

Synthesis of 4-Hydroxy-1*H*-pyrrole-2,3-dicarboxylic Acid Derivatives: Unusual Coupling of Acetylenic Esters and α -Amino Acids in the Presence of Cyclohexyl Isocyanide or *N,N'*-Dicyclohexylcarbodiimide

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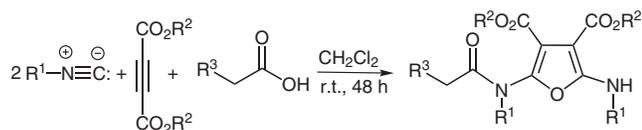
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Abstract: A facile and direct synthetic entry to 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylic acid derivatives is reported. It is based on the unusual ring annulation of acetylenic esters and α -amino acids with isocyanide or carbodiimide under neutral conditions in a one-step procedure.

Key words: pyrroles, α -amino acids, alkynes, isocyanides, *N,N'*-dicyclohexylcarbodiimide

Pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry and are useful for applications in medicine and agriculture.^{1,2} These compounds can have intrinsic biological activity and also constitute the structural feature of many biologically active compounds. The synthetic approaches to pyrrole derivatives are mostly multistep and low-yielding.^{3–7} Thus, development of new synthetic methods still remains an attractive goal.

In previous studies, we were interested in developing isocyanide–electron-deficient acetylene reactions (IMCRs/DAAD) under multicomponent conditions. This research led to the discovery of the reaction between isocyanides, acetylenes, and carboxylic acids for the first time.⁸ In our recent investigations, treatment of aliphatic carboxylic acids and derivatives with dialkyl acetylenedicarboxylates and alkyl isocyanides, at 25 °C, led to the formation of 2,5-diaminofuran derivatives (Scheme 1).⁹



Scheme 1

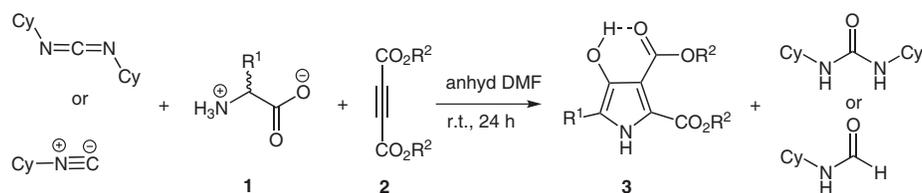
Among other interesting syntheses, we could prepare nicotinamide and isonicotinamides.¹⁰ In a related study in the multicomponent area, we incorporated α -amino acids under similar conditions. To this end, as a preliminary step in IMCRs/DAAD and α -amino acids reactions, we synthesized dialkyl 4-hydroxy-5-alkyl(or aryl)-1*H*-pyrrole-2,3-dicarboxylates in good yields. Furthermore, this

unusual coupling of acetylenes and α -amino acids in the presence of carbodiimides such as *N,N'*-dicyclohexylcarbodiimide led to the same functionalized pyrrole rings in good yields, better than in the previous method.

To our surprise, in a one-pot reaction between α -amino acids and dialkyl acetylenedicarboxylates (DAADs) in the presence of isocyanide or carbodiimide, dialkyl 4-hydroxy-5-alkyl(or aryl)-1*H*-pyrrole-2,3-dicarboxylate derivatives form as products (Table 1). It should be noted here that the synthesis of dialkyl 4-hydroxy-5-alkyl(or aryl)-1*H*-pyrrole-2,3-dicarboxylates has been reported earlier by Kolar et al. and also Noguchi via amino esters in the presence of sodium methoxide in 11% yield.⁷

The reactions of cyclohexyl isocyanide or *N,N'*-dicyclohexylcarbodiimide with α -amino acids **1** in the presence of dialkyl acetylenedicarboxylates **2** proceeded spontaneously at 25 °C in anhydrous *N,N*-dimethylformamide and were completed within 24 hours, to produce dialkyl 4-hydroxy-5-alkyl(or aryl)-1*H*-pyrrole-2,3-dicarboxylates **3** in 70–95% yields (Table 1). The structures of compounds **3a–h** were deduced from their elemental analyses, IR spectra, and high-field ¹H and ¹³C NMR spectra. The mass spectrum of **3a** displayed the molecular ion (M⁺) peak at *m/z* = 276; this is consistent with the dialkyl 4-hydroxy-5-alkyl(or aryl)-1*H*-pyrrole-2,3-dicarboxylate structure. The IR spectrum of **3a** exhibited absorption bands due to the carbonyl group of the esters at 1645 and of NH at 3250 cm⁻¹. The ¹H NMR spectrum of **3a** contained three single sharp lines, readily recognized as arising from methoxy (δ = 3.83 and 3.86) and hydroxy (δ = 8.84) protons. A fairly broad singlet (δ = 10.32) was observed for the NH group, and the phenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ¹H-decoupled ¹³C NMR spectrum of **3a** showed twelve distinct resonances in agreement with the structure of dimethyl 4-hydroxy-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate.

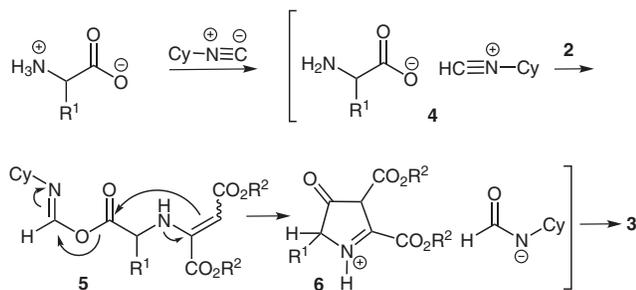
Although the mechanistic details of the reaction are not clearly known, the rationalization presented earlier may also be invoked here. In the reaction of isocyanide as an example, it is conceivable^{8,11} that the initially formed ion pair **4** results from the reaction between an α -amino acid and the isocyanide (Scheme 2).^{11a,b} The reaction of ion pair **4** with acetylene **2** leads to the formation of enaminone **5**, and the final product **3** results from ring annulation of enaminone **5** due to intramolecular interactions and elimination of substituted formamide followed by aroma-

Table 1 Reactions of α -Amino Acids **1** and Dialkyl Acetylenedicarboxylates **2** in the Presence of Cyclohexyl Isocyanide or *N,N'*-Dicyclohexylcarbodiimide

α -Amino acid 1	R^2	Product 3	Yield ^a (%) of 3 from	
			CyNC	DCC
	Me	3a 	80	90
	Et	3b 	80	90
	Me	3c 	85	95
	Et	3d 	80	95
	Me	3e 	70	85
	Me	3f 	70	90
	Me	3g 	80	95
	Et	3h 	80	95

^a Isolated yields.

tization by hydrogen migration (Scheme 2). When *N,N'*-dicyclohexylcarbodiimide is used instead of isocyanide, the first step is the activation of the α -amino acid by attachment of the acid to *N,N'*-dicyclohexylcarbodiimide and then formation of the enaminone. Pyrrole **3** is formed by intramolecular ring annulation and aromatization.



Scheme 2

In conclusion, two one-pot approaches to the addition of α -amino acids to electron-deficient acetylenes for the synthesis of a series of dialkyl 4-hydroxy-5-alkyl(or aryl)-1*H*-pyrrole-2,3-dicarboxylate derivatives have been reported. The present one-pot general method for the addition of α -amino acids to active acetylenes has the advantage that not only can the reaction be performed under neutral conditions, but it also affords good yields of products. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

Dimethyl and diethyl acylenedicarboxylates, α -amino acids, CyNC, and DCC were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed on a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. ^1H and ^{13}C NMR spectra were measured (CDCl_3 soln) on a Bruker DRX-500 Avance spectrometer at 500.1 and 125.7 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Merck silica gel (230–240 mesh) was used for chromatography columns.

Dimethyl 4-Hydroxy-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**3a**); Typical Procedure

A soln of CyNC (0.11 g, 1 mmol) or DCC (0.21 g, 1 mmol) in anhyd DMF (3 mL) was added dropwise over 10 min to a magnetically stirred soln of amino(phenyl)acetic acid (**1a**; 0.51 g, 1 mmol) and dimethyl acylenedicarboxylate (**2a**; 0.14 g, 1 mmol) in anhyd DMF (2 mL) at r.t. The reaction mixture was subsequently stirred for 24 h. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (silica gel, hexane–EtOAc, 5:1).

Yield: 0.22 g (80%); pale yellow crystals; mp 115–117 °C.

IR (KBr): 3250 (NH), 1645 (2 CO_2Me), 1464 and 1434 (Ph), 1228 (C–O of ester) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 3.83 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 7.16 (t, $^3J_{\text{H,H}} = 7.4$ Hz, 1 H, CH of Ph), 7.32 (t, $^3J_{\text{H,H}} = 7.9$ Hz, 2 H, 2 CH of Ph), 7.74 (d, $^3J_{\text{H,H}} = 7.5$ Hz, 2 H, 2 CH of Ph), 8.84 (s, 1 H, OH), 10.32 (br s, 1 H, NH).

^{13}C NMR (125 MHz, CDCl_3): δ = 51.81 and 51.87 (2 OCH_3), 104.85 ($\text{C}_5_{\text{pyrrole}}$), 117.65 ($\text{C}_3_{\text{pyrrole}}$), 117.80 ($\text{C}_2_{\text{pyrrole}}$), 124.95 (2 CH of Ph), 126.77 (CH of Ph), 128.60 (2 CH of Ph), 129.74 (C_{ipso}), 146.44 ($\text{C}_4_{\text{pyrrole}}$), 160.0 (CO_2Me), 167.37 (CO_2Me).

MS (EI, 70 eV): m/z (%) = 276 [$\text{M}^+ + 1$] (7), 275 [M^+] (30), 243 (100), 211 (44), 183 (9), 155 (46), 128 (7), 104 (9), 89 (4), 77 (19), 59 (3), 53 (7).

Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_5$ (275.26): C, 61.09; H, 4.76; N, 5.09. Found: C, 61.15; H, 4.68; N, 5.10.

Diethyl 4-Hydroxy-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (**3b**)

Pale yellow crystals; mp 96–98 °C.

IR (KBr): 3305 (NH), 1639 (2 CO_2Et), 1464 and 1408 (Ph), 1242 (C–O of ester) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 1.39 (t, $^3J_{\text{H,H}} = 7.1$ Hz, 3 H, OCH_2CH_3), 1.43 (t, $^3J_{\text{H,H}} = 7.2$ Hz, 3 H, OCH_2CH_3), 4.38 (q, $^3J_{\text{H,H}} = 7.1$ Hz, 2 H, OCH_2CH_3), 4.43 (q, $^3J_{\text{H,H}} = 7.2$ Hz, 2 H, OCH_2CH_3), 7.26 (t, $^3J_{\text{H,H}} = 7.5$ Hz, 1 H, CH of Ph), 7.42 (t, $^3J_{\text{H,H}} = 7.7$ Hz, 2 H, 2 CH of Ph), 7.76 (d, $^3J_{\text{H,H}} = 7.8$ Hz, 2 H, 2 CH of Ph), 9.09 (s, 1 H, OH), 9.52 (br s, 1 H, NH).

^{13}C NMR (125 MHz, CDCl_3): δ = 14.31 and 14.41 (2 OCH_2CH_3), 61.04 and 61.31 (2 OCH_2CH_3), 105.04 ($\text{C}_5_{\text{pyrrole}}$), 117.45 ($\text{C}_3_{\text{pyrrole}}$), 117.84 ($\text{C}_2_{\text{pyrrole}}$), 124.59 (2 CH of Ph), 126.99 (CH of Ph), 128.89 (2 CH of Ph), 129.70 (C_{ipso}), 146.94 ($\text{C}_4_{\text{pyrrole}}$), 160.22 (CO_2Et), 167.21 (CO_2Et).

MS (EI, 70 eV): m/z (%) = 304 [$\text{M}^+ + 1$] (6), 303 [M^+] (19), 257 (100), 229 (10), 211 (47), 183 (7), 155 (26), 104 (12), 89 (4), 77 (7), 53 (9).

Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_5$ (303.31): C, 63.36; H, 5.65; N, 4.62. Found: C, 63.40; H, 5.60; N, 4.70.

Dimethyl 5-Benzyl-4-hydroxy-1*H*-pyrrole-2,3-dicarboxylate (**3c**)

Pale yellow crystals; mp 146–148 °C.

IR (KBr): 3265 (NH), 1647 (2 CO_2Me), 1476 and 1437 (Ph), 1283 (C–O of ester) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 3.83 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.97 (s, 2 H, PhCH_2), 7.22 (d, $^3J_{\text{H,H}} = 7.3$ Hz, 2 H, 2 CH of Ph), 7.26 (t, $^3J_{\text{H,H}} = 7.8$ Hz, 1 H, CH of Ph), 7.32 (t, $^3J_{\text{H,H}} = 7.5$ Hz, 2 H, 2 CH of Ph), 8.27 (s, 1 H, OH), 8.84 (br s, 1 H, NH).

^{13}C NMR (125 MHz, CDCl_3): δ = 30.09 (PhCH_2), 51.87 and 51.88 (2 OCH_3), 104.65 ($\text{C}_5_{\text{pyrrole}}$), 116.38 ($\text{C}_3_{\text{pyrrole}}$), 117.54 ($\text{C}_2_{\text{pyrrole}}$), 126.89 (CH of Ph), 128.55 (2 CH of Ph), 128.91 (2 CH of Ph), 137.70 (C_{ipso}), 145.89 ($\text{C}_4_{\text{pyrrole}}$), 159.82 (CO_2Me), 167.19 (CO_2Me).

MS (EI, 70 eV): m/z (%) = 290 [$\text{M}^+ + 1$] (5), 289 [M^+] (26), 257 (100), 225 (5), 197 (18), 169 (22), 143 (13), 103 (22), 91 (84), 80 (19), 57 (34).

Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_5$ (289.28): C, 62.28; H, 5.23; N, 4.84. Found: C, 62.30; H, 5.30; N, 4.90.

Diethyl 5-Benzyl-4-hydroxy-1*H*-pyrrole-2,3-dicarboxylate (**3d**)

Pale yellow crystals; mp 127–129 °C.

IR (KBr): 3260 (NH), 1635 (2 CO_2Et), 1479 and 1443 (Ph), 1268 and 1211 (C–O of ester) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 1.33 (t, $^3J_{\text{H,H}} = 7.1$ Hz, 3 H, OCH_2CH_3), 1.41 (t, $^3J_{\text{H,H}} = 7.1$ Hz, 3 H, OCH_2CH_3), 3.97 (s, 2 H, PhCH_2), 4.29 (q, $^3J_{\text{H,H}} = 7.1$ Hz, 2 H, OCH_2CH_3), 4.40 (q, $^3J_{\text{H,H}} = 7.1$ Hz, 2 H, OCH_2CH_3), 7.20 (d, $^3J_{\text{H,H}} = 7.5$ Hz, 2 H, 2 CH of Ph), 7.24 (t, $^3J_{\text{H,H}} = 7.2$ Hz, 1 H, CH of Ph), 7.30 (t, $^3J_{\text{H,H}} = 7.5$ Hz, 2 H, 2 CH of Ph), 8.42 (s, 1 H, OH), 9.25 (br s, 1 H, NH).

¹³C NMR (125 MHz, CDCl₃): δ = 14.29 and 14.33 (2 OCH₂CH₃), 29.99 (PhCH₂), 60.82 and 60.96 (2 OCH₂CH₃), 104.40 (C5_{pyrrole}), 116.55 (C3_{pyrrole}), 117.43 (C2_{pyrrole}), 126.71 (CH of Ph), 128.40 (2 CH of Ph), 128.76 (2 CH of Ph), 137.90 (C_{ipso}), 145.93 (C4_{pyrrole}), 160.17 (CO₂Et), 166.96 (CO₂Et).

MS (EI, 70 eV): *m/z* (%) = 318 [M⁺ + 1] (18), 317 [M⁺] (33), 243 (13), 225 (14), 214 (7), 197 (16), 169 (16), 143 (8), 103 (17), 91 (27), 80 (11), 53 (7).

Anal. Calcd for C₁₇H₁₉NO₅ (317.34): C, 64.34; H, 6.03; N, 4.41. Found: C, 64.40; H, 5.98; N, 4.45.

Dimethyl 4-Hydroxy-5-isopropyl-1*H*-pyrrole-2,3-dicarboxylate (3e)

Yellow viscous oil.

IR (KBr): 3380 (NH), 1727 and 1683 (CO₂Me), 1429 and 1341 (Ph), 1254 and 1209 (C–O of ester) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.29 (d, ³J_{H,H} = 7.0 Hz, 6 H, 2 CH₃ of *i*-Pr), 3.10 (sept, ³J_{H,H} = 7.0 Hz, 1 H, CH of *i*-Pr), 3.88 (s, 3 H, OCH₃), 3.93 (s, 3 H, OCH₃), 8.19 (s, 1 H, OH), 8.85 (br s, 1 H, NH).

¹³C NMR (125 MHz, CDCl₃): δ = 21.14 (2 CHMe₂), 24.87 (CHMe₂), 51.79 and 51.84 (2 OCH₃), 104.05 (C5_{pyrrole}), 114.95 (C3_{pyrrole}), 124.40 (C2_{pyrrole}), 144.84 (C4_{pyrrole}), 159.98 (CO₂Me), 167.33 (CO₂Me).

MS (EI, 70 eV): *m/z* (%) = 242 [M⁺ + 1] (7), 241 [M⁺] (8), 210 (13), 186 (100), 126 (37), 91 (20), 71 (36), 57 (71), 55 (70).

Anal. Calcd for C₁₁H₁₅NO₅ (241.24): C, 54.77; H, 6.27; N, 5.81. Found: C, 54.68; H, 6.17; N, 5.78.

Dimethyl 5-sec-Butyl-4-hydroxy-1*H*-pyrrole-2,3-dicarboxylate (3f)

Pale yellow crystals; mp 94–96 °C.

IR (KBr): 3455 (NH), 1717 and 1658 (2 CO₂Me), 1484 and 1436 (Ph), 1264 and 1230 (C–O of ester) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 0.88 (t, ³J_{H,H} = 7.4 Hz, 3 H, MeCHCH₂Me), 1.27 (d, ³J_{H,H} = 7.1 Hz, 3 H, MeCHCH₂Me), 1.64 (m, 2 H, MeCHCH₂Me), 2.86 (m, ³J_{H,H} = 7.2 Hz, 1 H, MeCHCH₂Me), 3.88 (s, 3 H, OCH₃), 3.93 (s, 3 H, OCH₃), 8.19 (s, 1 H, OH), 8.85 (br s, 1 H, NH).

¹³C NMR (125 MHz, CDCl₃): δ = 11.88 (MeCHCH₂Me), 18.86 (MeCHCH₂Me), 28.87 (MeCHCH₂Me), 31.85 (MeCHCH₂Me), 51.80 and 51.85 (2 OCH₃), 104.68 (C5_{pyrrole}), 115.20 (C3_{pyrrole}), 123.50 (C2_{pyrrole}), 145.32 (C4_{pyrrole}), 159.99 (CO₂Me), 167.34 (CO₂Me).

MS (EI, 70 eV): *m/z* (%) = 255 [M⁺] (16), 224 (10), 223 (41), 208 (7), 194 (100), 162 (18), 106 (19), 80 (13), 53 (30).

Anal. Calcd for C₁₂H₁₇NO₅ (255.27): C, 56.46; H, 6.71; N, 5.49. Found: C, 56.50; H, 6.90; N, 5.50.

Dimethyl 4-Hydroxy-5-(1*H*-indol-3-ylmethyl)-1*H*-pyrrole-2,3-dicarboxylate (3g)

Colorless crystals; mp 200–202 °C.

IR (KBr): 3395 (NH), 3255 (NH), 1649 (2 CO₂Me), 1481 and 1449 (Ph), 1283 and 1220 (C–O of ester) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 3.80 (s, 3 H, OCH₃), 3.96 (s, 3 H, OCH₃), 4.13 (s, 2 H, CH₂), 7.11 (s, 1 H, CH), 7.13 (t, ³J_{H,H} = 7.1 Hz, 1 H, CH), 7.24 (t, ³J_{H,H} = 7.2 Hz, 1 H, CH), 7.41 (d, ³J_{H,H} = 7.1 Hz, 1 H, CH), 7.54 (d, ³J_{H,H} = 7.8 Hz, 1 H, CH), 8.11 (s, 1 H, OH), 8.35 and 8.80 (br s, 2 H, 2 NH).

¹³C NMR (125 MHz, CDCl₃): δ = 19.95 (CH₂), 51.76 and 51.83 (2 OCH₃), 104.50 (C5_{pyrrole}), 111.25 (CH), 111.80 (C3_{indole}), 115.90 (C3_{pyrrole}), 117.90 (C2_{pyrrole}), 118.77 (CH), 119.95 (CH), 122.46

(CH), 122.58 (CH), 126.97 (C3_aindole), 136.53 (C7_aindole), 145.29 (C4_{pyrrole}), 159.73 (CO₂Me), 167.32 (CO₂Me).

MS (EI, 70 eV): *m/z* (%) = 329 [M⁺ + 1] (5), 328 [M⁺] (28), 296 (13), 263 (2), 235 (1), 207 (1), 180 (6), 148 (7), 132 (10), 117 (100), 104 (5), 90 (9), 77 (3), 53 (2).

Anal. Calcd for C₁₇H₁₆N₂O₅ (328.32): C, 62.19; H, 4.91; N, 8.53. Found: C, 62.20; H, 5.00; N, 8.56.

Diethyl 4-Hydroxy-5-(1*H*-indol-3-ylmethyl)-1*H*-pyrrole-2,3-dicarboxylate (3h)

Colorless crystals; mp 194–196 °C.

IR (KBr): 3410 (NH), 3255 (NH), 1639 (2 CO₂Et), 1481 and 1444 (Ph), 1280 and 1217 (C–O of ester) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.32 (t, ³J_{H,H} = 7.05 Hz, 3 H, OCH₂CH₃), 1.43 (t, ³J_{H,H} = 7.20 Hz, 3 H, OCH₂CH₃), 4.12 (s, 2 H, CH₂), 4.27 (q, ³J_{H,H} = 7.05 Hz, 2 H, OCH₂CH₃), 4.43 (q, ³J_{H,H} = 7.15 Hz, 2 H, OCH₂CH₃), 7.07 (s, 1 H, CH), 7.13 (t, ³J_{H,H} = 7.2 Hz, 1 H, CH), 7.23 (t, ³J_{H,H} = 7.8 Hz, 1 H, CH), 7.39 (d, ³J_{H,H} = 8.0 Hz, 1 H, CH), 7.56 (d, ³J_{H,H} = 7.8 Hz, 1 H, CH), 8.10 (s, 1 H, OH), 8.45 and 8.87 (br s, 2 H, 2 NH).

¹³C NMR (125 MHz, CDCl₃): δ = 14.33 (2 OCH₂CH₃), 19.96 (CH₂), 60.82 (2 OCH₂CH₃), 104.50 (C5_{pyrrole}), 111.24 (CH), 111.93 (C3_{indole}), 116.05 (C3_{pyrrole}), 117.69 (C2_{pyrrole}), 118.77 (CH), 119.89 (CH), 122.39 (CH), 122.53 (CH), 126.97 (C3_aindole), 136.53 (C7_aindole), 145.31 (C4_{pyrrole}), 159.93 (CO₂Me), 167.08 (CO₂Me).

MS (EI, 70 eV): *m/z* (%) = 357 [M⁺ + 1] (8), 356 [M⁺] (31), 310 (18), 263 (2), 235 (1), 207 (1), 194 (4), 130 (6), 117 (100), 103 (1), 90 (3), 77 (2), 53 (2).

Anal. Calcd for C₁₉H₂₀N₂O₅ (356.37): C, 64.04; H, 5.66; N, 7.86. Found: C, 64.00; H, 5.70; N, 7.90.

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