Selenium Dioxide Oxidations in the Indole Area. Synthesis of β-Carboline Alkaloids

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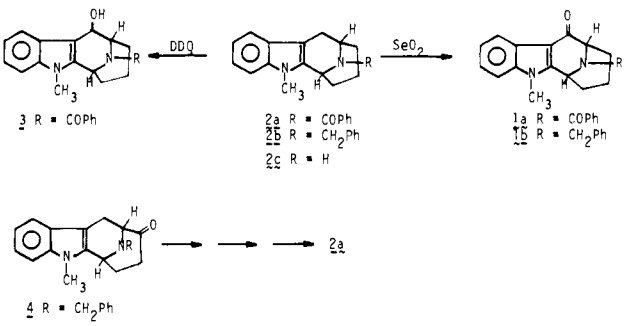
Abstract: A number of different piperidoindole systems have been subjected to oxidation with selenium dioxide. The bonding between the indole and piperidine unit has been varied to provide different systems, the oxidation of which has led to formation of either 2-acyl- or 3-acylindoles or fully aromatic β-carbolines, depending on the substrate chosen. The pattern of reactivity observed was in complete agreement with the ene mechanism proposed for selenium dioxide oxidations, and this can be employed to predict the regiochemistry of the oxidation. Use of this technology has resulted in a two-step synthesis of the indole alkaloid canthin-6-one (**30a**).

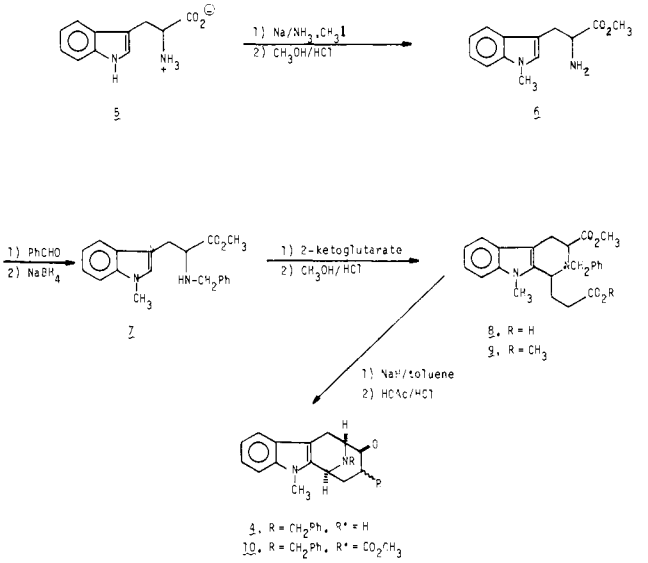
Selenium dioxide has been shown to be an effective reagent for regioselective incorporation of oxygen functionality at allylic positions;[1] in a previous communication[2] we reported use of this technology for preparation of 3-acylindoles.[3] Moreover, the reagent has been employed in our laboratory to prepare β-carbolines, a class of compounds that have been shown to bind tightly to the benzodiazepine receptor in vitro and were found to be benzodiazepine receptor antagonists in vivo.[4-8] In this paper, we wish to present further work with selenium dioxide in the indole area that has led to preparation of 3-acylindoles, β-carboline alkaloids, and canthin-6-ones, some of which have been found to bind to the benzodiazepine receptor in vitro.

There are relatively few methods for the preparation of 3-acylindoles; most notable for the present discussion are the thioketal approach of Stadler,[9] the 2,3-dichloro-5,6-dicyanoquinone (DDQ) method developed by Yonemitsu et al.,[10] and the work with selenium dioxide.[2,3] Previously we reported using DDQ to synthesize 3-acylindoles from tetrahydro-β-carbolines,[3] and although Yonemitsu and co-workers reported that DDQ "...is the only reagent for the selective oxidation of the side chains at C-3 of indoles",[11] as far back as 1979, we were able to prepare the tetracyclic ketone **1b** utilizing SeO_2,[2,3] as illustrated below. Oxidation of the tertiary amine **2b** with selenium dioxide over a period of several days afforded the desired 3-acylindole **1b** in 47% yield accompanied by varying amounts of benzaldehyde.[2,3] Oxidative cleavage of the benzyl group and formation of salts or organoselenium byproducts were felt to account for this low yield. These problems were overcome by conversion of the N_b-benzylamine into the N_b-benzamide derivative **2a**. Selenium dioxide oxidation of benzamide **2a** did indeed provide an improved yield (90%) of the 3-acylindole **1a**. This approach is the method of choice in this system, for treatment of **2a** with dichlorodicyanoquinone gave the alcohol **3** instead of the desired ketone **1a** that was absent from the initial reaction (Scheme I). On treatment of alcohol **3** with DDQ, the blue color characteristic of a charge-transfer complex[12] slowly formed, and only a small amount of the 3-acyl species **1a** was obtained (see Experimental Section).

Scheme I



Scheme II



The tetracyclic ketone **4** was the key substrate in this series and can be obtained in kilogram quantities.[13a] Wolff-Kishner reduction of **4** provided the tetracyclic N_b-benzyl derivative **2b**, which was converted into the secondary amine **2c** on catalytic hydrogenation. The benzamide **2a** was then formed from **2c** by treatment with benzoyl chloride.

The synthesis of tetracyclic ketone **4** is based upon work reported earlier by Yoneda[13b] but with some important modifications that have significantly increased the overall yield and efficiency of the preparation. As outlined in Scheme II, *dl*-tryptophan (**5**)

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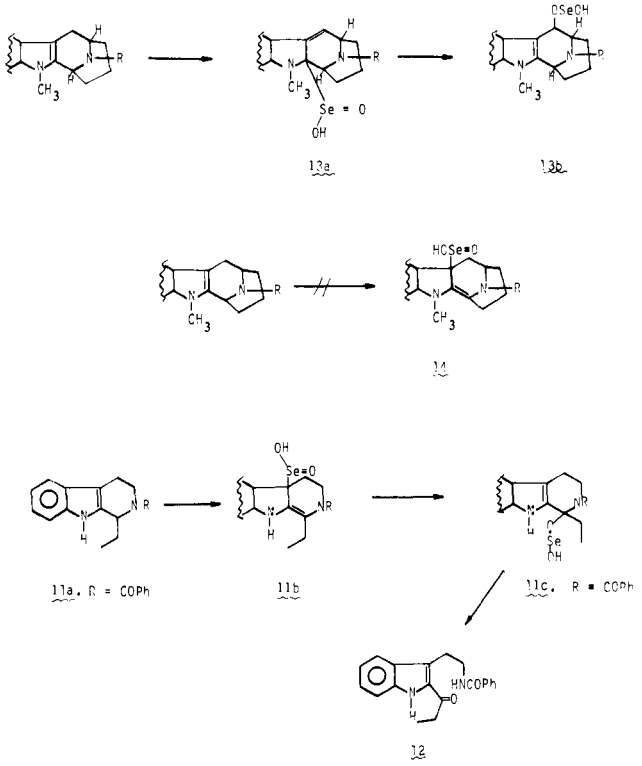
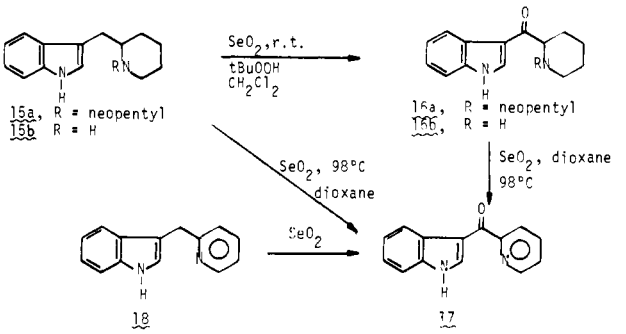
Scheme III



Scheme IV



was alkylated with methyl iodide in liquid ammonia, according to the procedure of Yamada et al.[13c] This reaction proceeded in yields of 70–90% to furnish N_a-methyltryptophan, which was esterified in methanolic hydrogen chloride to give the hydrochloride salt of methyl ester **6**. The ester was converted into N_a-methyl-N_b-benzyltryptophan methyl ester (**7**) on stirring **6** (free base) with benzaldehyde at room temperature, followed by reduction of the imine that resulted with sodium borohydride.[13b,d]

The synthesis of the tetrahydro-β-carboline **9** was accomplished by Yoneda in 59% yield by a Pictet–Spengler condensation of the hydrochloride salt of **7** with methyl 3-formylpropionate in aqueous methanol. This step presented the most difficulty in the earlier preparation of **4**;[13b] in contrast, the yield of this transformation was greatly improved by utilizing the Pictet–Spengler reaction in aprotic media.[13a] Application of this modification in refluxing benzene to the condensation of **7** and 2-ketoglutaric acid resulted, initially, in poor yields of the tetrahydro-β-carboline-1-propionic acid due to the insolubility of 2-ketogluturate in the reaction medium. When a 2:1 mixture of benzene and dioxane, however, was employed in this sequence, a 97% yield of crystalline **8** was obtained. Under these conditions, decarboxylation occurs spontaneously; the 1-carboxylic acid intermediate was not observed. The acid **8** was subsequently esterified with methanolic hydrogen chloride to provide the diester **9**, in an overall yield of 92% from **7**.

Dieckman condensation of diester **9** according to Yoneda's procedure[13b] generated the β-keto ester **10** in 84% yield, which was subsequently decarboxylated[13e] to provide **4**. In summary, the key tetracyclic ketone **4** can now be prepared (kilogram quantities) in an overall yield of 48% from *dl*-tryptophan (**5**) and in 73% yield from N_a-methyl-N_b-benzyltryptophan methyl ester (**7**), compared to a previously published yield of 39%.[13b,c]

There have been several recent reports regarding the manner in which allylic oxidations are mediated by selenium dioxide.[14-16] The mechanism proposed by Sharpless and Lauer[14] is the most widely accepted one; it consists of a three-step sequence that begins with an ene reaction, followed by a [2,3]-sigmatropic rearrangement that generates a readily solvolizable Se^{II} ester.[14,15] As shown in Scheme III, the possibility exists for selenium dioxide to attack either one of two allylic positions to generate intermediate **13a** (indole 2-position) or **14** (indole 3-position). The formation of intermediate **14**, which would ultimately lead to oxidation at the 2-position, would result in formation of a strained bridgehead double bond[17] in the bicyclo[3.3.1]azanonane system and therefore does not occur. The Sharpless mechanism accurately predicts that in system **2**, oxidation should take place to form intermediate **13b** via **13a**, which ultimately leads to the formation of a 3-acylindole in complete agreement with experimental results.

In contrast to this, the reactivity of 1-ethyl-2-acyl-1,2,3,4-tetrahydro-β-carboline (**11a**) toward selenium dioxide is more typical of the pathway expected for *N*-acyl-β-carbolines because the bridgehead position, present in **2**, no longer influences the transition state. Attack, therefore, can occur at the indole 3-position, which subsequently results in oxidation at the β-carboline 1-position (2-position using the numbering system for indoles) of the tetrahydro-β-carboline to furnish the 2-acylindole **12**. The initial ene step would generate the selenium intermediate **11b**. Since the 3-position of indoles is more reactive toward electrophiles than the 2-position, it is not surprising that **11b** forms preferentially in this case and leads to the 2-acylindole **12** via **11c**, as shown at the bottom of Scheme III.

In the previous examples, the piperidine ring served as the C ring in both the bicyclo[3.3.1]azanonane **2** and the tetrahydro-β-carboline **11a**, which imparts a distinct reactivity pattern to those systems. In this regard, it was decided to disconnect this ring from position 2 of the indole in order to extend this study. It had been reported earlier[18] that oxidation of the indolopyridine **18** with SeO_2 gave the ketone **17**; however, isolation was hampered by organoselenium byproducts formed via this process (Scheme IV). The report, however, of Sharpless[19] on allylic oxidations employing a combination of selenium dioxide and *tert*-butyl hydroperoxide seemed encouraging. The peroxide/selenium dioxide mixture was reported to reoxidize the organoselenium byproducts formed in this oxidation, permitting the process to proceed with a catalytic amount of selenium dioxide, therefore decreasing the problem of the removal of colloidal selenium during the workup. When the neopentyl derivative **15a** was reacted with the peroxide/selenium dioxide reagent, no 3-acylindole **16a** was found;[20] however, stirring the free amine **15b**[20] under analogous conditions gave a 43% yield of the desired crystalline 3-acylindole **16b**. Omission of the peroxide from this process led to the recovery of starting amine **15b**. It was felt that the yield of **16b** (see above) was low simply due to overoxidation to **17**. In order to examine this and also to observe whether oxidation to **18** occurred first on the pathway to **17**, or if 3-acylindole **16b** may have been an intermediate in this process, we subjected the ketone **16b** to treatment with sel-

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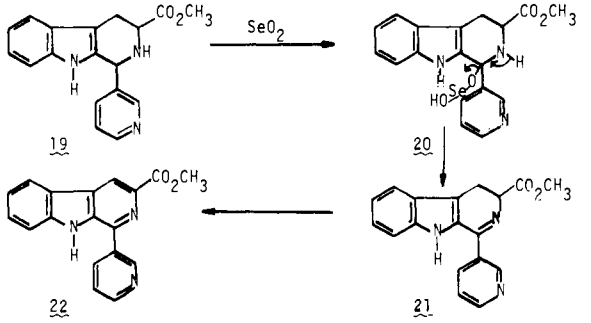
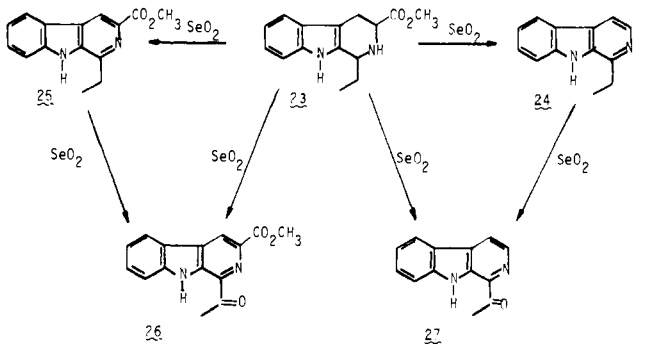
(20) Campos, O. Ph.D. Thesis, University of Wisconsin—Milwaukee. Campos, O.; Cook, J. M., manuscript in preparation.

Scheme V



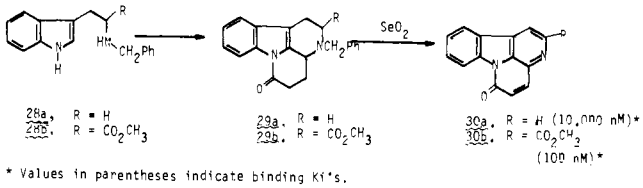
Scheme VI



enium dioxide, under conditions analogous to conversion of **15b** into **17**. This reaction resulted in formation of the ketone **17** in quantitative yield; it appears therefore that **16b** is operating as an intermediate on the way to **17**, at least to some extent. The ability to convert either **2b** or **15b** into 3-acylindoles again provides a route to these interesting molecules, presumably via the mechanism outlined at the top of Scheme III. The piperido derivative **15b** employed in this investigation was prepared by reduction of 3-indoyl-2′-pyridylcarbinol, and the neopentyl derivative **15a** was synthesized from **15b** via reduction of the 3-indolyl-2′-*N*-(trimethylacetyl)piperidylmethane intermediate (see Experimental Section).

In a related area, it was found that the N_b-H tetrahydro-β-carboline **19** demonstrated an affinity for the benzodiazepine receptor,[4] and it became necessary to convert this base into the fully aromatic β-carboline **22** for further biological testing (Scheme V). Although aromatization of ring C of **19** with palladium on carbon or with sulfur failed to provide significant amounts of **22**, selenium dioxide was employed very effectively to perform this transformation. Earlier, in the case of the *N*-acyltetrahydro-β-carboline **11a**, aromatization of ring C via intermediate **11c** was prohibited. In the following case, however, attack of selenium dioxide at position 3 of the indole followed by rearrangement would provide the organoselenium intermediate **20** (similar to **11c**), which would undergo elimination of selenous acid to provide the 3,4-dihydro-β-carboline **20**. Such a compound is known to aromatize readily with generation of the 14π β-carboline system.[21] A number of fully aromatic β-carbolines have been found in nature (see for example, some of the Harmala alkaloids).[22] In light of the facility with which **19** was converted into **22** with SeO_2, it was decided to treat 1-ethyl-1,2,3,4-tetrahydro-β-carboline **23** with this reagent. After 14 h of heating **23** with selenium dioxide in refluxing dioxane, four β-carbolines were present in the mixture. After isolation and purification, these bases were identified as 1-ethyl-β-carboline (**24**), 1-ethyl-3-(methoxycarbonyl)-β-carboline (**25**), 1-acetyl-3-(methoxycarbonyl)-β-carboline (**26**), and 1-acetyl-β-carboline (**27**), as illustrated in Scheme VI. The major product (32%) of this sequence was the indole alkaloid 1-acetyl-3-(methoxycarbonyl)-β-carboline (**26**), recently isolated from *Vestia lycioides* Wild by Faini and Castillo.[23] The base **26** had been prepared earlier by Faini et al. albeit in low yield, and was also synthesized previously in our laboratories, although the route was more complex[24] than the two-step process described here. The other three β-carbolines, **24**, **25**, **27**, were obtained in approximately equal amounts, with a total yield of 39%. The β-carboline alkaloid **27** was recently isolated from *Ailanthus malabarica* by Joshi and co-workers.[25]

Scheme VII



* Values in parentheses indicate binding Ki's.

Apparently the first step in the oxidation of **23** is the formation of the fully aromatic β-carboline, which is not unexpected in light of the 14π electron system that results. Moreover, the 1-ethyl derivatives **24** and **25**, when oxidized independently with selenium dioxide, afforded the 1-acetyl derivatives **26** and **27**, respectively, in good yields. Presumably, the mechanism operating here is similar to the one that was illustrated earlier in Scheme V. Two of these β-carbolines were examined for their effects on benzodiazepine receptors.[4]

Finally, we wish to report a short, simple synthesis of the alkaloid canthin-6-one (**30a**) and the corresponding 2-methoxycarbonyl derivative **30b**. Canthin-6-one has been isolated from a variety of plants,[26,27] and the present preparation of this molecule was based on observations made in our laboratory on the Pictet–Spengler reaction in aprotic media.[28] Facile entry into the hexahydrocanthin-6-one skeleton was accomplished by heating N_b-benzyltryptamine (**28a**) and 2-ketoglutaric acid in refluxing toluene for several days.[3,29] Although the 1-propionic acid intermediate was also isolated from this sequence, this material could be further lactamized into **29a** by additional heating in the presence of *p*-toluenesulfonic acid (overall yield 82%). Prior experience gained from studies on the oxidation of N_b-benzyl derivative **2b** with selenium dioxide had shown that benzaldehyde was observed as a byproduct during this oxidation. Therefore, it was decided to carry out this oxidation on the N_b-benzyl derivative **29a** rather than the corresponding secondary amine. Treatment of **29a** with selenium dioxide in refluxing dioxane did provide a 33–40% yield of the alkaloid canthin-6-one (**30a**) accompanied by benzaldehyde, as predicted. This transformation corresponds to removal of the N_b-benzyl group and incorporation of three double bonds into the molecule in a simple, one-pot reaction. There have been several syntheses of **30b** reported in the literature;[30–32] however, to our knowledge, the two-step sequence reported here is the shortest, to date. Although canthin-6-one (**30a**), as expected, does not bind tightly to the benzodiazepine receptor, the planar 2-substituted derivative **30b** would be expected to possess greater affinity for this receptor.[4] For this reason, the synthetic approach to canthin-6-one, outlined in Scheme VII, is admirably suited for preparation of gram quantities

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(32) Oehl, R.; Lehzer, G.; Rosenmund, P. *Chem. Ber.* **1976**, *109*, 705.

of the 2-methoxycarbonyl derivative **30b**. Simply substituting N_b-benzyltryptophan methyl ester **28b** for **28a** in this process gave the hexahydro derivative **29b**.[29] This material was converted with selenium dioxide in refluxing dioxane into 2-(methoxycarbonyl)-canthin-6-one (**30b**) in 66% yield. Activation of the ring by the ester functionality may be responsible for the more facile oxidation in the case of **29b** as compared to the canthin-6-one system **29a** itself. Furthermore, the 2-methoxycarbonyl analogue **30b** was found to be a potent inhibitor of [^{3}H]diazepam, binding in vitro with an IC_{50} of 100 nM;[33] this corresponds to a value intermediate between those found for diazepam and chlorodiazaepoxide.

In summary, selenium dioxide has been shown to be an excellent oxidizing agent for the formation of aromatic compounds such as β-carbolines and canthin-6-ones; moreover, when aromatization of ring C is prohibited by N_b-amide formation, 2-acylindoles (for example **12**) can be obtained in high yields. Under certain circumstances, this reagent can also be employed for the preparation of 3-acylindoles, generally in systems where aromatization of ring C is prohibited and in which oxidation of position 2 is blocked in one fashion or another. The selenium dioxide oxidation of substituted indoles provides results entirely consistent with the mechanism proposed by Sharpless and Lauer. When the juxtaposition of the indole and piperidine ring in the bases employed for this study is varied, the pattern of reactivity observed and reported should provide a rational basis on which to plan the use of selenium dioxide in the synthesis of indole alkaloids. The one-step conversion of **29a** into **30a** and the analogous transformation of **29b** into **30b** in 66% yield provide ample evidence for the strength of this approach.

Experimental Section

Microanalyses were performed on an F and 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 EM-360 and Varian CFT-20 ^{13}C NMR spectrometers. IR spectra were taken on a Beckman Acculab-1 instrument, while mass spectra (EI/CI) were obtained on a Hewlett-Packard 5855 GC–mass spectrometer.

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. Tryptophan, α-ketoglutaric acid, propionaldehyde, *tert*-butyl hydroperoxide, and selenium dioxide were purchased from Aldrich Chemical, while the Pd/C catalyst was obtained from Pfaltz and Bauer.

The preparation of 1-ethyl-2-benzyl-1,2,3,4-tetrahydro-β-carboline (**11a**),[12] 1-(3-pyridyl)-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**19**),[34] 1-ethyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**23**),[34] and 2-(methoxycarbonyl)-3-benzyl-1,2,3,3a,4,5-hexahydrocanthin-6-one (**29b**)[29] has been described elsewhere.

5-Methyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indol-11-one (1b). A solution of the tetracyclic benzylamine **2b** (5.2 g, 0.0161 mol) and SeO_2 (2.38 g, 0.021 mol) in dioxane (80 mL) was stirred at 98 °C for 4 days. After this period, no change was observed by TLC (alumina, 5% EtOAc/benzene eluent). The temperature was dropped to 40 °C, additional SeO_2 was added, and again the mixture was refluxed at 98 °C. This process was repeated until all the starting material was consumed (the total time of reaction was 10 days). The crude mixture was then filtered through Celite to remove the black selenium, the solvent was removed under reduced pressure, and ethyl acetate was added to the crude residue. The ethyl acetate solution was washed twice with H_2O, dried with Na_2SO_4, filtered, and the solvent removed under reduced pressure. Column chromatography of the crude oil on alumina (benzene/$CHCl_3$/methanol gradient) yielded the tetracyclic ketone **1b** (2.56 g, 47%), starting material (**2b**, 420 mg), and small amounts of two other compounds whose structures have not been unambiguously determined.

1b; mp 188–189 °C (acetone); UV (EtOH) nm 307 (ε 1.22 × 10^4), 267 (ε 1.77 × 10^4), 248 (ε 2.0 × 10^4); IR (KBr) 3070 (CH), 2960, 2940, 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10–2.27 (m, 6 H), 3.36 (t, 1 H, bridgehead), 3.56 (s, 3 H, NCH_3), 3.73 (s, 2 H, NCH_2Ph), 4.03 (m, 1 H, bridgehead), 7.25 (m, 8 H), 8.00–8.40 (m, 1 H); mass spectrum (70 eV), *m/e* 331 (M + 1, 14.8), 330 (M$^+$, 54.8), 316 (43.7), 273 (17.0), 239 (36), 225 (8.9), 211 (6), 197 (10.4), 183 (25.2), 168 (10.4), 149 (4.4), 105 (7.4), 91 (16.3), 78 (B$^+$, 100), 77 (29.6), 52 (22.2), 51 (22.2). SeO_2 was freshly sublimed.

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.40; H, 6.90; N, 8.53.

5-Methyl-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indol-11-one (1a). A flask was charged with the benzamide **2a** (5.2 g, 15.8 mmol), SeO_2 (2.27 g, 20.5 mmol), and dioxane (80 mL). The mixture was heated to reflux for 2 days, and the solvent was evaporated under reduced pressure. A saturated solution of $NaHCO_3$ (150 mL) and CH_2Cl_2 (200 mL) was added to the residue. The organic layer was separated, and the aqueous fraction was extracted with CH_2Cl_2 (2 × 100 mL). The organic fractions were combined, the solvent was evaporated, and the residue was crystallized from MeOH to obtain **1a** (4.9 g, 90%): mp 188–189 °C (MeOH); IR (KBr) 1660 and 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50–2.00 (m, 6 H), 3.56, 3.66 (2 s, 3 H, rotomers), 4.35 (s, br, 1 H), 6.15 (s, br, 1 H), 7.30 (m, 8 H), 8.10 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.36, 26.24, 27.23, 27.52, 29.84, 61.77, 109.44, 113.46, 121.51, 121.61, 122.98, 123.08, 123.36, 123.56, 123.83, 126.77, 128.49, 129.97, 134.63, 137.70, 150.24, 169.30, 189.51; mass spectrum (CI, CH_4), *m/e* 345 (100, M + 1).

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.81; N, 8.14. Found: C, 76.62; H, 5.92; N, 8.22.

5-Methyl-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole (2a). The amine **2c** (6.2 g, 27 mmol) was dissolved in a mixture of dry pyridine (60 mL) and dry benzene (120 mL). Benzoyl chloride (6.2 g, 44 mmol) was added dropwise, and the solution was heated to 60–70 °C for 1 h. Water (200 mL) was added to the reaction, the organic layer was separated, and the aqueous layer was extracted with benzene (1×). The combined organic fractions were washed with saturated $NaHCO_3$ and then washed again with brine. The solvent was dried (K_2CO_3) and evaporated, and the solid that formed was crystallized from benzene/hexane to give **2a** (6.03 g, 68%): mp 132–133 °C; IR (KBr) 1625 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.00–2.00 (m, 8 H), 3.30, 3.60 (2 s, 3 H, rotomers), 4.10 (m, 1 H), 5.95 (m, 1 H), 7.00–7.60 (m, 9 H); ^{13}C NMR (Me_2SO-d_6) δ 16.50, 26.37, 27.96, 28.83, 31.79, 43.41, 49.79, 107.54, 109.38, 117.59, 118.64, 120.78, 125.59, 126.20, 128.43, 129.43, 133.69, 136.03, 136.71, 168.26; mass spectrum (CI, NH_3), *m/e*, 331 (M + 1).

Anal. Calcd for $C_{22}H_{22}N_2O$: C, 80.00; H, 6.67; N, 8.48. Found: C, 80.13; H, 6.89; N, 8.43.

5-Methyl-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole (2b). The tetracyclic ketone **4**[13] (30 g, 91 mmol) in diethylene glycol (500 mL) and hydrazine (36 mL) were heated to 110 °C and then cooled to 35 °C. Potassium hydroxide (42 g) was then added, and the solution was heated. The solvent was distilled off until the pot temperature reached 220 °C, and the reaction was held at this temperature for 3 h. The reaction mixture was cooled, poured onto ice water (2 L), and extracted with CH_2Cl_2 (3 × 400 mL). The organic fractions were combined, washed with brine (1 L), and dried (K_2CO_3). The solvent was removed under reduced pressure to provide **2b** (28.2 g, 98%) as an oil: IR (film) 3030, 3000, 1500 (ω), 1470 (strong), 1220 (strong), 770, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16–2.17 (m, 6 H), 2.60 (m, 2 H), 3.30 (m, 1 H, bridgehead), 3.40 (s, 3 H, NCH_3), 3.56 (s, 2 H, NCH_2Ph), 3.87 (br, 1 H, bridgehead), 6.90–7.63 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 16.44 (t), 21.98 (t), 28.55 (t), 29.54 (q), 33.41 (t), 50.57 (d), 51.41 (d), 57.81 (t), 107.74 (s), 108.50 (d), 117.76 (d), 118.53 (d), 120.40 (d), 126.56 (d), 127.97 (d), 128.11 (s), 128.52 (d), 134.37 (s), 136.86 (s), 139.64 (s); mass spectrum (CI, NH_3), *m/e* 317 (M + 1).

5-Methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (2c). The tertiary amine **2b** (20.9 g, 66 mmol) was dissolved in EtOH (150 mL) and HOAc (45 mL). Palladium on carbon (10%, 4 g) was added, and the mixture was hydrogenated at 45 psi for 7 days. The catalyst was removed by filtering over Celite, afterwhich aqueous NH_3 (14%) was added. The solution was then extracted with CH_2Cl_2, and the solvent was removed under reduced pressure to furnish **2c** (14.3 g, 96%) as a white solid: mp 155–157 °C; IR (KBr) 3510, 3420, 3050, 2930, 2860, 1465, 1230, 1040, 895, 840, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10–2.40 (m, 6 H), 2.76 (s, 1 H), 3.10 (d, 1 H) 3.40 (s, 3 H), 3.60 (s, br, 1 H), 4.23 (s, br, 1 H), 4.90 (s, br, 1 H), 7.00–7.67 (m, 4 H); mass spectrum (70 eV), *m/e* (rel abundance) 226 (M$^+$, 60), 209 (3), 183 (100), 168 (17), 167 (10), 155 (6), 149 (8), 144 (22), 141 (3), 128 (7), 116 (6), 110 (12).

5-Methyl-11-hydroxy-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole (3). The benzamide **2a** (100 mg, 0.3 mmol) was dissolved in 5 mL of THF/water (9:1). To this solution was added DDQ (136 mg, 0.6 mmol) dissolved in THF dropwise, and the reaction was allowed to stir for 2 h. At this time the benzamide **2a** or the ketone

(33) Skolnick, P.; Cain, M.; Cook, J. M., unpublished results.
(34) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 6976.
(35) Mueller, W. H.; Preub, R.; Winterfeldt, E. *Chem. Ber.* **1977**, *110*, 2424.

1a were not present, as demonstrated by TLC (Al_2O_3, 25% EtOAc/benzene). The reaction was filtered over SiO_2 (40 g) and eluted with acetone. The solvent was evaporated and the residue dissolved in CH_2Cl_2 and washed twice with aqueous NaOH (10%). The CH_2Cl_2 fraction was chromatographed on Al_2O_3 to give 100 mg (95%) of **3**: mp 229–230 °C; IR (KBr) 3700–3100 (br), 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–2.20 (m, 6 H), 3.43 and 3.76 (2 s, rotomers, 3 H), 4.35 (s, br, 1 H), 4.87 (d, 1 H, J = 6 Hz), 6.11 (s, br, 1 H), 7.15–7.80 (m, 9 H); mass spectrum (CI, CH_4), m/e (rel abundance) 347 (38, M + 1), 329 (100); EI, m/e 346.1681 ($C_{22}H_{22}N_2O_2$ requires 346.1681).

Oxidation of 3. Oxidation of alcohol **3** with activated MnO_2 in THF led to quantitative conversion of the alcohol to the ketone **1a**.

When the alcohol **3** was treated with DDQ in methanol, no charge-transfer complex (blue) formed initially, but with time (ca. 2 h), the blue coloration did appear and TLC indicated the formation of only a small amount of the ketone **1a**. The structure of the major product of this reaction remains to be unambiguously determined.

N_a-Methyltryptophan Methyl Ester (6). N_a-Methyltryptophan methyl ester (**6**) was prepared according to the procedure of Yamada et al.[13c] Thus, metallic sodium (22 g) and $Fe(NO_3)_3 \cdot 9H_2O$ (1.4 g) were added to liquid ammonia (3 L) in an acetone/CO_2 bath with stirring. After 1 h, tryptophan (**5**, 82 g, 0.4 mol) was added, followed by dropwise addition of methyl iodide (76 g, 0.535 mol), and stirring was continued for an additional 30 min. The cooling bath was removed and the ammonia allowed to evaporate overnight. The residue was dissolved in hot water and filtered, and the pH of the filtrate was adjusted to pH 5 with glacial acetic acid. Precipitation of N_a-methyltryptophan occurred upon cooling. N_a-methyltryptophan (73.2 g) was collected by filtration and dissolved in saturated methanolic hydrogen chloride (1 L), and the solution that resulted was refluxed for 4 h. After cooling, the crystalline product was filtered and washed with methanol to provide N_a-methyltryptophan methyl ester–hydrochloride; 115 g, 80% yield; mp 227–229 °C (lit.[13c] mp 227.5 °C dec); IR (KBr) 3000, 2630, 2370 (NH_3^+), 1740 cm^{-1} (ester); ^1H NMR ($CDCl_3$, free base) δ 1.50 (s, 2 H, NH_2), 3.10, (d, 2 H, J = 5 Hz), 3.53 (s, 3 H, OCH_3), 3.62 (s, 3 H, NCH_3), 3.76 (m, 1 H), 6.76 (s, 1 H), 7.13 m (3 H), 7.51 (m, 1 H).

N_a-Methyl-N_b-benzyltryptophan Methyl Ester (7). N_a-Methyl-N_b-benzyltryptophan methyl ester (**7**) was prepared by the method of Kametani et al.[13d] N_a-methyltryptophan methyl ester (**6**, 48.8 g, 0.20 mol) was liberated from the hydrochloride salt by treatment with aqueous ammonia (14%), followed by extraction with $CHCl_3$. To a solution of **6** in methanol (300 mL) was added benzaldehyde (25.4 g, 0.24 mol), followed by stirring for 6 h until formation of the Schiff base was complete (TLC). Sodium borohydride (3.04 g, 0.08 mol) was then added in small portions with stirring at 0–5 °C over a period of 3 h. The reaction mixture was stirred for 1 h after addition was complete and until TLC analysis indicated no benzaldehyde remained. Acetic acid was added to destroy excess $NaBH_4$, and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ and basified with aqueous NH_3 (14%), followed by extraction with $CHCl_3$. The organic layer was separated and dried (K_2CO_3). Removal of solvent under reduced pressure gave a yellow oil to which 200 mL of methanolic hydrogen chloride was added; N_a-methyl-N_b-benzyltryptophan methyl ester–hydrochloride was collected by filtration: 67.4 g, 94% yield; mp 225–227 °C (lit.[13b] mp 224–226 °C); IR (thin film, NaCl, free base), 3320 (NH), 1730 cm^{-1} (ester); ^1H NMR ($CDCl_3$, free base) δ 1.90 (s, 1 H, NH), 3.05 (d, 2 H, J = 6 Hz), 3.40 (s, 3 H, OCH_3), 3.48 (s, 3 H, NCH_3), 3.65 (m, 3 H), 6.66 (s, 1 H), 7.04 (m, 8 H), 7.50 (m, 1 H).

2-Benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (8). To a solution of N_a-methyl-N_b-benzyltryptophan methyl ester (**7**, 6.70 g, 0.0208 mol) in refluxing benzene (100 mL) was added a solution of 2-oxoglutaric acid (3.44 g, 0.023 mol) in dioxane (50 mL) dropwise. After the mixture was held at reflux for 20 h (water collected in a Dean–Stark trap), the solvent was removed under reduced pressure to provide an orange oil, which crystallized from methanol/benzene (8:1) to give 4.46 g of colorless crystals. Column chromatography of the mother liquor on silica gel gave an additional 3.74 g upon elution with $CHCl_3$; overall yield 8.2 g, 97% yield: mp 197–199 °C; IR (KBr) 1725 (ester), 1705 cm^{-1} (acid C=O); ^1H NMR ($CDCl_3$) δ 1.83–2.66 (m, 4 H), 3.13 (d, 2 H, J = 8 Hz), 3.56 (s, 3 H), 3.83 (s, 3 H), 7.30 (m, 9 H); mass spectrum (70 eV), m/e 406 (M^+, 1), 388 (6), 362 (5), 334 (11), 333 (41), 298 (22), 185 (17), 184 (100), 170 (12), 169 (14), 168 (17), 144 (20), 91 (37), 78 (54).

Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; H, 6.89. Found: C, 70.71; H, 6.46; N, 6.92.

Methyl 2-Benzyl-3-(methylcarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (9). 2-Benzyl-3-(methoxycarbonyl)-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic acid (**8**, 52.8 g, 0.13 mol) was dissoled in methanolic hydrogen chloride solution (250 mL) and the mixture held at reflux for 2.5 h. After removal of solvent under reduced pressure, the residue was dissolved in methylene chloride (200 mL), neutralized with aqueous NH_3 (14%), washed with brine, and dried over K_2CO_3. The product solidified upon removal of CH_2Cl_2. Recrystalization from methanol gave 49.6 g of the diester, 91% yield: mp 137–140 °C (lit.[13b] mp 137–140 °C); IR (KBr) 1730 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ 2.00 (m, 2 H), 2.43 (m, 2 H), 3.05 (d, 2 H, J = 8 Hz), 3.43 (s, 3 H), 3.61 (s, 3 H), 3.73 (s, 2 H, benzyl methylene), 3.76 (s, 3 H), 4.02 (m, 2 H), 7.00–7.63 (m, 9 H); mass spectrum (70 eV), m/e 421 (M + 1, 8), 420 (M^+, 24), 362 (8), 361 (24), 334 (12), 333 (100), 273 (20), 243 (18), 184 (26), 183 (60), 182 (26), 170 (26), 169 (14), 168 (28), 92 (10), 91 (83), 78 (14), 77 (14).

Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.72; N, 6.66. Found: C, 71.37; H, 6.43; N, 6.70.

Methyl 5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole-8-carboxylate (10). The β-keto ester **10** was prepared according to the method of Yoneda.[13b] To a solution of diester **9** (10.5 g, 0.025 mol) in toluene (50 mL) was added NaH (1.66 g, 0.069 mol) in toluene (50 mL). The reaction mixture was brought slowly to reflux, followed by the dropwise addition of a solution composed of CH_3OH (1 mL) and toluene (9 mL). The mixture was refluxed for 2 h, after which it was stirred at room temperature overnight. Acetic acid was then added (5 mL), followed by addition of saturated $NaHCO_3$ solution until neutral pH. The mixture was extracted with benzene and dried (Na_2SO_4). Removal of solvent under reduced pressure and then addition of CH_3OH gave **10** (8.28 g) as a crystalline product, 85.3% yield: mp (CH_3OH) 146–148 °C (lit.[13b] mp 148–150 °C); IR (KBr) 1670, 1630 cm^{-1} (β-keto ester, lit.[13b] 1670, 1625 cm^{-1}); ^1H NMR ($CDCl_3$) δ 1.20 (m, 2 H), 2.40 (m, 1 H) 2.80 (m, 1 H) 3.05 (m, 2 H), 3.60 (s, 3 H), 3.66 (s, 3 H), 3.73 (s, 2 H, benzyl methylene), 4.10 (m, 1 H), 7.00–7.60 (m, 9 H); mass spectrum (70 eV), m/e 389 (M + 1, 4), 388 (M^+, 15), 315 (57), 297 (69), 283 (87), 223 (48), 220 (39), 197 (37), 170 (98), 91 (100), 78 (88).

5-Methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cycloocta[*b*]indole (4). The β-keto ester **10** (24 g, 0.061 mol) was refluxed for 6 h in a mixture composed of acetic acid (110 mL), concentrated hydrochloric acid (145 mL), and water (35 mL). After removal of solvent under reduced pressure, the residue was neutralized with 10% NaOH (250 mL). The solution was extracted with CH_2Cl_2 and dried (Na_2SO_4). The CH_2Cl_2 extract was filtered through 30 g of alumina followed by crystallization of the resulting oil from ethyl acetate to provide **4** (18.3 g, 89.7% yield): mp 131–132.5 °C (lit.[13e] mp 131.5–133 °C); IR (KBr) 1710 cm^{-1} (s, ketone); ^1H NMR ($CDCl_3$) δ 1.83–2.70 (m, 4 H), 2.83 (m, 2 H), 3.16 (m, 1 H), 3.57 (s, 3 H, NCH_3), 3.73 (s, 2 H, benzyl methylene), 4.10 (m, 1 H), 7.00–7.60 (m, 9 H); mass spectrum (70 eV), m/e 331 (M + 1, 32), 330 (M^+, 74), 302 (18), 274 (74), 273 (100), 108 (27), 91 (18).

Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.24; H, 6.89, N, 8.78.

Oxidation of 1-Ethyl-2-benzoyl-1,2,3,4-tetrahydro-β-carboline with SeO_2. The amide **11a** (2.5 g, 78 mmol) was dissolved in dry dioxane (750 mL), and SeO_2 (1 equiv) was added. The reaction was heated at reflux for 4.5 h. More SeO_2 (0.5 equiv) was added, and heating was continued for 2 h (TLC indicated all starting material was consumed). The mixture was filtered through Celite and the filtrate concentrated to a solid, which was dissolved in *N,N*-dimethylformamide and heated at reflux for 3 h. The solvent was removed and the residue taken up in ethyl acetate. This solution was filtered through Celite and washed with sodium carbonate solution and then with water. The organic layer was subsequently concentrated under reduced pressure to provide a solid weighing 2.2 g (91.2%). This compound was identical with the 2-acylindole **12**, whose properties have been reported elsewhere.[12]

3-Indolyl 2-Piperidyl Ketone (16b) from 3-Indolyl-2′-piperidylmethane (15b). To a solution of selenium dioxide (550 mg, 5.0 mmol, freshly sublimed) in CH_2Cl_2 (10 mL) was added 70% *tert*-butyl hydroperoxide (2.8 mL, 20 mmol) in one portion. The mixture was stirred for 0.5 h at room temperature. The temperature was lowered to 0 °C, and a solution of 3-indolyl-2′-piperidylmethane (**15b**, 2.14 g, 10 mmol) in CH_2Cl_2 (10 mL) was added in one portion. The reaction mixture was stirred at room temperature for 14 days. Water and ethyl acetate (60 mL) were added, and the organic phase was separated. The organic layer was washed with a solution of 10% KOH followed by shaking with water. The ethyl acetate solution was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. Benzene was added to the crude residue, which was then decolorized with Norit, and after 24 h of standing, ketone **16b** (0.98 g, 43%) precipitated from solution as a white crystalline solid: mp 208–210 °C (acetone); IR (KBr) 3406 (br OH enolic), 3300 (sharp NH), 1620 (carbonyl), 1590 cm^{-1}; ^1H NMR (pyridine-d_5) δ 1.20–2.20 (m, 6 H), 2.70 (m, 1 H), 3.17 (m, 1 H), 3.60 (1 H), 4.20 (1 H), 7.13–7.83 (m, 4 H), 8.40–9.90 (m, 2 H); mass spectrum (CI) m/e 229 (M + 1); UV (EtOH) λ nm 304, 256, 240.

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.68; H, 7.02; N, 12.28. Found: C, 73.44; H, 7.34; N, 12.06.

The reaction was repeated under the same conditions, except that stirring was continued for 22 days. The ketone was produced this time in 20% yield.

The reaction was also attempted without the *tert*-butyl hydroperoxide under the same conditions as above (CH_2Cl_2 as solvent); after 3 weeks at room temperature, only starting material could be found (IR and TLC).

3-Indolyl 2-Pyridyl Ketone (17) from 3-Indolyl-2′-piperidylmethane (15b). To a solution of the 3-indolyl-2′-piperidylmethane (**15b**, 1.25 g) in dioxane (45 mL) was added selenium dioxide (0.8 g, 7.28 mmol). The reaction mixture was stirred at 98 °C for 30 min. Thin-layer chromatography (alumina) indicated 100% conversion to the pyridyl ketone **17**. The black selenium formed in this process was separated by filtration and the black precipitate washed with hot dioxane (3×). The dioxane was removed under reduced pressure, and the crude residue that remained was dissolved in methanol and was subsequently decolorized with charcoal. Selenium kept slowly precipitating out of solution. The material was then filtered on an alumina column to yield the crystalline ketone **17** (1.15 g, 89%): mp 190–191 °C (lit.[18] mp 191 °C); IR (KBr) 3180, 1600 (carbonyl), 1585, 1560, 740, 700, 640 cm^{-1}; ^1H NMR (Me_2SO-d_6/$CDCl_3$) δ 7.10–8.80 (m, 9 H), 11.8 (br s, 1 H); mass spectrum (70 eV), *m/e* 222 (M^+, 57.6), 194 (15.2), 145 (12.1), 144 (100), 116 (21.2), 89 (15.2), 79 (9.1); UV (EtOH) λ nm 327.5 (ϵ 2.76 × 10^{10}), 267.5 (ϵ = 2.92 × 10^{10}), 256.2 (ϵ 3.09 × 10^{10}).

3-Indolyl 2-Pyridyl Ketone (17) from 3-Indolyl 2′-Piperidyl Ketone (16b). A solution of 3-indolyl 2-piperidyl ketone (**16b**, 1.0 g, 4.67 mmol) and selenium dioxide (1.24 (**16b**, 11.2 mmol) in dioxane (40 mL) was stirred overnight at 98 °C. The solution was cooled to room temperature, dimethylformamide added, and the mixture stirred an additional 40 min at 90 °C. The reaction mixture was filtered through Celite and the solvent removed under reduced pressure. Methanol was added to the crude residue, and the solution was decolorized with Norit and filtered through Celite. The methanol was removed under reduced pressure, benzene was added to the crude oil, and the solution was allowed to crystallize. The crystals were filtered from benzene to yield 3-indolyl 2-pyridyl ketone (**17**, 0.62 g, 58%). TLC of the crude oil indicated 100% conversion to the pyridyl ketone **17**.

The reaction was repeated with SeO_2 (1.2 moles for each mole of amine), and the time of reflux was decreased to 0.5 h. The treatment with DMF was omitted in the workup, and pyridyl ketone **17** was isolated in 89% yield. This was identical with the pyridyl ketone (mp 191 °C) obtained in the previous experiment.

3-Indolyl-2′-piperidylmethane (15b). To a solution of 3-indolyl-2′-pyridylcarbinol (3.3 g, 0.015 mol) in butanol (200 mL) at reflux was rapidly added sodium (0.33 mol). After 0.5 h at reflux, all the sodium had disappeared. The solution was cooled in an ice bath and ice water added; the two layers that formed were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The solvent from the butanol layer was removed under reduced pressure and the residue combined with the CH_2Cl_2 extracts. The methylene chloride solution was then washed with aqueous HCl (3 × 100 mL, 3 M). The combined aqueous extracts were made strongly alkaline with aqueous NaOH (14%) and extracted with methylene chloride (4 × 100 mL). The organic extracts were dried (Na_2SO_4) and filtered, and the methylene chloride was removed to give the piperidyl derivative **15b** (1.9 g). The crude solid was purified by column chromatography on alumina (eluent benzene/chloroform/methanol), which gave pure **15b** (1.4 g, 43%): mp 158 °C (recrystallized from benzene, lit.[36] mp 156–156.5 °C); IR (KBr) 3280 (NH), 3040, 3000 ,1450, 1350, 990, 800 cm^{-1}; ^1H NMR (pyridine-d_5) δ 1.43–2.00 (6 H), 2.56 (1 H, m), 3.00 (5 H), 7.0–8.00 (6 H).

3-Indolyl-2′-pyridylcarbinol.[37] To a solution of ethylmagnesium bromide (0.06 mol) in diethyl ether (40 mL, 1.5 M solution) stirred with a mechanical stirrer and held at −50 °C (under N_2) was added dropwise a solution of indole (7.0 g, 0.06 mol) in ether (35 mL) over a period of 5 min. The mixture was stirred continuously at −50 °C for a period of 20 min and then allowed to stir at room temperature for 1 h.

The temperature was again lowered to −50 °C, and CH_2Cl_2 (60 mL, dried over $CaSO_4$) was added in order to solubilize the indolylmagnesium bromide. Then 5.2 mL (0.05 mol) of 2-pyridinecarboxaldehyde (5.2 mL, 0.05 mol) in CH_2Cl_2 (40 mL) was added dropwise over a period of 20 min, while the temperature was held below −25 °C. The solution was stirred at −30 °C for 4 h, and the reaction mixture was quenched with NH_4Cl solution. A methylene chloride insoluble solid was filtered from the solution and discarded after washing with methylene chloride. The organic layer was separated and the aqueous layer extracted with ethyl acetate (4×). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Crystals precipitated from the solution to provide 3-indolyl-2′-pyridylcarbinol (5.8 g). Column chromatography on silica gel of the mother liquor yielded an additional 1.8 g of the 3-indolyl-2′-pyridylcarbinol (7.6 g, total yield 71%): mp 162–163 °C (MeOH) (lit.[37] mp 161–162 °C); IR (KBr) 3240 (br OH), 1590 (C=C), 1000 (strong C—O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 5.75 (d, *J* = 4.0 Hz, 1 H exchanged D_2O), 6.00 (d, *J* = 4.0 Hz, 1 H, CHOH), 6.70–8.00 (m, 9 H), 8.46 (dd, 1 H); mass spectrum, *m/e* 224 (M^+, 49), 205 (37), 146 (29), 130 (28), 116 (65), 117 (100).

3-Indolyl-2′-*N*-(trimethylacetyl)piperidylmethane. To a solution of 3-indolyl-2′-piperidylmethane (1.2 g, 0.0056 mol) in dry pyridine (20 mL) held at 80 °C was added trimethylacetyl chloride (2.1 mL, 0.017 mol) over a period of 2 min. The reaction mixture was stirred at this temperature for 4 h. The mixture was cooled to room temperature and the pyridine removed under reduced pressure. Water was added to the crude oil and the solution extracted with methylene chloride. The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The solid residue was dissolved in hot benzene and allowed to crystallize. The first crop of white crystals yielded 0.9 g of product, and concentration of the mother liquors gave an additional 0.6 g of the amide (overall yield 1.5 g, 90%): mp 154–155 °C; IR (KBr) 3208, 1600 (C=O amide) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9 H), 1.60 (br, 6 H), 2.80–3.50 (3 H, m), 4.00–4.50 (br, 1 H), 5.00 (br s, 1 H), 6.90–7.50 (m, 5 H), 7.55–7.90 (m, 1 H); mass spectrum (70 eV), *m/e* 298 (M^+, 19.4), 241 (2.4), 213 (3.0), 211 (4.2), 168 (100), 156 (4.8), 130 (61.8), 103 (9.1), 85 (76.4), 84 (95.1), 77 (8.5).

3-Indolyl-2′-*N*-neopentylpiperidylmethane (15a). To a solution of 3-indolyl-2′-*N*-(trimethylacetyl)piperidylmethane (1.32 g, 0.0045 mol) in dry dioxane (20 mL) was added $LiAlH_4$ (0.10 g, 0.0022 mol) in three portions. The reaction mixture was stirred at reflux (under N_2) for 30 h. The mixture was cooled in an ice bath, whereupon ethyl acetate and water were added and the organic layer was separated. The water layer was extracted three times with ethyl acetate; the combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was dissolved in ethanol and allowed to crystallize. The white crystalline product **15a** (1.24 g, 97%) was filtered from the solution: mp 87–89 °C; IR (KBr) 2430 (indole NH), 3060, 2950, 2940, 2860, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 9 H), 1.45 (br, 7 H), 2.30 (3 H), 2.87 (3 H), 6.80–8.00 (6 H); mass spectrum (70 eV), *m/e* 282 (8.2), 269 (1.8), 239 (1.1), 225 (14.7), 196 (7.9), 168 (4.1), 154 (99.2), 153 (19.9), 138 (9.3), 131 (21), 130 (42.1), 117 (6.3), 97 (13.9), 96 (100), 84 (41.7).

Anal. Calcd. for $C_{19}H_{28}N_2$: C, 80.28; H, 9.86; N, 9.86. Found: C, 80.41; H, 9.90; N, 10.08.

1-(3-Pyridyl)-3-(methoxycarbonyl)-β-carboline (22). A suspension of selenium dioxide (26 mg, 1.5 mmol, freshly sublimed) and 1-(3-pyrido)-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**19**,[34] 50 mg, 0.16 mmol) was heated in acetic acid (10 mL) at reflux for several hours until such time that TLC (silica gel, 10% CH_3OH/CH_2Cl_2) indicated the absence of starting material. The selenium dioxide was removed by filtration through Celite, afterwhich the Celite was washed with hot acetic acid. The acetic acid was removed from the combined acid layers under reduced pressure to provide the crude acetate salt of **22** (55 mg). The free base was obtained by dissolving the salt in water (25 mL) and bringing the pH to 9 with cold aqueous ammonia (14%). The precipitate that formed was collected and dried to provide **22** (38 mg, 77%): mp 252–254 °C; IR (KBr), 1715 cm^{-1}; ^1H NMR (CF_3CO-OH) δ 4.30 (s, 3 H), 7.50–8.10 (m, 3 H), 8.40–8.90 (m, 2 H), 9.20–9.80 (m, 4 H); mass spectrum (CI), *m/e* 304 (M + 1).

Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.26; N, 13.86. Found: C, 71.40; H, 4.43; N, 13.95.

Oxidation of 1-Ethyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (23) with Selenium Dioxide. To a solution of 520 mg (2.01 mmol) of the β-carboline **23** (520 mg, 2.01 mmol) in dioxane (40 mL) was added selenium dioxide (223 mg, 2.01 mmol), and the mixture was stirred for 14 h at 98 °C. The black selenium that precipitated from the reaction was filtered through Celite, and the dioxane was removed under reduced pressure. Dimethylformamide was added, and the solution was stirred an additional 2 h at reflux. The reaction mixture was filtered through Celite, and the dimethylformamide was removed under reduced pressure. Methanol was added and the solution refrigerated to crystallize. Yellow crystals were filtered from the solution to yield 1-acetyl-3-(methoxycarbonyl)-β-carboline (**26**, 170 mg). The mother liquor was chromatographed on silica gel to provide **24**, **25**, **26**, and **27**.

1-Acetyl-3-(methoxycarbonyl)-β-carboline (26): mp 228–230 °C (lit.[23,24] mp 234–236 °C); IR (KBr) 3400, 3180, 2960, 1710 (C=O, ester), 1670 (C=O, ketone), 1625, 1590, 1430, 1370, 1260, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.90 (s, 3 H), 4.05 (s, 3 H), 7.20–7.70 (m, 3 H), 8.15 (1 H, d, *J* = 8.0 Hz), 10.50 (1 H); mass spectrum (70 eV), *m/e* 268

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(M^+, 100), 236 (30), 210 (27), 209 (19), 208 (38), 194 (35), 166 (15), 154 (10), 140 (12), 139 (11).

1-Ethyl-3-(methoxycarbonyl)-β-carboline (25): pale golden needles, mp 209-211 °C; IR (KBr) 3340, 3050, 3940, 1705 (C=O, ester), 1490, 1425, 1345, 1250, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 7 Hz), 3.07 (q, 2 H, J = 7 Hz), 3.98 (s, 3 H), 7.10-7.60 (m, 3 H), 3.13 (d, 1 H, J = 7 Hz), 8.68 (s, 1 H), 9.83 (1 H); mass spectrum (70 eV), m/e 254 (M^+, 100).

1-Acetyl-β-carboline (27): white crystals, mp 216-217 °C (lit.[25] mp 203-205 °C); IR (KBr) 3340, 1670 (C=O, ketone), 1495, 1210, 1170, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.90 (s, 3 H), 7.30-7.60 (m, 4 H), 8.20 (d, 1 H, J = 5.0 Hz), 8.60 (d, 1 H, J = 5.0 Hz), 10.60 (1 H); mass spectrum (70 eV), m/e 210 (M^+, 92), 168 (100), 167 (70), 141 (24), 140 (84), 115 (28).

1-Ethyl-β-carboline (24): white crystals, mp 192-194 °C (lit.[35] mp 192-194 °C; IR (KBr) 3440, 3120, 2980, 2880, 2780, 1620, 1560, 1500, 1315, 1235, 1220, 820, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (t, 3 H, J = 7.5 Hz), 3.20 (q, 2 H, J = 4.5 Hz), 7.20-7.70 (m, 3 H), 7.83 (d, 1 H, J = 6.0 Hz), 8.18 (d, 1 H, J = 8.0 Hz), 8.42 (d, 1 H, J = 6.0 Hz), 8.93 (br, 1 H); mass spectrum (70 eV), m/e 196 (M^+, 80), 195 (100), 168 (32), 154 (10), 140 (22), 127 (8), 115 (10).

3-Benzyl-1,2,3,3a,4,5-hexahydrocanthin-6-one (29a).[3] N_b-Benzyltryptamine hydrochloride (**28a**, 10 g, 35 mmol) was basified with aqueous NH_3 (14%) and extracted with chloroform. The solvent was evaporated to give an oil, which was dissolved in benzene (100 mL). α-Ketoglutaric acid (5.2 g, 35.6 mmol) was dissolved in dioxane (60 mL) and added dropwise to the refluxing solution of amine **28a**. The mixture was refluxed for 7 days. Water removal was accomplished via a Dean-Stark trap. The solvent was evaporated under reduced pressure and the residue then dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with saturated aqueous $NaHCO_3$ solution and then chromatographed on Al_2O_3 to give 9.04 g (82%) of the lactam **29a**: mp 171-173 °C; IR (KBr) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60-2.20 (m, 1 H), 2.20-2.95 (m, 6 H), 3.28 (d overlapping m, 3 H, J_d = 14 Hz), 4.10 (d, 1 H, J = 14 Hz), 7.15-7.40 (m, 8 H), 8.30 (m, 1 H); mass spectrum (70 eV), m/e (rel abundance), 316 (M^+, 15), 315 (12), 259 (10), 196 (100), 167 (30), 153 (10), 91 (55).

Anal. Calcd for $C_{21}H_{20}N_2$: C, 79.75; H, 6.33; N, 8.86. Found: C, 79.69; H, 6.46; N, 8.97.

The methylene protons of the benzyl group are diastereotopic and are split into doublets (J = 17 Hz).

Canthin-6-one (30a).[3] The amine **29a** (870 mg, 2.75 mmol) and SeO_2 (366 mg) were added to dioxane (80 mL). The mixture was heated to reflux for 1 day. An additional portion of SeO_2 (300 mg) was added and the mixture held at reflux for 2 days. The reaction was cooled to room temperature before each addition of SeO_2 was carried out. The solvent was evaporated under reduced pressure, and the residue was chromatographed on SiO_2 [eluent EtOAc/benzene, (1:3)] to provide canthin-6-one (**30a**), 200 mg, 33%: mp 152 °C ($MeOH-H_2O$, lit. mp 160-161 °C);[30-32] IR (KBr) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (d, 1 H, J = 9 Hz), 7.20-8.10 (m, 5 H), 8.40 (dd, 1 H, J_1 = 9 Hz, J_2 = 2 Hz), 8.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 116.02 (d), 117.08 (d), 122.37 (d), 124.20 (s), 125.39 (d), 128.13 (s), 128.75 (d), 129.81 (s), 130.06 (s), 130.63 (d), 136.06 (s), 139.28 (d), 145.50 (d), 159.18 (s); mass spectrum (CI, NH_3), m/e 221 (M + 1, 100).

2-(Methoxycarbonyl)canthin-6-one (30b). The amine **29b**[29] (2.0 g, 5.35 mmol) and SeO_2 (4.1 g, 37 mmol) were added to dioxane (250 mL), and the mixture was heated to reflux for 34. The black selenium was removed by filtration over Celite, and the solvent was removed under reduced pressure. The resulting slurry was diluted with MeOH, and the solid that crystallized was removed by filtration to furnish **30b** (980 mg, 66%): mp 249-250 °C; IR (Nujol) 1670, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.20 (s, 3 H), 7.10 (d, J = 10 Hz), 7.40-8.00 (m, 2 H), 8.00-8.50 (m, 2 H), 8.60-8.90 (m, 1 H), 9.00 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 53.14, 117.26, 118.33, 122.77, 124.03, 125.93, 129.89, 130.78, 131.26, 135.57, 139.48, 139.75, 144.15, 159.18, 165.54; mass spectrum, m/e 278.0684 ($C_{16}H_{10}N_2O_3$ requires 278.0691).

Registry No. 1a, 84133-23-3; **1b**, 84133-22-2; **2a**, 84133-24-4; **2b**, 84133-25-5; **2c**, 84133-26-6; **3**, 84133-27-7; **4**, 22282-00-4; **6**, 724-42-5; **6**·HCl, 888-17-5; **7**, 21469-60-3; **8**, 60702-96-7; **9**, 19171-89-2; **10**, 2738-25-2; **11a**, 75304-06-2; **12**, 75304-07-3; **15a**, 84133-29-9; **15b**, 5275-05-8; **16b**, 71491-91-3; **17**, 61364-26-9; **18**, 5580-44-9; **19**, 84133-32-4; **22**, 84133-30-2; **23**, 75304-03-9; **24**, 20127-61-1; **25**, 75304-04-0; **26**, 66154-37-8; **27**, 50892-83-6; **28a**, 15741-79-4; **29a**, 65284-99-3; **29b**, 60702-98-9; **30a**, 479-43-6; **30b**, 84133-31-3; 3-indolyl-2'-pyridylcarbinol, 51626-59-6; 3-indolyl-2'-*N*-(trimethylacetyl)piperidylmethane, 84133-28-8; 3-indolyl-2'-piperidylmethane, 5275-05-8; 2-oxoglutaric acid, 328-50-7; indole, 120-72-9; 2-pyridine carboxaldehyde, 1121-60-4; trimethylacetyl chloride, 3282-30-2; selenium dioxide, 7446-08-4; **5**, 73-22-3.

Nocardicin A: Biosynthetic Experiments with Amino Acid Precursors

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Abstract: In radioisotope and stable-isotope tracer studies using growing cells of *Nocardia uniformis* subsp. *tsuyamanensis* (ATCC 21806), L-methionine, L-serine, and L-(*p*-hydroxyphenyl)glycine were shown to be the most efficient amino acid precursors of the homoseryl, β-lactam, and aryl segments of the monocyclic β-lactam antibiotic nocardicin A (**1**). $^3H/^{14}C$ double-label experiments demonstrated (a) that β-lactam formation takes place at the β-carbon of serine substantially without loss of tritium label at this position and (b) that the α-hydrogens of both L- and D-(*p*-hydroxyphenyl)glycine are lost during incorporation at both sites in **1**. The data suggest a peptide origin for the antibiotic as is known for penicillin and that β-lactam formation is most simply interpreted as taking place by nucleophilic displacement of presumably activated seryl hydroxyl by amide nitrogen.

Nocardicin A (**1**) is the principal and most active member[1] of a family of β-lactam antibiotics isolated[2] from *Nocardia uniformis* subsp. *tsuyamanensis*. It shares with the very recently discovered sulfazecin (**2**)[3] and related monobactams[4] a monocyclic β-lactam ring but is additionally unusual with regard to its ether-linked homoseryl, oxime, and (*p*-hydroxyphenyl)glycine units. These structural features raise a number of questions of biosynthetic importance that have been the focus of efforts in this laboratory.[5]

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