dl-5, 83477-75-2; 5R, 83541-02-0; 6aS, 83477-77-4; 6bS, 83477-78-5; 6cR, 83477-79-6; 6dR, 83477-80-9; 7a, 83477-82-1; 7b, 83477-83-2; 7d, 83477-81-0; 11, 83477-84-3; 12, 83477-85-4; 14R (R = Pr-i), 83540-97-0; 14S (R = Pr-i), 83541-68-8; 15RS (R = Pr-i), 83477-86-5; 15RR (R = Pr-i), 83477-87-6; 15SR (R = Pr-i), 83477-88-7; 15RR (R = Et), 83477-89-8; 15RS (R = Et), 83477-90-1; 15SS (R = Pr-i), 83478-00-6; 16RS, 83540-98-1; 16SR, 83540-99-2; 16SS, 83541-00-8; 17RS, 83477-91-2; 17SR, 83477-92-3; 17SS, 83477-94-5; 17RR, 83477-95-6; 18RS, 83477-96-7; 18RR, 83477-97-8; 18SS, 83486-41-3; 19SS, 83477-98-9; 19SR, 83541-01-9; 20SS, 83477-93-4; i, 83477-99-0; L-malic acid, 97-67-6; O-benzylhydroxylamine hydrochloride, 2687-43-6; diethyl D-malate, 7554-28-1; dl-malic acid, 617-48-1.

Dichlorodicyanoquinone Oxidations in the Indole Area. Synthesis of Crenatine

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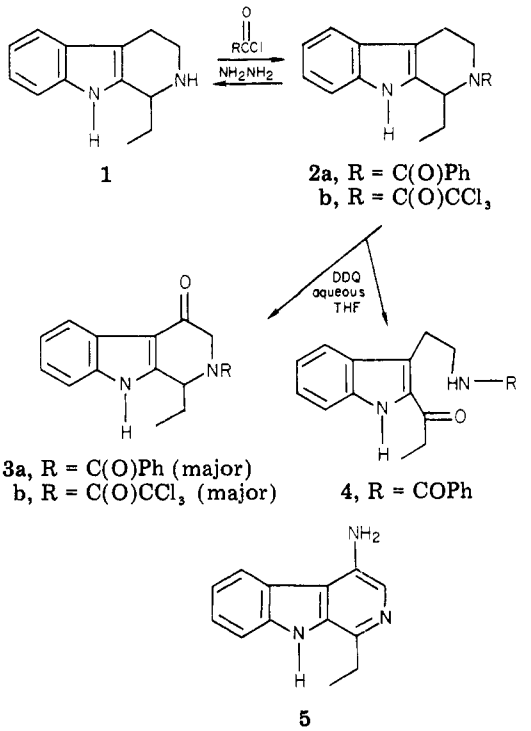
Received May 18, 1982

The influence of temperature on the reaction of dichlorodicyanoquinone (DDQ) with 1,2,3,4-tetrahydro-β-carbolines has been explored. The DDQ oxidation of amide **2a**, when performed at room temperature, gave **3a** (3-acylindole)/**4** (2-acylindole) in a ratio of ca. 1:1, while this was increased to 2:1 at 0 °C and to ca. 5:1 at −78 °C. This method for preparation of 4-oxo-β-carbolines has been employed for synthesis of the β-carboline alkaloid crenatine (**11**). In addition, treatment of the 4-oxotetrahydro-β-carboline (**3b**) with hydrazine gave 1-ethyl-4-amino-β-carboline (**12**) which should provide access to a series of 4-substituted β-carbolines.

Previously, we have demonstrated that a carbonyl group located at the 3-position of β-carbolines was important for binding to the benzodiazepine (Valium) receptor(s).[1-4] It has, therefore, become of interest to develop access to other substituted β-carbolines, including the 4-oxo derivatives. In this vein, both selenium dioxide (SeO_2)[5] and dichlorodicyanoquinone (DDQ)[6a] have been recently employed for the preparation of 3-acylindoles.[6b] Several alkaloids such as borrecapine[7a] and aristotelinone[7b] contain the 3-acylindole functionality; moreover, others contain functional groups which can be formally derived from 3-acylindoles such as crenatine[8,9] (**11**), 1-methoxycanthin-6-one,[10] and 4-hydroxy-β-carboline-1-carboxaldehyde, which was found recently to be a potent xanthine oxidase inhibitor.[11] Both SeO_2[5] and DDQ[6] offer excellent entries into these biologically important molecules, and we report recent work on DDQ oxidations of tetrahydro-β-carbolines which have resulted in the synthesis of the alkaloid crenatine (**11**).

Scheme I



Oikawa and Yonemitsu reported in 1977 that DDQ could be employed to oxidize 2,3-disubstituted indoles[6a,12] and tetrahydrocarbazoles to the corresponding carbonyl compounds. Use of this technology in our hands has permitted the conversion of 1,2,3,4-tetrahydro-β-carbolines into 3-acylindoles with remarkable ease; yields of this process were as high as 77% and reached a maximum when the oxidations were carried out at low temperature. The key

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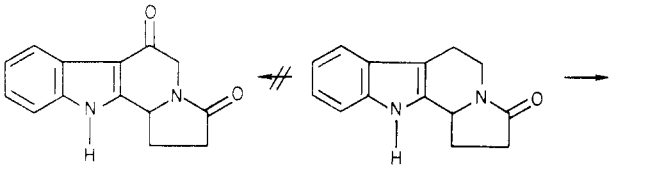
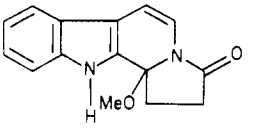
substrate 1-ethyl-1,2,3,4-tetrahydro-β-carboline (**1**) was prepared in 96% yield by a Pictet–Spengler reaction of tryptamine with propionaldehyde and subsequently converted into the corresponding amides **2a** and **2b** on treatment with benzoyl chloride or trichloroacetyl chloride, respectively (Scheme I). It was necessary to protect the amine **1** as an amide since charge-transfer complexes are known[13] to form between DDQ and amines, thus rendering the reagent less effective. Treatment of the benzamide **2a** with DDQ in an aqueous medium under a variety of conditions always furnished a mixture of the desired 3-acylindole **3a** and keto amide **4**, the product of attack at C-1 of the tetrahydro-β-carboline. Generally the ratio of **3a** to **4** increased with decreasing temperature (ca. 1:1 at room temperature, 2:1 at 0 °C, and 5:1 at −78 °C), and it is clear that lowering the temperature at which the DDQ oxidation is carried out favors oxidation of the tetrahydro β-carboline at carbon 4 in preference to reaction at C-1.

The related trichloroamide **2b** was oxidized with DDQ in methanol at −78 °C to provide the desired ketone **3b** in only 29% yield; however, when a solution of acetone/water (9:1) cooled to −78 °C was dropped into a mixture of solid DDQ and **2b**, a 77% yield of the 3-acylindole **3b** was obtained. Ethyl-β-carboline **5** was also isolated from this process in 6% yield; the lability of the trichloramide toward hydrolysis, as compared to the benzamide, may account for the formation of **5**. In spite of the propensity for **2a** to provide significant amounts of the amide **4**, the 3-acylindoles **3a** and **3b** returned only starting material when subjected to a similar oxidation. The usual blue coloration observed when DDQ is dissolved with indoles in solution was not observed with **3a** or **3b**. Since electron-withdrawing groups inhibit the formation of change-transfer complexes with DDQ, it is not surprising that the ketones **3a** and **3b** (vinylogous amides) are inert to DDQ oxidation. Similarly, the 2-acylindole **4** could not be oxidized with DDQ, and this reaction mixture did not take on a blue color at anytime. Furthermore, a carbonyl substituent located on the indole nitrogen (amide), such as that contained in hexahydrocanthin-6-one, likewise prevents the formation of the necessary charge-transfer complex and results in the recovery of the starting hexahydrocanthin-6-one derivative.[14]

For a related study the tetracyclic γ-lactam **6** was prepared by a Pictet–Spengler reaction of tryptamine and 2-oxoglutaric acid. Oxidation of **6** with DDQ in aqueous media failed to provide any of the desired 3-acylindole **7**;



7 6



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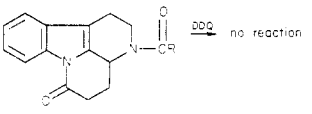
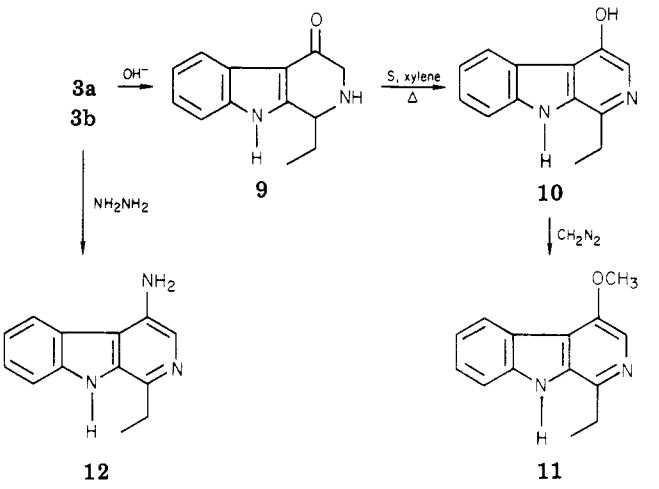
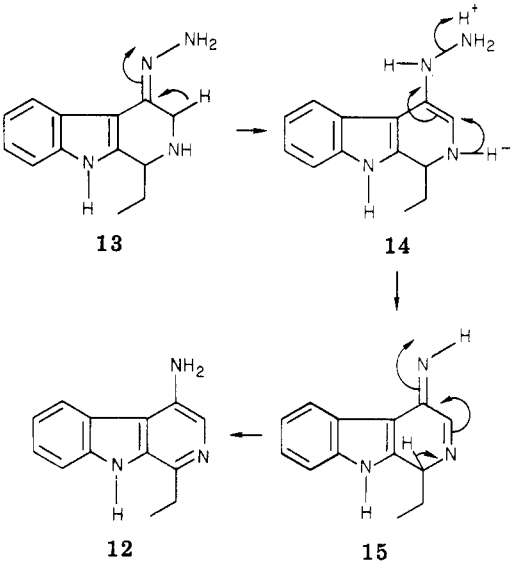
(14) Cain, M.; Cook, J., unpublished results:



Scheme II



Scheme III



however, when the oxidation was carried out in methanol at −78 °C the methyl ether **8** was obtained in 44% yield. The strain induced in ring C of **6** by the γ-lactam may be responsible for the failure to generate a 3-acylindole; the mechanism for the formation of **8** is not clear at the moment since both positions 1 and 4 were involved in the oxidation.

The ability to incorporate oxygen into **2b** in regiospecific fashion provides a simple route to the alkaloid crenatine. To our knowledge this is the first synthesis of a natural β-carboline with this particular functionality and should provide a pathway to other interesting 4-oxo-substituted β-carbolines of biological interest.[11]

As illustrated in Scheme II, removal of the protecting groups (amides) from **3a** or **3b** was best carried out in base with the amide at high dilution as a result of the limited solubility of these two compounds; furthermore, attempts to hydrolyze **3a** or **3b** under acidic conditions afforded an inseparable mixture of compounds. Although the trichloro amide function of **2b** can be easily cleaved in refluxing hydrazine to give **1**, use of these conditions with keto amide **3b** gave instead 1-ethyl-4-amino-β-carboline (**12**) in 68% yield. The proposed mechanism for this interesting transformation is outlined in Scheme III. Cleavage of the amide followed by formation of the hydrazone **13** would be expected to occur in routine fashion. Proton transfer to generate the enamine **14** followed by loss of ammonia

and prototropic rearrangement (see **15**) would give the 4-amino-β-carboline **12**. No attempt to maximize the yield of this process has been made to date. The formation of the base **12** is noteworthy since it provides a route, via diazonium ion chemistry, to a variety of 4-substituted β-carbolines for biological screening.

The 3-acylindole **9** was converted into the desired 1-ethyl-4-hydroxy-β-carboline (**10**) on heating with sulfur in xylene. This method proved superior to the use of either palladium on carbon or chloranil for oxidation and has been used previously in our laboratory to prepare benzodiazepine receptor antagonists.[4] Finally, the phenol **10** was then methylated with diazomethane to provide the natural product crenatine (**11**) in 63% yield.

Experimental Section

Microanalyses were performed on an F&M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. NMR spectra were recorded on Varian T-60 and EM-360 spectrometers and a Varian CFT-20 ^{13}C NMR spectrometer. IR spectra were taken on a Beckman Acculab-1 instrument, while electron-impact (EI) mass spectra were recorded on a Hitachi RMU-6 spectrometer. Chemical ionization (CI) mass spectra were obtained by using either a Finnigan GC/MS or Hewlett Packard 5855 gas chromatograph–mass spectrometer.

The analytical TLC plates used were E. Merck Brinkman UV active silica gel or alumina on plastic. Silica gel 60 and aluminum oxide for chromatography were purchased from EM Laboratories and J. T. Baker, respectively. Tryptamine, propionaldehyde, 2-oxoglutaric acid, trichloroacetylchloride, Diazald (for preparation of CH_2N_2), dichlorodicyanoquinone (DDQ), and hydrazine were purchased from Aldrich Chemical Co.

1-Ethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (1). Tryptamine (40 g, 250 mmol) was dissolved in 250 mL of 10% aqueous methanol. Propionaldehyde (21.75 g, 375 mmol) and concentrated sulfuric acid (14 mL) were added, and the solution was refluxed under N_2 for 6.5 h until no tryptamine was detected by TLC. The methanol was evaporated, and the resulting aqueous solution was basified with aqueous NH_3 (28%, 40 mL) and extracted with EtOAc (4 × 200 mL). The combined organic fractions were washed with brine (1 × 200 mL) and dried with K_2CO_3. The solvent was evaporated to obtain 48 g (96%) of **1**: mp 105–110 °C (EtOAc); IR (KBr) 3200–3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (br s, 1), 7.35 (m, 1), 7.10 (m, 3), 3.90 (m, 1), 3.20 (m, 2), 2.70 (m, 2), 1.60 (m, 3), 1.00 (t, 3, J = 8 Hz); MS (CI, CH_4), m/e (relative intensity) 201 (100, m + 1).

Anal. Calcd for $C_{13}H_{16}N_2$: C, 78.00; H, 8.00; N, 14.00. Found: C, 78.19; H, 7.66; N, 13.82.

1-Ethyl-2-benzoyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (2a). The tetrahydro-β-carboline **1** (33.4 g, 141.4 mmol) was dissolved in a mixture of dry pyridine (250 mL) and dry benzene (500 mL). To this solution was added benzoyl chloride (35 mL, 301.5 mmol) dropwise with stirring. The resulting solution was heated to 60–70 °C for 0.5 h. The reaction mixture was cooled and quenched with water (2000 mL). The layers were separated, and the aqueous layer was extracted with benzene (2 × 800 mL). The combined organic layers were washed with water (2 × 1000 mL), aqueous sodium carbonate (3 × 1000 mL), and water (4 × 2000 mL) to remove all the benzoic acid. The organic layer was then washed with brine (2 × 1000 mL) and dried (Na_2SO_4). The solvent was removed, and the resulting thick oil was taken up in methanol. The crystals which formed were collected by filtration to give **2a**: 36.6g (85.3%); mp 166–168 °C; IR (KBr) 3265, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.60 (m, 1), 7.80–6.80 (m, 9), 5.90 (m, 1), 4.10–3.00 (m, 2), 2.78 (m, 2), 2.00 (m, 2), 1.15 (t, 3, J = 7 Hz); MS (CI, NH_3), m/e (relative intensity) 305 (m + 1, 100).

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 78.95; H, 6.58; N, 9.21. Found: C, 78.75; H, 6.79; N, 9.12.

1-Ethyl-2-(trichloroacetyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (2b). The tetrahydro-β-carboline **1** (11.3 g, 56.5 mmol) was dissolved in CH_2Cl_2 (170 mL), and K_2CO_3 (10.35 g, 75 mmol) was added. To this suspension trichloracetyl chloride (13.65 g, 121 mmol) in CH_2Cl_2 (30 mL) was added dropwise at −78 °C. The suspension was stirred vigorously and allowed to warm to room temperature over 1 h. The reaction mixture was cooled, after which CH_2Cl_2 (300 mL) and water (200 mL) were added. The organic layer was separated, and the aqueous fraction was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic fractions were washed with 14% aqueous NH_3 (100 mL) and 5% aqueous HCl (400 mL). The organic layer was dried (Na_2SO_4) and then evaporated to give 11.7 g (60%) of **2b**: mp 187–188.5 °C (MeOH); IR (KBr) 3380 (br), 1670 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.20 (br s, 1), 7.70–7.00 (m, 4), 5.65 (t, 1, J = 7 Hz), 4.9–4.50 (m, 1), 3.8–3.50 (m, 1) 3.1–2.70 (m, 2), 2.2–1.80 (m, 2), 1.00 (t, 3, J = 7 Hz); MS (CI, CH_4), m/e (relative intensity) 349 (33), 347 (100), 345 (100), 311 (35), 309 (53).

Anal. Calcd for $C_{15}H_{15}N_2OCl_3$: C, 52.07; H, 4.34; N, 8.10. Found: C, 52.15; H, 4.59; N, 8.11.

The aqueous acidic fraction was basified with 14% aqueous ammonia, extracted with CH_2Cl_2 (150 mL), and dried with Na_2SO_4. The solvent was evaporated to yield 2.38 g (21%) of unreacted **1**.

Oxidation of 2a with DDQ. The benzamide **2a** (25 g, 82.2 mmol) was dissolved in aqueous tetrahydrofuran (90:10 THF/H_2O, 450 mL) and cooled in an ice bath (0 °C). Dichlorodicyanquinone (37.3 g, 164.4 mmol) dissolved in tetrahydrofuran (100 mL) was added dropwise over 1 h. The cooling bath was then removed, the stirring was continued for 2.5 h, at which time TLC (silica gel: EtOAc/$CHCl_3$, 1:19) indicated that no **2a** remained. The reaction mixture was concentrated to a pasty black solid. This material was chromatographed (twice) through a column (silica gel; EtOAc/$CHCl_3$, 1:19) to remove all reaction byproducts. The mixture of compounds **3a** and **4** which remained was separated by preparative HPLC (SiO_2). The amount of **3a** recovered was 13.04 g (50%): mp 130 °C; IR (KBr) 3200, 1640, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.25 (s, 1, D_2O exchangeable), 8.10 (m, 1) 7.60–7.00 (m, 8), 6.40 (t, 1), 4.30 (d, 2, J = 5 Hz), 2.10 (m, 2), 1.18 (t, 3); ^{13}C NMR ($CDCl_3$) δ 186.14 (s), 171.63 (s), 151.86 (s), 136.16 (s), 134.76 (s), 130.34 (d), 128.78 (d), 128.06 (s), 126.66 (d), 123.87 (d), 122.72 (d), 121.09 (d), 111.58 (d), 109.99 (s), 52.39 (t), 50.14 (d), 25.54 (t), 10.77 (q); MS (70 eV), m/e (relative intensity), 320 (2.6), 319 (21.9), 318 (71.8), 289 (44.1), 213 (100).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.47; H, 5.66; N, 8.80. Found: C, 75.00; H, 5.66; N, 8.75.

The amount of **4** which was isolated totaled 6.53 g (25%): mp 191–192 °C; IR (KBr) 3395, 3310, 1640, 1615 (sh), 1580 cm^{-1}; ^1H NMR (pyridine-d_5) δ 12.35 (br s, 0.5), 9.15 (br s, 0.5), 8.65–7.00 (m, 9), 4.85 (s, 0.5), 3.85 (m, 4.5), 3.10 (q, 2, J = 6 Hz), 1.20 (t, 3, J = 6 Hz); the signals at δ 4.86, 9.15, and 12.35 disappeared on addition of D_2O to the sample; moreover, a portion (0.5 H) of the signal at δ 3.85 also vanished; ^{13}C NMR (pyridine-d_5) δ 194.45, 167.96, 137.48, 136.10, 133.26, 131.34, 129.14, 127.50, 128.66, 127.93, 126.04, 121.58, 120.37, 112.80, 41.75, 33.93, 25.10, 8.30; MS (70 eV), m/e (relative intensity) 321 (1.0), 320 (3.9), 200 (14.2), 199 (100), 198 (23.2), 158 (43.0), 130 (28.2), 105 (72.3), 77 (60.8).

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 75.00; H, 6.25; N, 8.75. Found: C, 74.87; H, 6.35; N, 8.77.

When this reaction was carried out at 25 °C the yields of **4** and **3a** were 41% and 47%, respectively, with an overall yield of 94%.

Oxidation of 2a with DDQ at −78 °C. The benzamide **2a** (400 mg, 1.32 mmol) and DDQ (657 mg, 2.89 mmol) were mixed together until a uniform color was observed. The mixture of powders was cooled on a dry ice–acetone bath. The solvent mixture, (THF/H_2O, 9:1) was also cooled in the same cooling bath, and the slurry which resulted (20 mL) was added slowly to the mixture of powders. The slurry was stirred and allowed to warm to room temperature. The solution was then poured into aqueous NaOH (1 N, 50 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with HCl (10%, 50mL), dried (Na_2CO_3), and chromatographed on Al_2O_3 to yield **4** and **3a** in 12% and 71% yields, respectively.

1-Ethyl-2-(trichloroacetyl)-4-oxo-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (3b). The trichloroamide **2b** (5 g, 14.53 mmol) and DDQ (7.26 g, 32 mmol) were mixed together until a uniform color was obtained and cooled to −78 °C. A solution of 90% aqueous acetone (100 mL) was cooled to −78 °C, and the resultant slurry was added slowly to the mixture of powders. After the addition, the reaction was allowed to warm to room temperature over 45 min. The solution was poured into saturated

$NaHCO_3$ (100 mL) and extracted with $CHCl_3$ (3 × 200 mL). The combined organic fractions were washed with brine (100 mL), dried with Na_2CO_3, and filtered over SiO_2 (300 g). The SiO_2 was eluted with 5% MeOH/$CHCl_3$ to give 4.0 g (77%) of **3b**: mp 234–237 °C (MeOH); IR (KBr) 3250 (br), 1670, 1630 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.10–7.85 (m, 1), 7.60–7.05 (m, 4), 5.90 (t, 1, J = 8 Hz) 5.05 (d, 1, J = 18 Hz), 4.15 (d, 1, J = 18 Hz), 1.95 (q, 2, J = 6 Hz), 1.02 (t, 3, J = 6 Hz); MS (CI, CH_4), m/e (relative intensity) 363 (33), 361 (98), 359 (100), 325 (30), 323 (35).

The methylene protons of the carbon α to the ketone are diastereotopic and are split into doubles (J = 18 Hz).

Anal. Calcd for $C_{15}H_{13}N_2O_2Cl_3$: C, 50.28; H, 3.63; N, 7.82. Found: C, 50.16; H, 3.31; N, 7.69.

1-Ethyl-β-carboline **5** (170 mg, 6%) was also obtained from this reaction after chromatography and was identical in all respects with an authentic sample.[6b]

1-Ethyl-2-(trichloroacetyl)-4-oxo-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (3b). The trichloroamide **2b** (100 mg, 0.3 mmol) was added to DDQ (109 mg, 0.87 mmol), and the two powders were mixed together. Methanol (40 mL) cooled to −78 °C was added dropwise to the powder. The reaction mixture was allowed to warm to room temperature over 2 h. The solvent was evaporated, aqueous NaOH (10%, 20 mL) added, and the solution which resulted extracted with EtOAc (3 × 50 mL). The combined organic fractions were evaporated and chroamtographed on SiO_2 (MeOH/EtOAc gradient) to give 30 mg (29%) of **3b**.

1-Ethyl-4-amino-9*H*-pyrido[3,4-*b*]indole (5). The keto amide **3b** (250 mg, 0.70 mmol) was dissolved in hydrazine (25 mL, 85%) and was heated to reflux for 6.5 h. The reaction mixture was poured into water (100 mL), extracted with $CHCl_3$ (3 × 50 mL), and dried with Na_2CO_3. The solvent was evaporated, and the residue was chromatographed on SiO_2 with a $CHCl_3$/EtOAc gradient to yield 100 mg (68%) of **5** as an oil: ^1H NMR ($CDCl_3$) δ 10.36 (br s, 1), 8.70 (d, 1, J = 8 Hz), 8.55 (s, 1), 8.30–7.70 (m, 3), 4.50 (br s, 2), 3.35 (q, 2, J = 8 Hz) 1.50 (t, 3, J = 8 Hz); mass spectrum (CI, CH_4), m/e 212 (m + 1). The picrate of **5** was prepared; mp 283 °C. Anal. Calcd for $C_{19}H_{16}N_6O_7$: C, 51.82; H, 3.64; N, 19.09. Found: C, 51.97; H, 3.38; N, 18.86.

Preparation of the Tetracyclic γ-Lactam 6. Tryptamine (11 g, 69 mmol), α-oxoglutaric acid (10 g, 69 mmol), and *p*-toluenesulfonic acid (200 mg) were added to dioxane (200 mL), benzene (200 mL), and methanol (50 mL). The mixture was heated to reflux for 2 days. The reaction was cooled, after which aqueous sodium hydroxide (1 N, 100 mL) was added, and the solution which resulted was extracted with EtOAc (4 × 200 mL). The solvent was reduced, and the solid which precipitated was crystallized from EtOAc to provide **6**: 7g (45%); mp 245–247 °C; IR (KBr) 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.20 (br s, 1), 7.50–6.90 (m, 4), 5.15–4.75 (m, 1) 4.50–4.15 (m, 1), 3.50 (m, 1), 3.00–1.60 (m, 6); ^{13}C NMR (Me_2SO-d_6) δ 172.20, 136.07, 134.50, 126.39, 120.88, 113.49, 117.71, 111.06, 1[illegible].39, 53.56, 36.83, 30.90, 26.31, 20.63; mass spectrum (CI, CH_4), m/e 227 (m + 1).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.34; H, 6.19; N, 12.39. Found: C, 74.26; H, 5.98; N, 12.50.

Reaction of 6 with DDQ at −78 °C To Give 8. The γ-lactam **6** (500 mg, 2.2 mmol) was dissolved in MeOH/THF (30 mL, 1:1) and cooled to −78 °C. Dichlorodicyanoquinone (1020 mg, 4.5 mmol) dissolved in THF (10 mL) was added dropwise to the γ-lactam **6**. The mixture was allowed to warm to room temperature over 4 h. Aqueous sodium hydroxide (10%, 50 mL) was added, and the reaction mixture was extracted with EtOAc (4 × 125 mL) and dried with K_2CO_3. The solvent was evaporated, and the residue was chromatographed on SiO_2 (EtOAc–CH_3OH gradient) to provide **8**: 250 mg (44%); mp 113–116 °C dec; IR (KBr) 1680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.60–6.95 (m, 5), 6.30 (d, 1, J = 6 Hz) 4.50–4.10 (m, 1), 3.60–3.00 (m, 1), 3.15 (s, 3), 2.90–2.50 (m, 2); mass spectrum (CI, CH_4), m/e 255 (M + 1).

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 70.95; H, 5.48; N, 10.50.

1-Ethyl-4-oxo-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (9). A suspension of amide **3b** (3 g, 8.38 mmol) in 1 N NaOH (3 L) was prepared and heated to 70 °C for 16.5 h. The reaction mixture was cooled and extracted with $CHCl_3$ (4 × 500 mL) and EtOAc (1 × 500 mL). The combined organic fractions were dried (K_2CO_3) and evaporated to yield 9: 1.4 g (78%); mp 235–240 °C; IR (KBr) 3220 (br), 1620 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.70–8.45 (m, 1), 8.25–7.55 (m, 4) 4.43 (dd, 1, J_1 = 9 Hz, J_2 = 5 Hz), 3.70 (s, 2), 2.60–1.80 (s, 3), 1.15 (t, 3, J = 7 Hz); MS, m/e (relative intensity) 214 (12), 185 (100), 170 (42).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.90, H, 6.54; N, 13.08. Found: C, 73.20; H, 6.59; N, 13.07.

Preparation of 9 from 3a. The ketone **3a** was added to sodium hydroxide (6 N, 4000 mL). This mixture was heated to reflux (108 °C) for 3 h. The reaction mixture was cooled and continuously extracted with chloroform for 2 days. The material recovered on removal of the organic solvent was recrystallized from methanol to provide **9** (2.2 g, 65.4%).

1-Ethyl-4-hydroxy-9*H*-pyrido[3,4-*b*]indole (10). The ketone **9** (500 mg, 2.34 mmol) and sulfur (5 g) were added to xylene (500 mL). The suspension was heated to reflux for 17 h, cooled, and washed with H_2SO_4 (1 N, 3 × 200 mL). The aqueous acidic fractions were combined and neutralized to pH 7 with $NaHCO_3$. The neutral, aqueous fraction was extracted with EtOAc (3 × 200 mL), and the combined organic fractions were dried (Na_2SO_4) and evaporated to give **10**: 422 mg (85%); mp 242–245 °C (EtOAc); ^1H NMR (Me_2SO-d_6) δ 12.50 (br s, 1), 9.02 (d, 1, J = 8 Hz), 8.65 (s, 1), 8.40–7.80 (m, 3), 3.33 (q, 2, J = 8 Hz), 1.46 (t, 4, J = 8 Hz); mass spectrum (CI, CH_4) m/e 213 (m + 1). A picrate of the base was prepared for analysis; mp 255–256 °C (MeOH).

Anal. Calcd for $C_{19}H_{15}N_5O_8$: C, 51.70; H, 3.40; N, 15.87. Found: C, 51.32; H, 3.25; N, 15.58.

1-Ethyl-4-methoxy-9*H*-pyrido[3,4-*b*]indole (Crenatine, 11). The phenol **10** (75 mg, 0.35 mmol) was dissolved in MeOH (10 mL) and added to 3 equiv of CH_2N_2 in ether at −78 °C. The solution was allowed to warm to room temperature overnight. The solvent was evaporated, and the residue was chromatographed on SiO_2 (eluent EtOAc) to yield crenatine (**11**); 50 mg (63%); mp 174 °C (lit.[8] mp 177–179 °C); ^1H NMR ($CDCl_3$) δ 10.00 (br s, 1), 8.95 (d, 1, J = 7 Hz), 8.55 (s, 1), 8.30–7.60 (m, 3), 4.42 (s, 3), 3.35 (q, 2, J = 8 Hz), 1.50 (t, 3, J = 8 Hz); mass spectrum (CI, CH_4), m/e 227 (m + 1).

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Registry No. **1**, 6678-86-0; **2a**, 75304-06-2; **2b**, 83478-55-1; **3a**, 75314-80-6; **3b**, 83478-56-2; **4**, 75304-07-3; **5**, 83478-57-3; **5** picrate, 83478-58-4; **6**, 32283-51-5; **8**, 83478-59-5; **9**, 83478-60-8; **10**, 83478-61-9; **10** picrate, 83478-62-0; **11**, 26585-14-8; DDQ, 84-58-2; tryptamine, 61-54-1; propionaldehyde, 123-38-6; benzoyl chloride, 98-88-4; trichloroacetyl chloride, 76-02-8; α-oxoglutaric acid, 328-50-7.