 and 122.1 (Ph), 99.3 (C3), 61.8 (CH_2O), 61.6 (CH), 60.3 (CH_2O), 44.0 (CH_2), 14.1 (CH_3), 13.8 (CH_3). Anal. calcd. for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.36; N, 7.44. Found: C, 57.37; H, 5.21; N, 7.29.

1-Benzyl-4-(carboxymethyl-amino)-5-oxo-2,5-dihydro-*1H*-pyrrole-2,3-dicarboxylic acid diethyl ester **12d**: White crystals; 170 mg (87%); mp = 102–103°C; IR: 3360-3095 (NH, OH), 1741, 1722, 1699 and 1659 (C═O); ^{1}H NMR ($CDCl_3$) δ: 10.21 (br, 1H, OH), 7.35–7.22 (m, 5H, Ph), 7.04 (br, 1H, NH), 4.95 (d, $J_{H\text{-}H}$ = 15.1 Hz, 1H, CH_2Ph), 4.80 (m, 1H, NC$\underline{H}_2CO_2H$), 4.60 (m, 1H, NC$\underline{H}_2CO_2H$), 4.58 (s, 1H, CH), 4.16 (q, $J_{H\text{-}H}$ = 7.1 Hz, 2H,

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CH_2O), 4.15 (d, $J_{H\text{-}H} = 15.1$ Hz, 1H, CH_2Ph), 4.06 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, CH_2O), 1.22 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3), 1.20 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 174.6 (CO), 168.2 (CO), 167.7 (CO), 164.6 (CO), 146.1 (C4), 136.2, 129.0, 128.8 and 128.2 (Ph), 99.5 (C3), 61.5 (CH_2O), 61.1 (CH), 60.1 (CH_2O), 45.5 (CH_2), 43.9 (CH_2), 14.3 (CH_3), 14.1 (CH_3). Anal. calcd. for $C_{19}H_{22}N_2O_7$: C, 58.46; H, 5.68; N, 7.18. Found: C, 58.29; H, 5.33; N, 7.02.

4-(Carboxymethyl-amino)-1-methyl-5-oxo-2,5-dihydro-*1H*-pyrrole-2,3-dicarboxylic acid 3-ethyl ester **13a**: White crystals; 110 mg (77%); mp = 111–112°C; IR: 3410–3100 (NH, 2 × OH), 1741, 1720, 1699 and 1660 (C═O); ^{1}H NMR (CD_3COCD_3) δ: 9.04 (br, 2H, 2 × OH), 7.30 (br, 1H, NH), 4.66 (m, 1H, $NC\underline{H}_2CO_2H$), 4.62 (s, 1H, CH), 4.56 (m, 1H, $NC\underline{H}_2CO_2H$), 4.13 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, CH_2O), 2.89 (s, 3H, CH_3N), 1.18 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (CD_3COCD_3) δ: 172.0 (CO), 170.3 (CO), 166.2 (CO), 165.3 (CO), 146.3 (C4), 99.4 (C3), 62.8 (CH), 60.3 (CH_2O), 44.0 (CH_2), 28.2 (CH_3N), 14.5 (CH_3). Anal. calcd. for $C_{11}H_{14}N_2O_7$: C, 46.16; H, 4.93; N, 9.79. Found: C, 45.98; H, 4.77; N, 9.61.

4-(Carboxymethyl-amino)-1-isobutyl-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylic acid 3-ethyl ester **13b**: White crystals; 140 mg (85%); mp = 84–85°C; IR: 3390–3090 (NH, 2 × OH), 1745, 1720, 1698 and 1660 (C═O); ^{1}H NMR ($CDCl_3$) δ: 9.95 (br, 2H, 2 × OH), 7.14 (br, 1H, NH), 4.74 (s, 1H, CH), 4.62 (m, 2H, $NC\underline{H}_2CO_2H$), 4.18 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, CH_2O), 3.60 (dd, $J_{H\text{-}H} =$ 13.9 and 9.0 Hz, 1H, CH_2N), 2.89 (dd, $J_{H\text{-}H} = 13.9$ and 6.3 Hz, 1H, CH_2N), 1.98 (m, 1H, CH), 1.26 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3), 0.88 (d, $J_{H\text{-}H} = 6.6$ Hz 3H, CH_3), 0.83 (d, $J_{H\text{-}H} = 6.8$ Hz 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 172.7 (CO), 171.6 (CO), 166.0 (CO), 165.0 (CO), 145.3 (C4), 98.7 (C3), 61.0 (CH), 60.6 (CH_2O), 49.2 (CH_2), 44.6 (CH_2), 27.2 (CH), 20.1 (CH_3), 19.7 (CH_3), 14.1 (CH_3). Anal. calcd. for $C_{14}H_{20}N_2O_7$: C, 51.22; H, 6.14; N, 8.53. Found: C, 50.97; H, 6.01; N, 8.45.

4-(Carboxymethyl-amino)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2,3-dicarboxylic acid 3-ethyl ester **13c**: White crystals; 150 mg (86%); mp = 151–152°C; IR: 3380–3095 (NH, 2 × OH), 1741, 1717, 1700 and 1659 (C═O); ^{1}H NMR ($CDCl_3$) δ: 10.15 (br, 2H, 2 × OH), 7.30 (m, 2H, Ph), 7.26 (m, 2H, Ph), 7.12 (m, 1H, Ph), 6.98 (br, 1H, NH), 5.13 (s, 1H, CH), 4.73 (m, 1H, $NC\underline{H}_2CO_2H$), 4.51 (m, 1H, $NC\underline{H}_2CO_2H$), 4.13 (q, $J_{H\text{-}H} =$ 7.1 Hz, 2H, CH_2O), 1.15 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 172.4 (CO), 172.0 (CO), 166.3 (CO), 166.0 (CO), 144.7 (C4), 136.0, 128.8, 126.1 and 121.7 (Ph), 98.5 (C3), 62.2 (CH), 61.0 (CH_2O), 44.2 (CH_2), 14.0 (CH_3). Anal. calcd. for $C_{16}H_{16}N_2O_7$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.04; H, 4.39; N, 7.97.

1-Benzyl-4-(carboxymethyl-amino)-5-oxo-2,5-dihydro-1H-pyrrole-2,3-dicarboxylic acid 3-ethyl ester **13d**: White crystals; 175 mg (96%); mp = 120–121°C; IR: 3400–3075 (NH, OH), 1740, 1718, 1700 and 1660 (C═O); ^{1}H NMR ($CDCl_3$) δ: 10.34 (br, 2H, OH), 7.32–7.21 (m, 5H, Ph),

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7.08 (br, 1H, NH), 5.10 (d, $J_{H\text{-}H} = 15.0$ Hz, 1H, CH_2Ph), 4.64 (m, 2H, $NC\underline{H}_2CO_2H$), 4.56 (s, 1H, CH), 4.18 (d, $J_{H\text{-}H} = 15.0$ Hz, 1H, CH_2Ph), 4.16 (q, $J_{H\text{-}H} = 7.1$ Hz, 2H, CH_2O), 1.25 (t, $J_{H\text{-}H} = 7.1$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 174.9 (CO), 172.3 (CO), 165.5 (CO), 164.9 (CO), 147.0 (C4), 135.1, 128.8, 128.5 and 128.1 (Ph), 98.9 (C3), 60.7 (CH_2O), 59.6 (CH), 45.5 (CH_2), 44.1 (CH_2), 14.0 (CH_3). Anal. calcd. for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.32; H, 4.88; N, 7.64.

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ACKNOWLEDGMENTS

We gratefully acknowledge the European Community (Grant HPRN-CT-1999-00084) and the BBSRC for financial support. We also thank Professor Chris Pickett for helpful discussions and suggestions.

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