***N*-(*tert*-Butoxycarbonyl)-2-methoxalyl-3-[β-(2-azabicyclo[2.2.0]-hex-5-en-2-yl)ethyl]indole (18).** To 10 mL of dry tetrahydrofuran cooled in a dry ice bath (−78 °C) and under N_2 was added 1.0 mL of 1.1 M *tert*-butyllithium in *n*-pentane followed by 120 mg (0.34 mmol) of indole **16** in 1 mL of dry tetrahydrofuran. The reaction mixture was allowed to stir for 1 h and was transferred by a double-ended needle to a flask containing 0.80 mL of dimethyl oxalate and 10 mL of dry tetrahydrofuran at room temperature. In order to minimize decomposition, it is important that the double-ended needle be kept cool (−78 °C) during the transfer of the lithiated indole. The reaction mixture was allowed to stir for 1 h followed by the addition of a saturated NaCl solution. The reaction mixture was extracted with ether. The ether extract was dried ($MgSO_4$), and the solvent was removed in vacuo. The excess dimethyl oxalate was removed in vacuo with slight warming to give 168 mg of the crude product as a yellow oil. This was further purified by silica gel thin-layer chromatography using 1:5:1 benzene–ethyl acetate–methanol containing 1% of diisopropylamine ($R_f \simeq 0.7$): IR (film) ν_{max} 3000 (m), 1705 (br s), 1450 (m), 1370 (s), 1330 (s), 1245 (m), 1140 (s), 1025 (m), 825 (m), 750 (s) cm^{-1}; ^1H NMR (C_6D_6, 80 MHz) δ 0.48 (t, J = 7 Hz, 3 H), 1.04 (s, 9 H), 1.25 (9, J = 7 Hz, 2 H), 2.0–2.6 (m, 5 H), 3.05 (d, J = 8.0 Hz, 1 H), 3.65–3.75 (m, 1 H), 5.76 (d, J = 3 Hz, 1 H), 6.00 (t, J = 3 Hz, 1 H), 6.5–7.2 (m, 3 H), 7.93 (d, J = 7 Hz, 1 H); high-resolution mass spectrum, m/e 438.2160 ($M^{+\cdot}$) ($C_{28}H_{28}N_3O_2$ requires 438.2182).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (Grant No. CHE-7807577) for support of this work.

Registry No. **1**, 16851-82-4; 1-2-*d*, 75400-55-4; **2**, 5175-27-2; **3**, 75400-56-5; **4a**, 75400-57-6; **4b**, 75400-58-7; **4c**, 75400-59-8; **4d**, 75400-60-1; **4e**, 75400-61-2; **5**, 75400-62-3; **6**, 60443-99-4; **7a**, 18276-13-6; **7b**, 75400-63-4; **7c**, 7697-46-3; **7d**, 75400-64-5; **7e**, 1072-83-9; **8**, 75400-65-6; **9**, 75400-66-7; **10**, 74185-41-4; **11**, 75400-67-8; **13**, 75400-68-9; **14**, 75400-69-0; **15**, 18132-19-9; **16**, 75400-70-3; **18**, 75400-70-3; chlorotrimethylsilane, 75-77-4; benzaldehyde, 100-52-7; benzoyl chloride, 98-88-4; propionaldehyde, 123-38-6; acetyl chloride, 75-36-5; *tert*-butoxycarbonyl azide, 4981-48-0; *N*-benzenesulfonylindole, 40899-71-6; dimethyl oxalate, 553-90-2; *N*-carboxy-2-methoxycarbonylindole, 75400-71-4.

Stereospecific Synthesis of *trans*-1,3-Disubstituted-1,2,3,4-tetrahydro-β-carbolines

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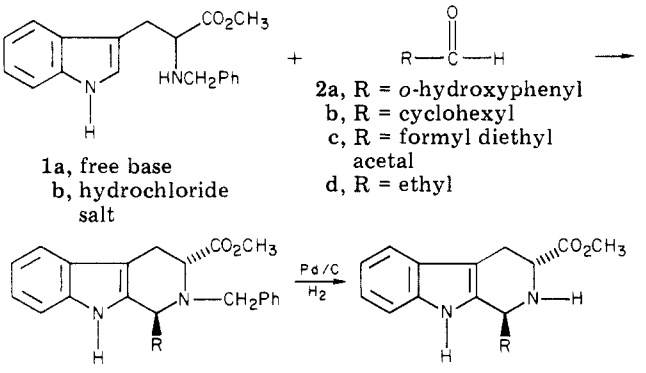
The Pictet–Spengler condensation of N_b-benzyltryptophan methyl ester **1a** with aldehydes **2a–d** has been found to occur in a stereospecific fashion. Stereoelectronic (antiperiplanar) attack of the 2,3-indole double bond on the intermediate benziminium ion **5b**, when combined with conformational analysis, has been employed to explain the complete stereospecificity of this cyclization. The N_b-benzyl derivatives (**3a–d**) were subjected to catalytic hydrogenation to provide the first stereospecific entry into *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines (**4a–d**).

Interest in β-carbolines has been stimulated recently by their demonstrated biological activity[1-3] and the high affinity some of these bases have shown for the benzodiazepine (Valium) receptor.[4-6] Several groups[7-11] have investigated the ratio of cis/trans isomers produced in the Pictet–Spengler reaction of tryptophan derivatives with aldehydes; however, in all of the reactions discussed in 7–10, mixtures of cis and trans diastereomers were reported with the exception of the harman substitution pattern (1-methyl) and, in fact, Brossi[12] has isolated cis and trans isomers (1-methy-3-carboxyl) in this series.

Scheme I[a]



[a] For convenience only one antipode of the intermediate is presented here, although *d,l*-tryptophan was employed for this study.

For some time 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines have been employed in our laboratory as intermediates for the synthesis of oxo-substituted β-carboline

(1) Cohen, G.; Collins, M. *Science* **1970**, *167*, 1749. Davis, U. E.; Walsh, M. J. *Ibid.* **1970**, *167*, 1005.
(2) Grabowska, G. M.; Antiewica, L.; Michaluk, J. *Diss. Pharm. Pharmacol.* **1972**, *14*, 423.
(3) Rahwan, R. G. *Toxicol. Appl. Pharmacol.* **1975**, *34*, 3–27.
(4) Fox, J. L. *Chem. Eng. News* **1980**, Feb 4th, 24 and work described therein.
(5) Braestrup, C.; Nielsen, M.; Olsen, C. E., *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2288.
(6) Skolnick, P.; Paul, S. M.; Rice, K. C.; Barker, S.; Cook, J. M.; Weber, R.; Cain, M. "In Vitro Inhibition of [^{3}H]-Diazepam Binding to Benzodiazepine Receptors by β-Carbolines", presented at the National Meeting of the American Chemical Society, Las Vegas, NV, Aug 24–30, 1980; Abstract no. 69.
(7) DeSilva, K. T. D.; King, D.; Smith, G. N. *J. Chem. Soc., Chem. Commun.* **1971**, 908.
(8) Brown, R. T.; Chapple, C. *J. Chem. Soc., Chem. Commun.* **1973**, 886.
(9) Hamaguchi, F.; Nagasaka, T.; Ohki, S. *Yakugaku Zasshi* **1974**, *94*, 351.
(10) Saxena, A. K.; Jain, P. C.; Anand, N. *Indian J. Chem.* **1974**, *12*, 892.
(11) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.
(12) Brossi, A.; Focella, A.; Teitel, S. *J. Med. Chem.* **1973**, *16*, 418.

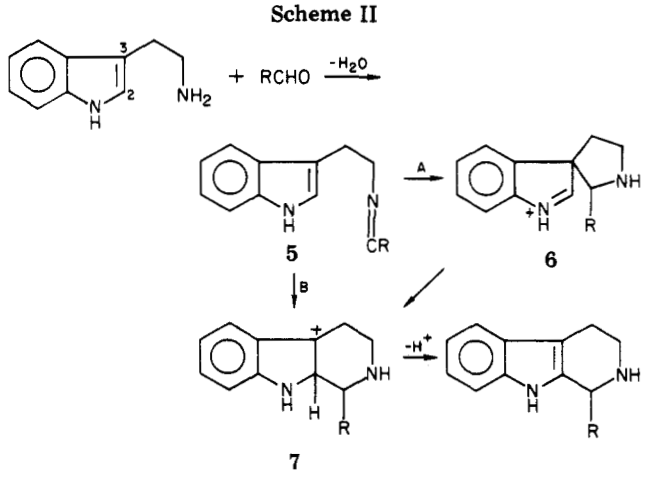
0022-3263/81/1946-0164$01.00/0

alkaloids such as pyridindolol[11] and 1-acetyl-3-(methoxycarbonyl)-β-carboline,[13] and we have recently reported a simple carbon NMR method which differentiates, unequivocally, between cis and trans stereoisomers in this area.[14]

In the course of investigations directed toward synthesis of 1,3-disubstituted-tetrahydro-β-carbolines for ^{13}C NMR studies, it was discovered that reaction of N_b-benzyltryptophan methyl ester (**1a**) with salicyaldehyde (**2a**) in refluxing toluene[11] provided the Pictet–Spengler product **3a** in 97% yield (Scheme I). It was clear from the ^{13}C NMR spectrum of **3a** that only one diastereomer had been produced in this reaction; however, the steric interactions in a 1,2,3-trisubstituted-1,2,3,4-tetrahydro-β-carboline were sufficiently complex to prohibit assignment of the stereochemistry by carbon NMR, in an unequivocal sense. It would, however, be a simple matter to assign the stereochemistry of the 1,3-disubstituted-tetrahydro-β-carbolines by either ^{13}C NMR[11] or by comparison of the product of debenzylation with authentic samples of *cis*- or *trans*-**4a** previously prepared by an independent route.[11] In this vein, the 2-benzyl derivative **3a** was subjected to catalytic hydrogenation (10% Pd/C, 40 psi) which resulted in a 51% yield of the trans stereoisomer **4a** accompanied by the product of hydrogenolysis, 2-(2-hydroxybenzyl)tryptophan methyl ester, whose structure has been reported elsewhere.[11] The yield of **4a** could be increased to 75% by performing the catalytic reduction at 25 psi; furthermore none of the cis diastereomer of **4a** was isolated from the reaction mixture nor was it observed by ^{13}C NMR spectroscopy. Since tryptophan methyl ester when reacted with salicyaldehyde gave a mixture of cis and trans isomers,[9,11] clearly the effect of the N_b-benzyl group was to direct this condensation in a stereospecific fashion. This was the first stereospecific synthesis in the N_a-H, tetrahydro-β-carboline area, and the reasons for this specificity will be made clear later (see below).

Because of the possibility that hydrogen bonding (hydroxy group of the salicyl moiety **2a**) might play a role in the stereospecificity of this condensation a second aldehyde, devoid of a hydroxyl group, was chosen as a substrate for the condensation. Cyclohexylcarboxaldehyde (**2b**) was heated for 12 h in refluxing benzene with N_b-benzyltryptophan methyl ester **1a** to provide the 1,3-disubstituted-tetrahydro-β-carboline **3b** in 87% yield. Again the ^{13}C NMR spectrum of **3b** indicated that only one stereoisomer (**3b**) had been formed in this sequence; therefore it was clear that the hydroxyl group was not required and played no role in the stereocourse of the condensation. Treatment of the N_b-benzyl derivative **3b** with hydrogen over 10% Pd/C gave a 70% yield of the *trans*-1-cyclohexyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**4b**) together with starting material (20%). Examination of the crude reaction mixture by TLC and ^{13}C NMR indicated that none of the cis diastereomer was present. The previous method reported in the literature for preparation of **4b** by the Pictet–Spengler reaction had furnished a mixture of cis and trans isomers;[11] therefore, the sequence (N_b-benzyl) above had again occurred in a stereospecific fashion.

Scheme II



In our earlier studies, it had been shown that $A^{(1,2)}$ strain between position 1 of the tetrahydro-β-carboline and the N_a substituent was the dominant factor in determining the cis/trans ratio during the Pictet–Spengler reaction of tryptophan with aldehydes; moreover, the larger the group at position 1, the more the condensation favored formation of the trans diastereomer.[14] In view of this, it was decided to condense **1a** with aldehydes which occupy a smaller molecular volume than **2a** and **2b**. For this purpose, glyoxal diethyl acetal[15] was chosen and heated with **1a** in refluxing benzene to furnish a 75% yield of the desired tetrahydro-β-carboline **3c**. This base **3c** was immediately converted to the 1,3-disubstituted-tetrahydro-β-carboline **4c** by catalytic hydrogenation in excellent yield. Again careful examination of the reaction mixture indicated only the presence of the trans diastereomer **4c**.

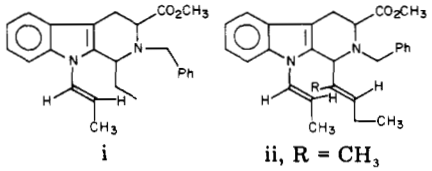
One further experiment, and perhaps the most significant, needs to be discussed. Propionaldehyde (**2d**, excess) and the hydrochloride salt **1b** were heated (cold-finger condenser) in a refluxing solution of methanol–water for 48 h. After workup, three compounds were isolated, one of which was found to be the desired N_b-benzyl derivative **4c** present in 46% yield. The other two products appeared to arise from attack of the indole nitrogen on **2d** followed by loss of water and a subsequent Pictet–Spengler reaction of the N_a-alkylated derivative with propionaldehyde.[16] The formation of the side products was avoided by heating **1b** with a slight excess of **2d** (see the Experimental Section) which furnished **3d** in better than 80% yield. When the 1-ethyl-2-benzyl compound [again present as a single diastereomer (^{13}C NMR)] was subjected to treatment with hydrogen over palladium on carbon, a 97% yield of *trans*-1-ethyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**4d**) was realized. Clearly this result demonstrates that the stereospecificity of this sequence is due in large measure to the effect of the N_b-alkyl group on the transition state and not the direct result of $A^{(1,2)}$ strain[14,17] on the system.

(13) Campos, O.; DiPierro, M.; Cain, M.; Mantei, R.; Gawish, A.; Cook, J. M. *Heterocycles* **1980**, *14*, 975.

(14) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 6976. Sandrin, J.; Soerens, D.; and Cook, J. M. *Heterocycles* **1976**, *4*, 1249.

(15) Glyoxal diethyl acetal was prepared conveniently by the method of Grohman [Grohman, K.; Noire, P. 172nd National Meeting of the American Chemical Socieity, San Francisco, CA, Aug 30–Sept 3, 1976; abstract no. 236].

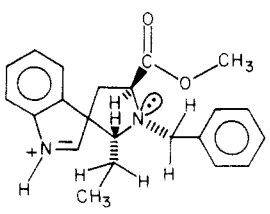
(16) In the initial series of condensations a 47-mol excess of propionaldehyde was employed. It is believed (NMR, mass spectra) the two byproducts i and ii were produced in this sequence although a rigorous proof of structure has not been completed. The two bases i and ii were not produced when the condensation was run with a slight excess of **2d**.



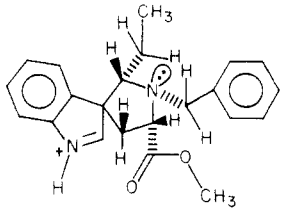
i ii, R = CH_3

(17) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

Scheme III



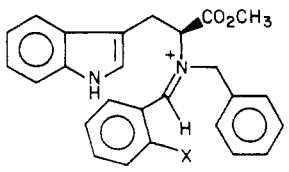
A[a]



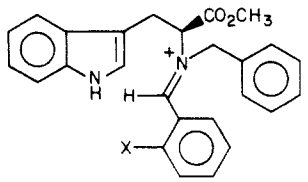
B[b]

[a] Spiroindolenine intermediate A: Attack on the benziminium ion from the bottom face of the C=N double bond. [b] Spiroindolenine intermediate B: Attack on the benziminium ion from the top of the C=N double bond. Models of this structure indicate a more crowded intermediate than in A, because the three substituents are eclipsed.

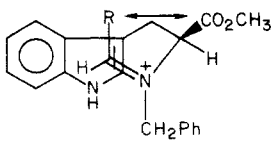
An examination of the mechanism of this condensation with regard to stereospecificity is not a simple matter. Although the Pictet–Spengler condensation is generally predicted to proceed through the spiroindolenine intermediate,[18,19] as shown in Scheme II (path A), Casnati[20] has shown that the cyclization can occur by direct attack at position 2 of the indole when very reactive electrophiles are involved (path B). Certainly the N_b-benzyl iminium ion, intermediate **5**, can be considered a reactive electrophile; therefore, both the spiroindolenine intermediate **6** (Scheme II) and the rearranged product **7** [formally attack at C-2 of the indole (schemes II and IV)] must be considered in the discussion of the stereocourse of this cyclization. To this end an examination of molecular models has been employed to understand the results centering first on the benziminium ion **5** itself. It is clear that the steric interactions which would develop in the transition state between the indole moiety and the phenyl group (or ethyl group) in stereoisomer **5a** during the cyclization are much



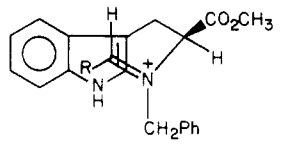
5a, X = H or OH



5b, X = H or OH



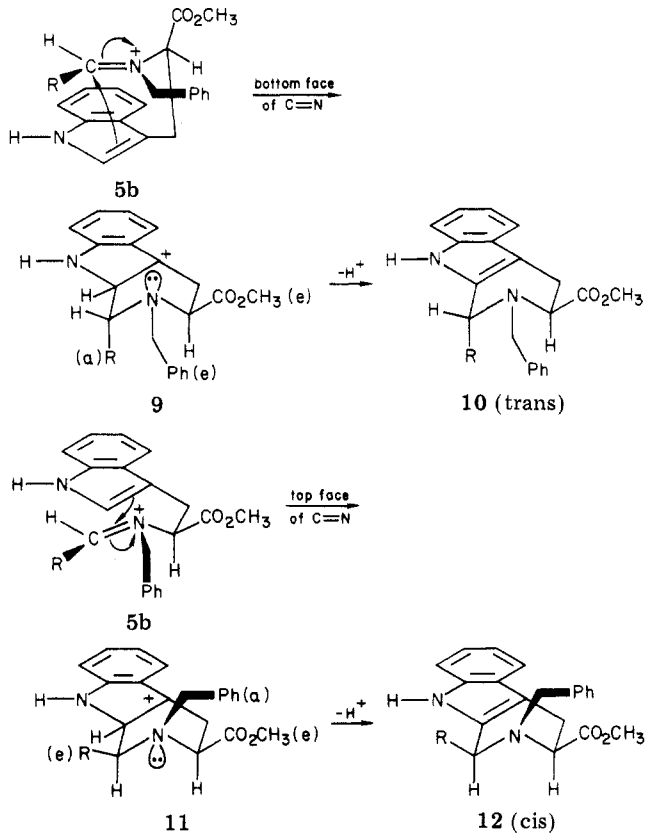
8a



8b

more repulsive (in a steric sense) than the interactions between the indole and the hydrogen atom of **5b**. More importantly, however, attack of the indole double bond on the iminium ion **8a** (*Z* isomer) is not favored for a 1,3-interaction would develop between the R group and the ester in the transition state as the electronic character of the imine (C=N bond) begins to approach sp^3 hybridization. This same 1,3 interaction would not develop in the *E* isomer **5b** (see structure **8b**); therefore stereoisomer **5b** is favored in this condensation.

Scheme IV

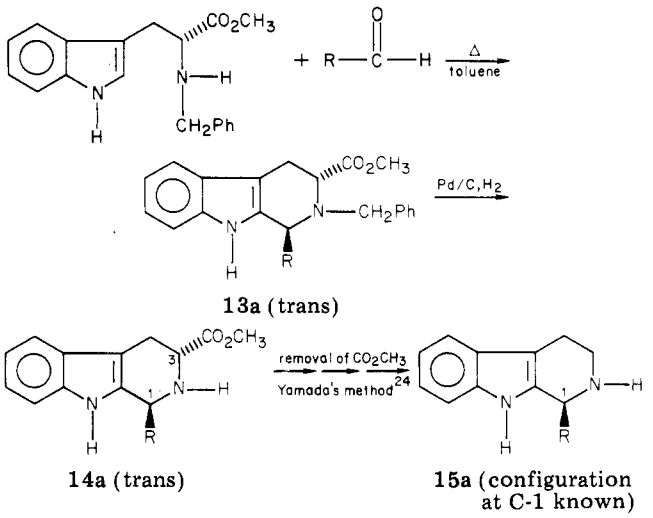


The initial attack of the indole double bond on the benziminium ion **5b** can be thought to occur from carbon-3 of the indole or from carbon-2 (see Scheme II) but regardless of this, the indole double bond is expected to attack **5b** with stereoelectronic control similar to the attack (antiperiplanar) of hydroxide ion on imidate salts reported by Deslongchamps.[22] This is the second factor which induces stereospecificity into this sequence.[23]

Illustrated in Scheme III are structures which result from attack of the indole double bond at C-3 on **5b** from the bottom face (A) and from the top face (B) of the C=N bond. The substituents at C-1, -2, and -3 are cis in structure B and are definitely more crowded (eclipsed) than those depicted in structure A; moreover attack on **5b** has occurred on the face opposite to the ester function which has also minimized interactions with this group during the cyclization. The stereospecificity of this sequence is even more obvious when the intermediates **9** and **11** (structure **7** in Scheme II) are examined, as illustrated in Scheme IV. Although we favor the spiroindolenine intermediate (Scheme III), it must be remembered that structures **9** and **11** can be derived both from direct electrophilic attack on the indole at C-2 and also from rearrangement of the spiroindolenines A and B, respectively, and hence intermediates **9** and **11** may play an important

(18) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119.
(19) For a review on the spiroindolenine intermediate, see: Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089.
(20) Casnati, G.; Dossena, A.; Pochini, A. *Tetrahedron Lett.* **1972**, 5277.
(21) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227.
(22) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463; *Heterocycles* **1977**, *7*, 1271.
(23) This sequence parallels the work of Deslongchamps in that attack of the nucleophile on the iminium ion **5a** occurs in an antiperiplanar fashion which involves the developing lone pair of electrons on the nitrogen. This is a four-electron process and therefore only anti addition is allowed (Gilchrist, T.; Storr, R. In "Organic Reactions and Orbital Symmetry"; Cambridge University Press: London, 1972). The approach has been employed by Stevens (Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032) and by Wenkert (Wenkert, E.; Chang, C.-J.; Chanta, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645) during the stereospecific synthesis of alkaloids.

Scheme V



role in the stereocourse of the reaction. Intramolecular attack, in a stereoelectronic sense,[23] on **5b** from the bottom face of the $C{=}N^+R_2$ bond (anti to the ester function) would generate **9** in which the benzyl group would occupy an equatorial position while the phenyl group at position-1 would be axial. This would give **10** which contains two equatorial groups accompanied by the 1-axial substituent. In a similar manner, attack on **5b** from the top face of the iminium ion double bond would generate the more crowded **11** which contains an axial benzyl function, equatorial methoxycarbonyl group, and the equatorial 1-phenyl moiety. Clearly the cis diastereomer **11** is the less stable of the two species since the 2-benzyl function occupies an axial position in the transition state; moreover, the cis isomer **11** suffers from the additional unfavorable interaction between the equatorial substituent at position 1 and the indole N_a-H function [$A^{(1,2)}$ strain].[14,17] It is, therefore, the combined influence of stereoelectronic control and conformational interactions which leads to complete stereospecificity in this condensation to provide tetrahydro-β-carboline **9** in preference to **11**.

Because of the above results, it should now be possible to prepare 1,3-disubstituted-tetrahydro-β-carbolines and 1-substituted-tetrahydro-β-carbolines of known absolute stereochemistry and a pathway for this is outlined in Scheme V. If optically active N_b-benzyltryptophan methyl ester of known chirality is reacted with aldehydes in refluxing toluene,[11] the trans derivative **13a** could be prepared and the absolute stereochemistry would be controlled by the stereospecificity of the condensation. In addition, carbon NMR[14] could then be employed to ensure the stereochemical integrity of the reaction product. Treatment of **13a** with hydrogen (Pd/C) would provide the *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carboline **14a** of known *absolute* stereochemistry. The trans nature of **14a** can be verified by carbon NMR spectroscopy.[11,14] In addition, the 3-methoxycarbonyl group could be removed by the method of Yamada[24] to provide optically pure 1-substituted-1,2,3,4-tetrahydro-β-carbolines of *known absolute configuration*. In order to obtain β-carbolines with the opposite configuration, the same sequence of reactions could be followed; however, the sequence would simply have to begin with N_b-benzyltryptophan methyl ester of opposite chirality to that illustrated at the top of Scheme V.

(24) Yamada, S. Y.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1976**, 61. Akimoto, H.; Yamada, S., et al. *Chem. Pharm. Bull.* **1974**, *22*, 2614.

In conclusion, a simple two-step sequence has been developed to prepare *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines in stereospecific fashion. The method is attractive for the 2-alkyl group necessary for the stereospecificity can be easily removed by catalytic hydrogenation. Moreover, the method does provide the first sequence which can be employed to prepare either 1-substituted- or 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines of known absolute stereochemistry.

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. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer and a Varian CFT-20 ^{13}C NMR spectrometer. Infrared spectra were taken on a Beckman Acculab-1 instrument, and mass spectra were recorded on Hitachi RMU-6, Finnigan GC/MS, and AEI MS-902 mass spectrometers.

Analytical TLC plates used were E. Merck Brinkman UV-active silica gel or alumina on plastic. The TLC plates were developed with the spray reagent ceric ammonium sulfate in 50% sulfuric acid. Cyclohexanecarboxaldehyde, benzaldehyde, acrolein diethyl acetal, propionaldehyde, and *dl*-tryptophan were purchased from Aldrich Chemical. The palladium on carbon catalyst was purchased from Pfaltz and Bauer, Inc.

The preparations of **1a**, **3a**, **4a**, and **3c** were described previously.[11]

2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-cyclohexane (3b). To a solution of N_b-benzyltryptophan methyl ester (**1a**; 3.0 g, 0.01 mol) in benzene (125 mL) was added cyclohexanecarboxaldehyde (**2b**; 1.7 g, 0.015 mol), and the mixture was refluxed for 12 h. The solvent was then removed under reduced pressure, and the oil that remained was crystallized from methanol to provide an 87% yield (3.5 g) of **3b**: mp 167–169 °C; IR (KBr) 3400 (NH), 1720 (ester) cm^{-1}; NMR ($CDCl_3$) δ 0.60–2.00 (10 H, m), 2.01–2.45 (1 H, m), 2.90–3.60 (5 H, 3 overlapping multiplets), 3.75 (3 H, s, OCH_3), 3.85–4.40 (1 H, m), 7.00–7.80 (10 H, m); M^+ at *m/e* 402.

Anal. Calcd for $C_{26}H_{30}O_2N_2$: C, 77.61; H, 7.46; N, 6.96. Found: C, 77.41; H, 7.30; N, 6.66.

Debenzylation of N_b-Benzyl-1-cyclohexyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (3b) To Give *trans*-1-Cyclohexyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (4b). The cyclohexyl derivative (**3b**; 1.96 g, 0.005 mol) was hydrogenated (25 psi) in a solution of ethanol (300 mL) and acetic acid (40 mL) for 8 h over 10% Pd/C (0.2 g). The catalyst was filtered from the mixture and the solvent was removed under reduced pressure. The residue was basified with ammonium hydroxide (14%) and extracted with chloroform. The residue was crystallized from methanol to provide **4b** (1.09 g, 70% yield). The remainder of the material was **3b**. The mother liquors were scrupulously examined for traces of the cis isomer; however, none could be found. The melting point [147–149 °C (lit.[11] mp 147–149 °C)] and IR and NMR spectra of **4b** were identical with those of *trans*-1-cyclohexyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**4b**) prepared by a different route.[11]

***trans*-1-Formyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole Diethyl Acetal (4c).** 2-Benzyl-1-formyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole diethyl acetal (**3c**; 10 g, 0.024 mol) was dissolved in a solution of absolute ethanol (150 mL) and acetic acid (45 mL). The mixture was subjected to catalytic hydrogenation (52.3 psi) for 24 h over 10% Pd/C (2.0 g). The catalyst was filtered from the mixture, and the solvent was removed under reduced pressure. The residue was treated with ammonium hydroxide (14%) and extracted with chloroform. The chloroform layer was dried over Na_2SO_4 and evaporated under reduced pressure to provide a crystalline solid (8.2 g, 0.024 mol), mp 124–125 °C (TLC on silica with benzene, R_f 0.69). This material was shown to be *trans*-1-formyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole diethyl acetal (**4c**). All spectral data were identical with the spectra obtained for the trans isomer previously isolated from the Pictet–Spengler reaction of tryptophan methyl ester and

glyoxal diethyl acetal (lit.[14] mp 125 °C). The mixture melting point of the two materials remained undepressed.

***trans*-2-Benzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-ethane (2d).** N_b-Benzyltryptophan methyl ester hydrochloride (**1b**; 4.05 g, 11.7 mmol) and propionaldehyde (**2d**; 1.0 mL, 13.7 mmol) were dissolved in a solution of methanol/water [75/25 (v/v), 70 mL]. The resulting mixture was refluxed (cold-finger condenser, dry ice–chloroform) for 48 h under nitrogen. The reaction was cooled and the solvent removed under reduced pressure. The oil which remained was taken up in chloroform and washed successively with ammonium hydroxide (14%, 50 mL) and brine solution. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The oil which remained was chromatographed on silica gel (100 g) to provide the *trans*-1,3-disubstituted-tetrahydro-β-carboline (**3d**, 3.25 g) in 80% yield: mp 149–150 °C (methanol); IR (KBr) 3380 (s), 1725 (s) cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 7.0 Hz), 1.72 (2 H, q, J = 7.0 Hz), 3.05 (2 H, d, J = 7 Hz), 3.50 (3 H, s), 3.53–4.10 (4 H, m), 7.00–7.70 (10 H, m); mass spectrum (indirect inlet, EI), m/e 348 (M^+, 1%), 346 (1), 344 (1), 319 (17), 121 (23), 91 (97).

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.56; H, 7.46; N, 8.17.

***trans*-3-(Methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-ethane (4d).** *trans*-N_b-Benzyl-1-ethyl-3-(carbomethoxy)tetrahydro-β-carboline (**3d**; 0.50 g, 1.44 mmol) was dissolved in a solution of methanol (200 mL) and glacial acetic acid (30 mL). The mixture was subjected to catalytic hydrogenation (Parr, 500 mL) over a Pd/C catalyst (0.050 g, 5%) at 50 psi for 20 h. TLC indicated the presence of only one material (R_f 0.20, silica gel, 1% methanol–chloroform); therefore the catalyst was filtered from the solution and the solvent was removed under reduced pressure. The oil which remained was dissolved in chloroform (250 mL) and the organic layer washed successively with ammonium hydroxide solution (80 mL, 14%) and brine. The organic layer was dried (Na_2SO_4), after which the solvent was removed under reduced pressure and the oil which remained was crystallized from hot methanol to provide the *trans*-1-ethyltetrahydro-β-carboline (**4d**, 155 mg). Recrystallization of the mother liquors gave additional quantities of **4d** (190 mg, combined yield 345 mg, 97%), mp 152–153 °C (lit.[14] mp 152–153 °C). The R_f and IR, proton NMR, and carbon NMR spectra of the trans derivative were identical with those previously reported for *trans*-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole-1-ethane[14] whose structure had been proven by carbon NMR and single-crystal X-ray analysis.[14] The mixture melting point of **4d** showed no depression.

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Notes

Interaction of Phenylhydrazones with Nitrosobenzene-Radical Intermediates

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Nitrones, along with benzene and nitrogen, are produced from the reaction of nitrosobenzene (1) and phenylhydrazones.[1] This reaction has been shown to follow second-order kinetics, and rates of reactions utilizing reactants substituted on meta and para positions of each of the three available aromatic rings have been correlated by using the Hammett treatment.[2] Yields of nitrones (based on phenylhydrazone) produced from this reaction have been found to be diminished in a nitrogen atmosphere vs. air, but use of excess nitrosobenzene resulted in higher yields. On the basis of these observations, the mechanism for the reaction of benzaldehyde phenylhydrazone (BPH, **2**) in Scheme I has been proposed.[1]

Phenyldiazene (**5**) is a short-lived, oxygen-sensitive species known to decompose to benzene and nitrogen via a bimolecular process, reportedly not including free radicals.[3] A possible modification of Scheme I, that also would account for benzene and nitrogen production, involves decomposition of intermediate **3** by a radical process. Hydroxyl hydrogen abstraction from **3** would yield nitroxide **6**, which, by reversal of a spin-trapping reaction, could yield nitrone **4** and phenyldiazo radical, $PhN_2^{\bullet}$. The latter is a potential source of nitrogen and phenyl radicals.

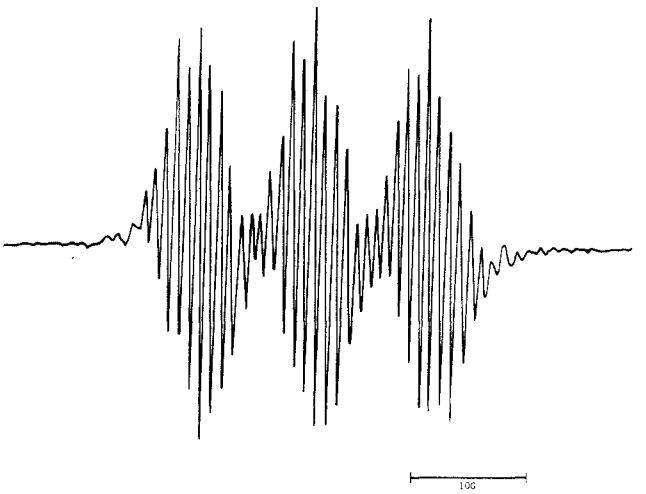

Figure 1. EPR spectrum from 1:2 BPH/nitrosobenzene reaction.

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