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Novel synthesis of the pyrrolo[2,1-*c*][1,4]benzodiazocine ring system via a Dieckmann condensation

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ABSTRACT

A novel four-step synthesis to the pyrrolo[2,1-*c*][1,4]benzodiazocine ring system is described. 1*H*-Pyrrole-2-carbaldehyde was alkylated with ethyl or methyl bromoacetate and the resulting ethyl or methyl (2-formyl-1*H*-pyrrol-1-yl)acetates oxidised with potassium permanganate to the corresponding 1-[(2-ethoxy or methoxy)-2-oxoethyl]-1*H*-pyrrole-2-carboxylic acids. The latter was converted into their acid chlorides by reaction with thionyl chloride and without isolation transformed into the respective methyl 2-({[1-(2-ethoxy or methoxy-2-oxoethyl)-1*H*-pyrrol-2-yl]carbonyl}amino)benzoates by reaction with methyl anthranilate. Dieckmann condensation of methyl 2-({[1-(2-methoxy-2-oxoethyl)-1*H*-pyrrol-2-yl]carbonyl}amino)benzoate provided the pyrrolo[2,1-*c*][1,4]benzodiazocine.

1. Introduction

The addition of medium-sized rings containing two nitrogen atoms as substituents in biologically active compounds is known to increase the pharmaceutical potency of the compounds. One example is the diazocine ring. The tethering of octahydro-1,4-diazocines to guanidine has produced derivatives of superior anti-hypertensive activity to that of guanidine.[1] Several methods have been employed for the synthesis of 1,4-diazocines. Sarges and Tretter[2] treated methyl β-bromomethyl-cinnamate with *N*,*N*′-dimethyl-ethylenediamine to give 1,4-dimethyl-2-phenylpiperidine-2-acetic acid methyl ester, which, after hydrolysis to the corresponding acid and treatment with triethylamine and dicyclohexylcarbodiimide, was transformed into 1,4-dimethyl-7-phenyl-1,2,3,4-tetrahydro-1,4-diazocin-5(8*H*)-one. The 7-naphthyl derivative was prepared analogously. 1,4-Dibenzyl-octahydro[1,4]diazocine was prepared by condensing *N*,*N*′-dibenzylethane-1,2-diamine with 1,3-dibromo-propane.[3] The first aromatic 1,4-diazocine derivatives were synthesised by Vogel and co-workers[4] in 1979. 3,8-Dioxatri-cyclo[5.1.0.0^{2,4}]octane was transformed into 3,8-bis(methylsul-fonyl)-3,8-diazatri-cyclo[5.1.0.0^{2,4}]oct-5-ene, which was thermally ring expanded to 1,4-bis(methylsulfonyl)-1,4-dihydro-1,4-diazocine and the methylsulfonyl groups removed with potassium in liquid ammonia to give the 1,4-dihydro-1,4-diazocine. NMR spectroscopy and X-ray crystallography used to prove the 10π electron aromatic character of these compounds. 3,8-Diazatricyclo[5.1.0.0^{2,4}]octanes were prepared from *cis*-benzenetriimine by *N*,*N*′-disubstitution, nitrosation and N_2O-elimination reactions. Their [π2s+σ2s+σ2s] cycloreversion to 1,4-dihydro-1,4-diazocines occurred at low temperature.[5] Reduction of *N*,*N*′-[(1*E*,2*E*)-1,2-diphenylethane-1,2-diylidene]dianiline with sodium to the corresponding dianion followed by substitution of 1,4-dichlorobutane gave directly 1,2,3,4-tetraphenyl-1,4,5,-6,7,8-hexahydro-1,4-diazocine. Three more tetraaryl derivatives were synthesised in this manner.[6]

So far, three pyrrolobenzodiazocine ring systems are known. Derivatives of 6,11-dihydropyrrolo[1,2-*b*][2,5]-benzodiazocine were obtained by heating 1-{2-[(acyl-amino)methyl]benzyl}pyrroles with phosphoryl chloride.[7] (2-Nitrophenyl)acetyl chloride, generated in situ from (2-nitrophenyl)acetic acid and thionyl chloride, was reacted with proline or 3-hydroxyproline to give (4-unsubstituted or 4-hydroxy)-1-[(2-nitrophenyl)acetyl]proline that was selectively reduced to the aniline analogue. The latter was cyclised with dicyclo-hexylcarbodiimide to give (2-unsubstituted or 2-hydroxy)-1,2,3,6,-11,12a-hexahydropyrrolo[2,1-*c*][1,4]benzodiazocine-5,12-dione.[8] [(3-Acetyl or 3-propionyl)-2-methyl-5-(2-nitrophenyl)-1*H*-pyrrol-1-yl]-acetic acid underwent catalytic hydrogenation and the 5-amino derivative was cyclised by thionyl chloride to give (2-acetyl or 2-propionyl)-3-methyl-5,6-dihydropyrrolo[1,2-*e*][1,5]benzodi-azocin-7(8*H*)-one.[9]

2. Results and discussion

We have previously described the synthesis of 4,5-dihy-dropyrrolo[1,2-*b*][2,5]benzodiazocin-6(11*H*)-imine or 6(11*H*)-one

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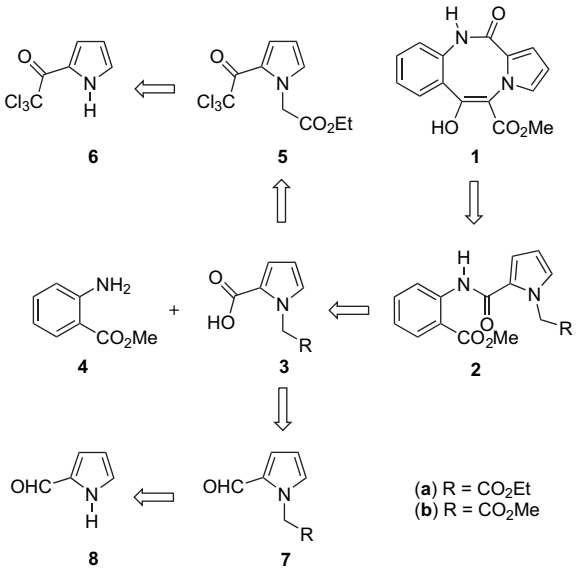
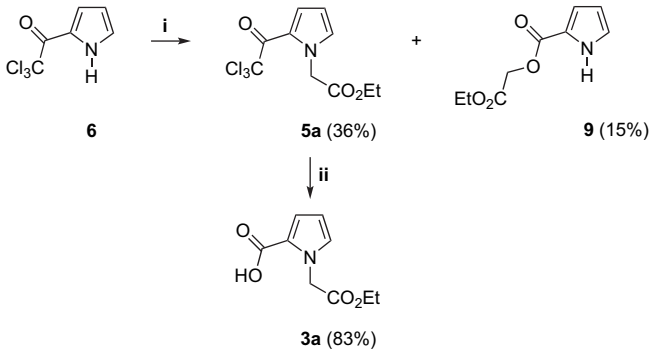
(erroneously described as pyrrolo[2,1-*c*][1,4]-benzodiazocines) by the cyclisation of 2-{[2-(aminomethyl)-1*H*-pyrrol-1-yl]-methyl}-benzonitrile or ethyl 2-{[2-(aminomethyl)-1*H*-pyrrol-1-yl]methyl}benzoate, respectively, with ethanolic sodium methoxide.[10] We now present a novel synthesis of the pyrrolo[2,1-*c*][1,4]-benzodiazocine ring system **1** shown in Scheme 1. The interest in this ring system stems from its close structural relation to the pharmacologically important 1,4-benzo-diazepine CNS agents.[11]



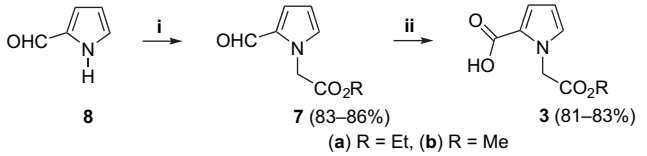
Scheme 1.

Initially we chose trichloroacetylpyrrole **6** as starting material. This compound was synthesised in 80% yield according to Bailey and Anderson[12] by reacting 1*H*-pyrrole with trichloroacetyl chloride. A literature search revealed only one example of N-alkylation of pyrrole **6** that is with chloroacetone and K_2CO_3 in acetone as solvent gave 3-methylpyrrolo[2,1-*c*][1,4]oxazin-1-one. The *N*-alkyl intermediate was not isolated.[13] In the first attempted synthesis (Scheme 2) of 1*H*-pyrrole-2-carboxylic acid **3a**, pyrrole **6** was alkylated with ethyl bromoacetate in acetone in the presence of K_2CO_3 to give unreacted starting material **6**, trichloro-acetylpyrrolyl ester **5a** and ethoxycarbonylmethyl ester **9**, in 46, 36 and 15% yields, respectively. The use of DMF, DMSO or THF instead of acetone as solvent resulted in lower yields of ester **5a**. The selective hydrolysis of ester **5a** with 2 M K_2CO_3 in acetone at room temperature furnished acid **3a** in 83% yield.



Scheme 2. Reagents and conditions: (i) $BrCH_2CO_2Et$, K_2CO_3, acetone; (ii) (a) 2 M K_2CO_3, acetone, (b) 2 M HCl.

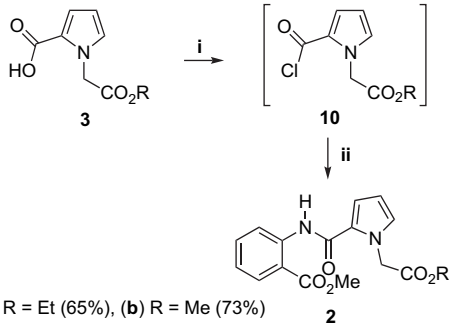
Since the acid **3a** was obtained from pyrrole **6** in only 30% overall yield, an alternative route was sought. Potassium permanganate in an acetone–water mixture has been used successfully by Rapoport and co-workers[14] to oxidise methyl 4-formyl-1-methyl-1*H*-pyrrole-2-carboxylate to 5-(methoxycarbonyl)-1-methyl-1*H*-pyrrole-3-carboxylic acid in 88% yield. More recently, similar oxidative conditions were used to convert 2-(2-formyl-1*H*-pyrrol-1-yl)thiophene-3-carbonitrile into 1-(3-cyanothiophen-2-yl)-1*H*-pyrrole-2-carboxylic acid,[15] and 1-(2-chloropyridin-3-yl)-1*H*-pyrrole-2-carbaldehyde into 1-(2-chloropyridin-3-yl)-1*H*-pyrrole-2-carboxylic acid.[16] For our purpose this entailed the N-alkylation of 1*H*-pyrrole-2-carbaldehyde **8** with ethyl bromoacetate in acetone containing K_2CO_3 to give ester **7a**, followed by oxidation of **7a** with potassium permanganate in a 1:1 v/v ratio of acetone and water at room temperature, to afford the acid **3a** (Scheme 3). Compounds **7a** and **3a** were obtained in 83 and 81% yields, respectively. Similarly, alkylation of aldehyde **8** with methyl bromoacetate gave ester **7b** in 86% yield and then oxidation of **7b** gave acid **3b** in 83% yield. In the ^1H NMR spectrum of **3a** in $CDCl_3$ the chemical shifts at 6.31, 6.98 and 7.56 ppm corresponding to H-4, H-3 and H-5 are all further downfield than the respective chemical shifts of **3b** in DMSO-d_6 at 6.15, 6.86 and 7.12 ppm corresponding to the same protons. Furthermore, the hydroxyl proton of **3b** appears as a broad singlet at 12.25 ppm, while the signal due to the hydroxyl proton of **3a** is very broad and cannot be detected.



Scheme 3. Reagents and conditions: (i) $BrCH_2CO_2Et$ or $BrCH_2CO_2Me$, K_2CO_3, acetone; (ii) $KMnO_4$, Me_2CO, H_2O.

According to our retrosynthetic plan the next step involved the acquisition of amides **2a**,**b**. The first attempt to couple anthranilic acid **4** with acids **3a**,**b** using *N*,*N*′-dicyclohexylcarbodiimide as coupling agent, failed. This reagent has been used successfully by Molteni[17] to couple 1-substitutedpyrrole-2-carboxylic acids with phenyl hydrazine.

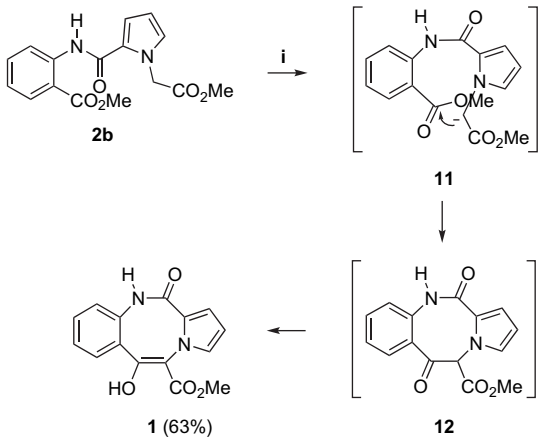
We have recently described the in situ conversion of 1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylic acid with thionyl chloride to its acid chloride and then reaction with aryl amines to yield the corresponding *N*-aryl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides.[18] Applying this method the acids **3a**,**b** (Scheme 4) were heated with thionyl chloride for 1 h in order to generate in situ the acid chlorides **10a**,**b**. Excess thionyl chloride was removed and then reaction with methyl anthranilate **4** took place in a 1:1 pyridine–toluene mixture, at room temperature for 48 h. The corresponding amides **2a**,**b** were isolated in 57 and 64% yields, respectively.



Scheme 4. Reagents and conditions: (i) $SOCl_2$, reflux; (ii) methyl anthranilate, pyridine.

In the key cyclisation step, compound **2b** was converted into pyrrolobenzodiazocine **1** by a Dieckmann condensation requiring

K_2CO_3 in DMSO at relatively high dilution. The first attempt involved dropwise addition of a solution of **2b** in DMSO to a suspension of K_2CO_3 in DMSO at room temperature. TLC examination of the reaction after 24 h revealed a very faint spot corresponding to starting material and a new polar spot. No change occurred after stirring for a further 64 h. When the reaction was repeated by heating the suspension of K_2CO_3 in DMSO to 60 °C while adding the solution of **2b** in DMSO dropwise and then stirring at that temperature for 48 h, two new spots together with a very faint starting material spot were detected by TLC. It is reasonable to assume that the deprotonated *transoid* **2b** overcomes the rotational barrier at 60 °C and transforms to the deprotonated *cisoid* **11** so that cyclisation can take place to give pyrrolobenzodiazocine **12**. The two new spots detected by TLC are very likely to correspond to a tautomeric mixture of pyrrolobenzodiazocines **12** and **1**. In order to isolate tautomer **1** the reaction mixture was cooled to 5 °C and then acidified with 2 M HCl to pH=3–4. Stirring for 1 h at 5 °C led to the isolation of pyrrolobenzodiazocine **1** in 63% yield (Scheme 5).



Scheme 5. Reagents and conditions: (i) (a) DMSO, K_2CO_3, 24 h, (b) 60 °C, 48 h, (c) 5 °C, 2 M HCl, 1 h.

3. Conclusion

In summary, we have developed a new and efficient four-step synthetic route to the pyrrolo[2,1-*c*][1,4]benzodiazocine ring system from commercially available 1*H*-pyrrole-2-carbaldehyde and methyl anthranilate. The steps leading to the product involve alkylation, carboxylic acid to acid chloride transformation, amide formation via acyl substitution and finally Dieckmann condensation.

4. Experimental

4.1. General methods

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer, as Nujol mulls between sodium chloride discs. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Nuclear magnetic resonance spectra were measured on Brüker Avance 250 or 400 spectrometers, using tetramethylsilane as internal standard. Mass spectra were obtained by use of JEOL JMS-AX 505W (low and high resolution) and Bruker Apex III (high resolution) instruments. Analytical TLC was carried out on Fluka silica gel 60 F_{254}. Preparative flash chromatography was carried out using Merck 9385 silica gel. Solvents and reagents were used as received from the manufacturers except for dichloromethane, ethyl acetate, hexane and methanol that were purified and dried according to recommended procedures.[19]

4.1.1. *Alkylation of 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone with ethyl bromoacetate*

To a stirred mixture of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone **6** (1.00 g, 5 mmol) and K_2CO_3 (1.38 g, 10.00 mmol) in dry acetone (15 mL) under argon, a solution of ethyl bromoacetate (1.17 g, 7 mmol) in acetone (15 mL) was added dropwise over a period of 30 min. Stirring was continued at room temperature for 24 h, the solvent was removed under reduced pressure, water (50 mL) was added and then extracted with ethyl acetate (3×15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give an oily residue. The residue was subjected to flash column chromatography on silica gel with [25% CH_2Cl_2/hexane] to give in the first fraction starting material **6**, in the second fraction ethyl [2-(trichloroacetyl)-1*H*-pyrrol-1-yl]acetate **5a** and in the third fraction 2-ethoxy-2-oxoethyl 1*H*-pyrrole-2-carboxylate **9**.

4.1.1.1. Ethyl [2-(trichloroacetyl)-1H-pyrrol-1-yl]acetate ***5a***. Yield (0.51 g, 36%), as colourless microcrystals (ethyl acetate/hexane); mp 71 °C. [Found: C, 40.19; H, 3.35; N, 4.58. $C_{10}H_{10}Cl_3NO_3$ requires: C, 40.23; H, 3.38; N, 4.69%.] ν_{max} (Nujol) 1662, 1740 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.78 (3H, t, *J*=7.2 Hz, CH_3), 4.26 (2H, q, *J*=7.2 Hz, CH_2), 5.01 (2H, s, CH_2), 6.31 (1H, dd, *J*=4.0, 2.9 Hz, H-4), 6.99 (1H, dd, *J*=4.0, 1.7 Hz, H-3), 7.57 (1H, dd, *J*=2.9, 1.7 Hz, H-5); δ_C (63 MHz, $CDCl_3$) 14.01, 51.77, 61.64, 95.23, 109.55, 121.76, 124.42, 133.56, 167.77, 179.18; *m*/*z* (EI) 297 (M^+, 19), 234 (14), 180 (88), 152 (61), 142 (15), 124 (100), 94 (16%).

4.1.1.2. 2-Ethoxy-2-oxoethyl-1H-pyrrole-2-carboxylate ***9***. Yield (0.14 g, 15%), as a pale yellow oil; ν_{max} (Nujol) 1554, 1665, 3355 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 1.20 (3H, t, *J*=7.1 Hz, CH_3), 4.14 (2H, q, *J*=7.1 Hz, CH_2), 4.79 (2H, s, CH_2), 6.20 (1H, dd, *J*=4.0, 2.9 Hz, H-4), 6.87 (1H, dd, *J*=4.0, 2.2 Hz, H-3), 7.14 (1H, dd, *J*=2.9, 2.2 Hz, H-5), 12.01 (1H, br s, NH); δ_C (63 MHz, DMSO-d_6) 14.19, 60.47, 60.94, 109.99, 116.12, 121.07, 125.00, 159.84, 168.24; *m*/*z* (ESI) 197.8 $[M+H]^+$, 219.8 $[M+Na]^+$; HRMS (ESI): $[M+H]^+$, found 198.0759. $C_9H_{12}NO_4$ requires 198.0766.

4.1.1.3. 1-(2-Ethoxy-2-oxoethyl)-1H-pyrrole-2-carboxylic acid ***3a***. To a solution of ethyl [2-(trichloroacetyl)-1*H*-pyrrol-1-yl]acetate **5a** (0.50 g, 1.67 mmol) in acetone (10 mL) was added aqueous 2 M K_2CO_3 (25 mL) and the mixture was stirred for 4 h at room temperature. Acetone was removed under reduced pressure, the solution was acidified with aqueous 2 M HCl to pH 3 and then extracted with ethyl acetate (3×15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to afford a residue that was purified by flash chromatography (33% ethyl acetate/hexane) to give compound **3a** (0.27 g, 83%), as colourless microcrystals (propan-2-ol). Mp 156–157 °C; ν_{max} (Nujol) 1713, 3012 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.27 (3H, t, *J*=7.2 Hz, CH_3), 4.23 (2H, q, *J*=7.2 Hz, CH_2), 5.01 (2H, s, CH_2), 6.31 (1H, dd, *J*=4.5, 2.5 Hz, H-4), 6.98 (1H, dd, *J*=4.5, 1.5 Hz, H-3), 7.56 (1H, dd, *J*=2.5, 1.5 Hz, H-5); δ_C (63 MHz, $CDCl_3$) 14.01, 51.77, 61.64, 109.55, 121.76, 124.42, 133.56, 161.84, 167.77; *m*/*z* (ESI) 220 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$ found 220.0580. $C_9H_{11}NNaO_4$ requires 220.0585.

4.1.2. *Preparation of ethyl or methyl (2-formyl-1H-pyrrol-1-yl)-acetates* ***7a,b****: general procedure A*

To a stirred mixture of 1*H*-pyrrole-2-carbaldehyde **8** (1.00 g, 10.51 mmol) and K_2CO_3 (2.90 g, 21.02 mmol) in dry acetone (15 mL) under argon, a solution of ethyl or methyl bromoacetate (12 mmol) in dry acetone (15 mL) was added dropwise over

a period of 30 min. The reaction mixture was left to stir at room temperature for 18 h and then the solvent was evaporated under reduced pressure. Water (50 mL) was added to the residue and then extracted with ethyl acetate (3×15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The oily residue was purified by dry flash chromatography [33% ethyl acetate/hexane] to afford ethyl or methyl (2-formyl-1*H*-pyrrol-1-yl)acetate **7a** or **7b**.

*4.1.2.1. Ethyl (2-formyl-1H-pyrrol-1-yl)acetate **7a**.* Yield (1.6 g, 83%), as a colourless oil; ν_{max} (Nujol) 1656, 1755 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.30 (3H, t, *J*=7.1 Hz, CH_3), 4.27 (2H, q, *J*=7.0 Hz, CH_2), 5.09 (2H, s, CH_2), 6.33 (1H, dd, *J*=4.0, 2.5 Hz, H-4), 6.95 (1H, dd, *J*=2.5, 1.5 Hz, H-5), 7.57 (1H, dd, *J*=2.9, 1.5 Hz, H-3), 9.57 (1H, s, CHO); δ_C (63 MHz, $CDCl_3$) 14.10, 50.23, 61.63, 110.19, 124.59, 131.67, 132.02, 168.33, 179.74; *m*/*z* (ESI) 182.1 $[M+H]^+$; HRMS (ESI): $[M+H]^+$, found 182.0813. $C_9H_{12}NO_3$ requires 182.0817.

*4.1.2.2. Methyl (2-formyl-1H-pyrrol-1-yl)acetate **7b**.* Yield (1.64 g, 86%), as a colourless oil; ν_{max} (Nujol) 1658, 1751 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.75 (3H, s, CH_3), 5.06 (2H, s, CH_2), 6.29 (1H, dd, *J*=4.2, 2.7 Hz, H-4), 6.92 (1H, dd, *J*=2.7, 1.5 Hz, H-5), 6.98 (1H, dd, *J*=4.2, 1.5 Hz, H-3), 9.52 (1H, s, CHO); δ_C (63 MHz, $CDCl_3$) 49.97, 52.36, 110.14, 124.52, 131.57, 131.97, 168.70, 179.66; *m*/*z* (ESI) 189.8 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 190.0484. $C_8H_9NNaO_3$ requires 190.0480.

*4.1.3. Preparation of 1-[(2-ethoxy or methoxy)-2-oxo-ethyl]-1H-pyrrole-2-carboxylic acids **3a**,**b**: general procedure B*

To a solution of ethyl or methyl (2-formyl-1*H*-pyrrol-1-yl)-acetates **7a** or **7b** (8.30 mmol) in acetone (100 mL) was added dropwise over 2 h a solution of $KMnO_4$ (2.70 g, 17 mmol) in acetone–water (200 mL, 1:1). After 4 h of stirring at room temperature, acetone was removed under reduced pressure and the remaining aqueous solution was acidified with 1.5 M HCl to pH 3 followed by the addition of aqueous 10% $NaHSO_3$ (10 mL). The mixture was extracted with ethyl acetate (3×30 mL) and the combined organic extracts were washed with water (30 mL) and then carefully with 5% w/v $NaHCO_3$ (3×30 mL). The combined bicarbonate extracts were carefully acidified with aqueous 1.5 M HCl to pH 3, extracted with ethyl acetate (3×30 mL), the combined organic extracts washed with brine (30 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure leaving 1-[(2-ethoxy or methoxy)-2-oxoethyl]-1*H*-pyrrole-2-carboxylic acid **3a** or **3b**.

*4.1.3.1. 1-(2-Ethoxy-2-oxoethyl)-1H-pyrrole-2-carboxylic acid **3a**.* Yield (1.32 g, 81%), as colourless microcrystals (propan-2-ol); mp 156–157 °C; identical in all respects to the corresponding compound described in Section 4.1.1.3.

*4.1.3.2. 1-(2-Methoxy-2-oxoethyl)-1H-pyrrole-2-carboxylic acid **3b**.* Yield (1.26 g, 83%), as colourless microcrystals (diisopropyl ether); mp 137–138 °C; ν_{max} (Nujol) 3012, 1713 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 3.69 (3H, s, CH_3), 5.13 (2H, s, CH_2), 6.15 (1H, dd, *J*=3.7, 2.5 Hz, H-4), 6.86 (1H, dd, *J*=3.7, 1.9 Hz, H-3), 7.12 (1H, dd, *J*=2.5, 1.9 Hz, H-5), 12.25 (1H, br s, OH); δ_C (63 MHz, DMSO-d_6) 50.81, 52.77, 108.63, 118.30, 123.38, 130.98, 162.82, 170.28; *m*/*z* (ESI) 205.9 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 206.0424. $C_8H_9NNaO_4$ requires 206.0429.

*4.1.4. Preparation of methyl 2-({[1-(2-ethoxy or methoxy-2-oxoethyl)-1H-pyrrol-2-yl]carbonyl}amino)benzoates **2a**,**b**: general procedure C*

1-[(2-Ethoxy or methoxy)-2-oxoethyl]-1*H*-pyrrole-2-carboxylic acid **3a** or **3b** (5.0 mmol) is dissolved in freshly distilled thionyl chloride (10 mL). The mixture was gently heated to reflux under argon for 1 h and then the excess thionyl chloride removed in vacuo. Dry toluene (10 mL) was added to the oily residue and evaporated in vacuo. The residue was dissolved in dry toluene (10 mL) and a solution of methyl anthranilate (0.75 g, 5.0 mmol) in dry pyridine (10 mL) was added dropwise under argon. The reaction mixture was stirred at room temperature for 48 h. The solvents were evaporated under reduced pressure, a 10% w/v solution of $NaHCO_3$ (50 mL) was added and extracted with dichloromethane (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvents removed under reduced pressure to afford a residue that was purified by flash chromatography (15% ethyl acetate/hexane) to give methyl 2-({[1-(2-ethoxy or methoxy-2-oxoethyl)-1*H*-pyrrol-2-yl]carbonyl}amino)benzoate **2a** or **2b**.

*4.1.4.1. Methyl 2-({[1-(2-ethoxy-2-oxoethyl)-1H-pyrrol-2-yl]carbonyl}amino)benzoate **2a**.* Yield (1.04 g, 65%), as colourless microcrystals (propan-2-ol); mp 165–166 °C; ν_{max} (Nujol) 3303, 1743, 1666, 1541 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.28 (3H, t, *J*=7.2 Hz, CH_3), 3.95 (3H, s, CH_3), 4.24 (2H, q, *J*=7.2 Hz, CH_2), 5.13 (2H, s, CH_2), 6.25 (1H, dd, *J*=3.9, 2.6 Hz, H-4), 6.82 (1H, dd, *J*=3.9, 1.8 Hz, H-3), 7.02–7.08 (2H, m, H-5, H-5′), 7.52 (1H, ddd, *J*=8.9, 7.6, 0.9 Hz, H-4′), 8.04 (1H, dd, *J*=8.0, 1.4 Hz, H-3′), 8.73 (1H, dd, *J*=8.6 Hz, H-6′), 11.76 (1H, br, NH); δ_C (63 MHz, $CDCl_3$) 14.29, 50.95, 52.53, 61.56, 108.74, 114.09, 114.83, 120.21, 122.03, 126.01, 129.20, 131.02, 134.70, 142.19, 160.10, 169.05, 169.15; *m*/*z* (ESI) 331.0 $[M+H]^+$, 353.0 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 353.1119. $C_{17}H_{18}N_2NaO_5$ requires 353.1113.

*4.1.4.2. Methyl 2-({[1-(2-methoxy-2-oxoethyl)-1H-pyrrol-2-yl]carbonyl}amino)benzoate **2b**.* Yield (1.09 g, 73%), as colourless microcrystals (propan-2-ol); mp 149–150 °C; ν_{max} (Nujol) 3307, 1760, 1692, 1667 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.77 (3H, s, CH_3), 3.95 (3H, s, CH_3), 5.14 (2H, s, CH_2), 6.26 (1H, dd, *J*=4.1, 2.7 Hz, H-4), 6.82 (1H, dd, *J*=2.5, 1.8 Hz, H-3), 7.01–7.08 (2H, m, H-5, H-5′), 7.52 (1H, ddd, *J*=8.8, 1.7 Hz, H-4′), 8.03 (1H, dd, *J*=8.0, 1.7 Hz, H-3′), 8.72 (1H, dd, *J*=8.6 Hz, H-6′), 11.76 (1H, br, NH); δ_C (63 MHz, $CDCl_3$) 50.64, 52.36, 52.39, 108.66, 113.99, 114.73, 120.21, 121.92, 125.84, 129.06, 130.86, 134.53, 141.99, 159.93, 169.02, 169.46; *m*/*z* (ESI) 339.0 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 339.0962. $C_{16}H_{16}N_2NaO_5$ requires 339.0957.

*4.1.5. Methyl 6-hydroxy-12-oxo-11,12-dihydropyrrolo-[2,1-c][1,4]-benzodiazocine-5-carboxylate **1***

To a stirred suspension of potassium carbonate (0.32 g, 2.37 mmol) in dry DMSO (80 mL) at 60 °C and under an atmosphere of argon, was added dropwise a solution of ester **2b** (0.25 g, 0.00079 mmol) in dry DMSO (80 mL). The reaction mixture was stirred at 60 °C for 48 h and then cooled to 5 °C before the pH was adjusted to 3–4 by addition of aqueous 2 M hydrochloric acid. Stirring was continued for 1 h at 5 °C, water (800 mL) was added and then extracted ethyl acetate (3×150 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure to give a residue. Crystallisation form ethyl acetate/hexane gave compound **1** (0.14 g, 63%) as colourless microcrystals; mp 225–226 °C; ν_{max} (Nujol) 3120, 2950, 1720, 1681 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.97 (3H, s, CH_3), 6.33 (1H, dd, *J*=3.7, 2.7 Hz, H-2), 6.97–7.05 (2H, m, H-1, H-3), 7.11 (1H, ddd, *J*=8.2, 7.2, 1.0 Hz, H-8), 7.57 (1H, ddd, *J*=8.1, 7.2, 1.0 Hz, H-9), 8.07 (1H, dd, *J*=8.1, 1.0 Hz, H-10), 8.81 (1H, dd, *J*=8.2, 1.0 Hz, H-7), 9.43 (1H, br s, OH), 11.83 (1H, br s, 1H, NH); δ_C (63 MHz, $CDCl_3$) 52.6, 77.39, 110.63, 110.83, 114.83, 120.24, 122.25, 122.53, 131.12, 134.89, 140.23, 142.12, 159.54, 169.13, 210.31; *m*/*z* (ESI) 284.9 $[M+H]^+$, 306.9 $[M+Na]^+$; HRMS (ESI): $[M+Na]^+$, found 307.0691. $C_{15}H_{12}N_2NaO_4$ requires 307.0695.

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