# β-Carbolines Derived from β-Methyltryptophan and a Stereoselective Synthesis of (2*RS*,3*SR*)-β-Methyltryptophan Methyl Ester [1]

Mohammad Behforouz*, Hamideh Zarrinmayeh, Mark E. Ogle, Tammy J. Riehle [2] and Frank W. Bell [2]

Department of Chemistry, Ball State University, Muncie, IN 47306

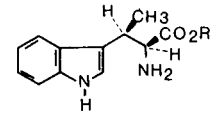
Received March 28, 1988

The methyl ester of isomer **A** of β-methyltryptophan (2*SR*,3*RS*; **2A**) was stereoselectively prepared by an efficient modified method through the reaction of α-methyl-*N*-(1-Methylethyl)-1*H*-indole-3-methanamine (**3**) with methyl nitroacetate to give the desired nitro compound as a mixture of two racemates **5A**, and **5B**. During the recrystallization process epimerization occurred and only racemate **5A** crystallized out. Catalytic hydrogenation of **5A** in the presence of acid stereoselectively yielded the desired amino acid ester **2A**. Pictet-Spengler condensation of **2A** with aldehydes under aprotic conditions followed by dehydrogenation gave excellent yields of β-carbolines **7a-i**, (R = methyl, ethyl, acetyl, phenyl, pyridine-2-yl, furan-2-yl, quinoline-2-yl, styryl, phenethyl). Also β-carbolines **7a,b,i** were synthesized by the Pictet-Spengler condensation of β-methyltryptophan under acidic aqueous conditions followed by esterification and dehydrogenation.

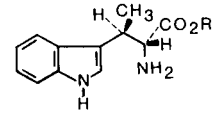
*J. Heterocyclic Chem.*, **25**, 1627 (1988).

## Stereoselective Synthesis of Methyl 2-Amino-3-(3-indolyl)-butanoate (β-Methyltryptophan Methyl Ester, 2*SR*,3*RS*; **2A**).

The amino acid β-methyltryptophan is an important structural moiety of a number of natural products such as telomycin [3], streptonigrin [4] and lavendamycin [5]. The stereochemistry of β-methyltryptophan isomers known as **A** (2*SR*,3*RS* racemate, **1A**) and **B** (2*RS*,3*RS* racemate, **1B**) has been determined through nmr studies by Turchin and coworkers [6]. It has been reported [4,6] that the natural β-methyltryptophan is one of the enantiomers of isomer **A**.



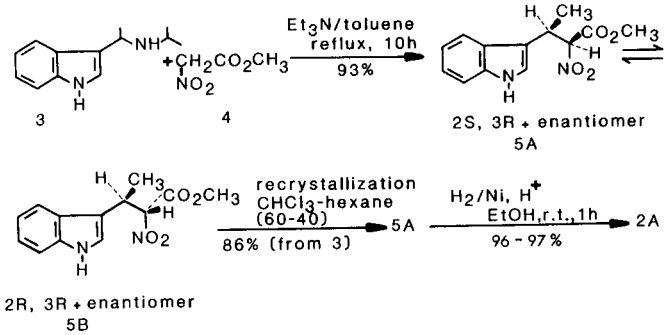
2S, 3R + enantiomer
1A; R = H
2A; R = $CH_3$



2R, 3R + enantiomer
1B; R = H
2B; R = $CH_3$

β-Methyltryptophan or its methyl ester is prepared either by the acetamidomalonate [7] or by the nitroacetate method [8-10]. The former is long, tedious and produces pure **1A** and **1B** in only 27%. The latter is shorter but is not stereoselective and gives a diastereomeric mixture of **2A** and **2B** in an overall yield of 42%. We have modified the nitroacetate method and have stereoselectively prepared pure **2A** in an excellent overall yield of 71% starting from indole. The modification involves 1) isolation of pure **5A** in the condensation step and 2) addition of acid and use of commercially available Raney nickel in place of Ni(W-4) in the hydrogenation step (Scheme I).

Scheme I




α-Methyl-*N*-(1-methylethyl)-1*H*-indole-3-methanamine (**3**) was prepared from indole by the method of Snyder and Matteson [7] in 85% yield [11] (lit [7] 60%). Condensation of **3** with nitroacetate **4** and triethylamine in toluene at 95-105° gave a mixture of racemates **5A** and **5B** (**5A**:**5B** = 2:1) in 93% yield [12]. Recrystallization of this mixture from chloroform-hexane (60:40) gave only **5A** in 86% overall yield. This indicates that during the recrystallization process eprimerization occurs and racemate **5B** is converted to the less soluble **5A** and this transformation is continued until nearly all of **5B** is converted to **5A**. This eperimerization is facilitated by the presence of triethylamine [13]. To prevent the interconversion of **5A** to **5B** in solutions, isomer **5A** must be prepared free of base. Hydrogenation of **5A** in the presence of Raney nickel in an ethanolic solution of trifluoroacetic acid gave **2A** and a small amount of **2B** (**2A**:**2B** = 97:3) in 94% yield [14]. Recrystallization with ethyl acetate afforded pure **2A**. Amino acid ester **2A** was identified as the methyl ester of isomer **A** of β-methyltryptophan [4,6] by a comparison of its melting range, tlc and $^1H$ nmr data with those of authentic samples. Isomers **A** and **B** of β-methyltryptophan were prepared by an unambiguous method [7] and treated with methanolic hydrogen chloride to produce the corresponding esters in about 92% yield.

β-Carbolines Derived from β-Methyltryptophan.

The chemistry of β-carbolines has long been of interest because of their occurrence in a large number of alkaloids [15] and neurochemical and behavioral activities [16,17].

β-Carbolines have been synthesized through various methods, among which the Pictet-Spengler condensation [18-21] is one of the most common methods. In this condensation tryptamines are reacted with aldehydes either in aqueous acidic [18-20] or in aprotic conditions in the presence or absence of acids [21] to yield 1,2,3,4-tetrahydro-β-carbolines which are then oxidized to the β-carbolines.

4-Substituted β-carbolines are shown to be active neurochemical agents in the mammalian brain [16,17]. Although a number of these derivatives have been prepared by various methods [16,22,23], to our knowledge only a few of the 4-methylsubstituted-β-carbolines have been synthesized [23,24].

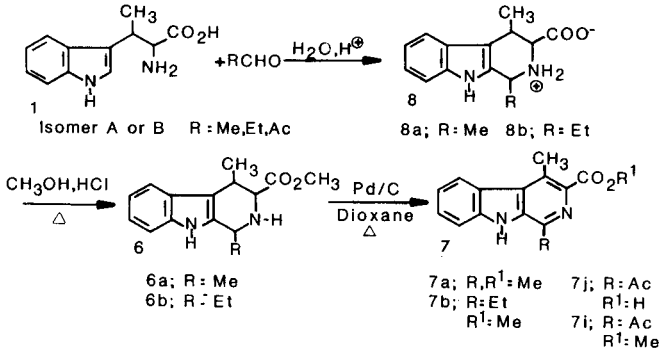
β-Carbolines **7a-i** from β-Methyltryptophan Methyl Ester under Aprotic Nonacidic Conditions (Method I).

β-Methyltryptophan methyl ester (**2A**) was prepared by the modified method and condensed with a number of aldehydes in refluxing toluene, xylene or diglyme under neutral conditions to give diastereomeric 1,2,3,4-tetrahydro-β-carbolines **6** in high yields. Pyruvaldehyde directly gave β-carboline **7i** under these conditions with little or no formation of the tetrahydro derivative **6**. Similar results in the condensation of *dl*-tryptophan with pyruvaldehyde have been reported by Faini and coworkers [25]. The crude mixtures of tetrahydro-β-carbolines were dehydrogenated to give β-carbolines **7**. In addition to the expected β-carboline **7g**, dehydrogenation of **6g** also gave β-carboline **7h** in a ratio of 8:1 (**7g**:**7h**). β-Carboline **7h** will be produced if the evolved hydrogen is catalytically added to the styryl double bond of either **6g** prior to dehydrogenation and/or to **7g**. Tables I and III show the reaction conditions, yields, melting ranges, elemental analyses and nmr data for these products.

β-Carbolines **7a,b,i** from β-Methyltryptophan under Aqueous Acidic Conditions (Method II).

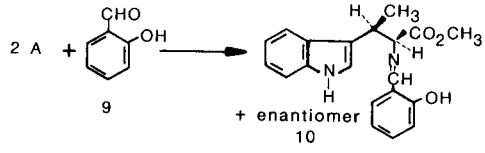
Isomers **A** (2*RS*,3*SR*,**1A**) and **B** (2*RS*,3*RS*,**1B**) of β-methyltryptophan were prepared according to the Snyder and Matteson method [7] and condensed with aldehydes in dilute solutions of sulfuric acid. The resulting Zwitterionic salts **8** of 1,2,3,4-tetrahydro-β-carbolines were converted to the methyl esters **6** by treatment with methanolic hydrogen chloride and then dehydrogenated to β-carbolines **7** [20]. Pyruvaldehyde did not produce the corresponding tetrahydro-β-carbolines **8** and **6** but rather gave β-carboline **7j** which upon methylation afforded β-carboline **7i**. Reactant ratios, yields, melting ranges, elemental analyses and nmr data are giving in Tables II and III.

Method II




As shown in Tables I and III the overall yields of β-carbolines are good to excellent and as expected [21a,b] the aprotic condensation (Method I) gives the products in higher yields than the aqueous acidic condensation (Method II). When salicylaldehyde was condensed with **2A**, the corresponding aldimine **10** and not the cyclic tetrahydro-β-carboline **6** was obtained [21b] (Scheme II).

Scheme II




Method I

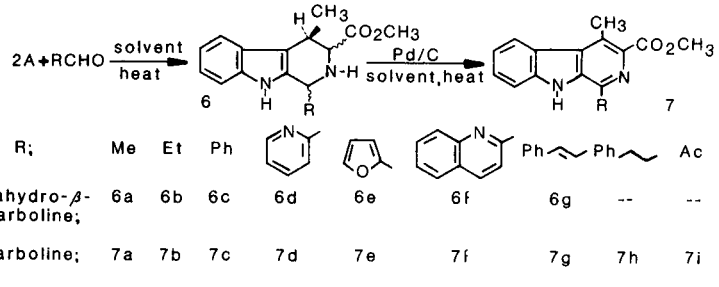
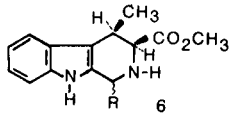
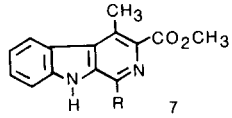


Table I

Tetrahydro-β-carbolines and β-Carbolines Prepared by Method I [a]



6



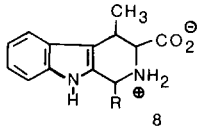
7

| Compound No. | R | Reaction Time (hours) | Yield (%) | Compound No. | R | Reaction Time (hours) [b] | Yield (%) | MP (°C) |
|---|---|---|---|---|---|---|---|---|
| **6a** | $CH_3$ | 24 [c] | 87 | **7a** | $CH_3$ | 10 | 87 | 213-214.5 [d] |
| **6b** | $C_2H_5$ | 4 [e] | 86 | **7b** | $C_2H_5$ | 3 | 87 | 167-169 [d] |
| **6c** | $C_6H_5$ | 2 [b] | 97 | **7c** | $C_6H_5$ | 3 | 85 | 266-267 [f] |
| **6d** | 2-pyridyl | 4 [b] | 95 | **7d** | 2-pyridyl | 3 | 89 | 168-169 [g] |
| **6e** | 2-furyl | 1-½ [b] | 97 | **7e** | 2-furyl | 3 | 95 | 209-210 [d] |
| **6f** | 2-quinolinyl | 16 [b] | 96 | **7f** | 2-quinolyl | 4 | 93 | 197-198 [h] |
| **6g** | styryl | 5 [b] | 88 | **7g** | styryl | 6 | 88 [i] | 172-173 [d] |

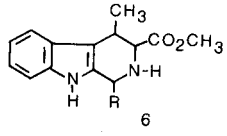
[a] Reaction of pyruvaldehyde with **2A** in refluxing xylene for 10 hours directly produced β-carboline **7i** in 89%, mp 182-184° [b] Refluxing xylene. [c] Refluxing toluene. [d] Purified by silica gel column chromatography. [e] Refluxing diglyme. [f] Recrystallized from ethanol-ethyl acetate. [g] Recrystallized from methanol-ethyl acetate. [h] Recrystallized from dichloromethane-hexane. [i]Dehydrogenation of **6g** gave 88% of a mixture of **7g**:**7h** = 78:10. Compound **7h** was recrystallized from dichloromethane-hexane, mp 172-173°.

Table II

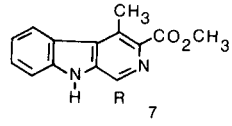
Tetrahydro-β-carbolines and β-Carbolines Prepared by Method II [a]



8



6



7

| Compound No. | R [b] | Yield (%) | Compound No. | R | Yield (%) | Compound No. | R | Isolated Yield (%) [c] | MP (°C) |
|---|---|---|---|---|---|---|---|---|---|
| **8a** | Me | 74 | **6a** | Me | 81 | **7a** | Me | 74 | 213-214.5 |
| **8b** | Et | 80 | **6b** | Et | 71 | **7b** | Et | 65 | 167-169 |

[a] The mole ratios of aldehydes to β-methyltryptophan were 9 to 2. [b] The reaction of pyruvaldehyde with β-methyltryptophan directly gave β-carboline **7j** in 66% yield which upon methylation and dehydrogenation gave **7i**. The yield of **7i** was 26% after silica gel column chromatography. [c] Purified by silica gel column chromatography.

Upon hydrolysis in an aqueous methanol solution in the presence of sulfuric acid at 60° compound **10** produced salicylaldehyde. Attempts to cyclize **10** by heat or heat in the presence of acids failed.

## EXPERIMENTAL

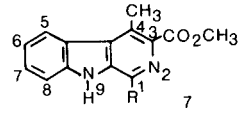
Melting points (uncorrected) were measured with a Thomas Hoover capillary apparatus and are in celcius. Infrared spectra were obtained with a Beckman IR-4250 grating spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian T-60 or FT80A spectrophotometers in deuteriochloroform or DMSO-$d_6$ with tetramethylsilane (TMS) as internal standard. Mass spectra were obtained with a Hewlett-Packard 5980A mass spectrometer at Ball State University or with an AEI MS-902 spectrometer at Baker Laboratories, Cornell University using electron impact ionization. Elemental analyses were performed by Midwest Microlabs, Ltd. or Canadian Microanalytical Service, Ltd.

Methyl 3-(3-Indolyl)-2-nitrobutanoate, 2*SR*,3*RS* Isomer (**5A**).

This compound was prepared according to a modified procedure based on previously known methods [8-10]. In a 1 ℓ three-necked flask equipped with a mechanical stirrer, a nitrogen inlet tube, a Claisen distilling head fitted with a thermometer and a condenser attached to a nitrogen bubbler, a solution of α-methyl-*N*-(1-methylethyl)-1*H*-indole-3-methanamine (**3**) [7] (10.1 g, 0.05 mole) in 125 ml of dry toluene was placed. To this, 5.06 g (0.05 mole) of triethylamine and 5.95 g (0.05 mole) of methyl nitroacetate [26] were added. The solution was stirred under nitrogen at room temperature for 45 minutes then 300 ml of dry toluene was added and the mixture was stirred under a slow stream of nitrogen at

Table III

Analytical and Spectral Data



| Compound No. | R | Molecular Formula | Elemental Analysis Calcd./Found C | H | N | $^1$H NMR (δ ppm) (solvent) |
|---|---|---|---|---|---|---|
| **7a** | $CH_3$ | $C_{15}H_{14}N_2O_2$ | 70.85<br>70.65 | 5.55<br>5.30 | 11.02<br>11.17 | (deuteriochloroform): 2.66 (s, $C_1$-$CH_3$), 3.1 (s, $C_4$-$CH_3$), 3.9 (s, -$OCH_3$), 7.2-7.6 (m, ArH), 8.23 (d, J = 8, ArH) and 9.9 (bs, NH) |
| **7b** | $C_2H_5$ | $C_{16}H_{16}N_2O_2$ | 71.62<br>71.69 | 6.01<br>6.48 | 10.41<br>10.68 | (deuteriochloroform): 1.36 (t, J = 7, $C_1$-C-$CH_3$), 3.06 (s, $C_4$-$CH_3$), 3.08 (q, J = 7, $C_1$-$CH_2$-C), 3.97 (s, -$OCH_3$), 7.2-7.6 (m, ArH), 8.25 (d, J = 8, ArH), 8.87 (bs, NH) |
| **7c** | $C_6H_5$ | $C_{20}H_{16}N_2O_2$ | 75.93<br>75.71 | 5.09<br>5.09 | 8.85<br>8.85 | (deuteriochloroform/deuteriodimethyl sulfoxide): 3.06 (s, $C_4$-$CH_3$), 3.9 (s, -$OCH_3$), 7.1-7.7 (m, ArH), 7.8-8.03 (m, ArH), 8.22 (d, J = 8, ArH), and 11.48 (bs, NH) |
| **7d** | 2-pyridyl | $C_{19}H_{15}N_3O_2$ | 71.91<br>72.01 | 4.76<br>4.81 | 13.24<br>13.14 | (deuteriochloroform): 3.14 (s, $C_4$-$CH_3$), 4 (s, -$OCH_3$), 7.1-8 (m, ArH), 8.3 (d, J = 8, ArH), 8.6-8.95 (m, ArH), and 11.55 (bs, NH) |
| **7e** | 2-furyl | $C_{18}H_{14}N_2O_3$ | 70.58<br>70.38 | 4.60<br>4.52 | 9.14<br>8.99 | (deuteriochloroform/deuteriodimethyl sulfoxide): 3.07 (s, $C_4$-$CH_3$), 3.98 (s, -$OCH_3$), 6.6-6.8 (m, ArH), 7.2-7.9 (m, ArH), 8.3 (d, J = 8, ArH), and 10.76 (bs, NH) |
| **7f** | 2-quinolinyl | $C_{23}H_{17}N_3O_2$ | 75.19<br>75.16 | 4.66<br>4.44 | 11.44<br>11.65 | (deuteriochloroform): 3.13 (s, $C_4$-$CH_3$), 4.05 (s, -$OCH_3$), 7.2-8 (m, ArH), 8.1-8.4 (m, ArH), 8.86 (d, J = 8, ArH) and 11.82 (bs, NH) |
| **7g** | $C_6H_5CH=CH$ | $C_{22}H_{18}N_2O_2$ | 77.17<br>76.65 | 5.29<br>5.31 | 8.18<br>7.81 | (deuteriochloroform): 2.9 (s, $C_4$-$CH_3$), 3.86 (s, -$OCH_3$), 6.8-7.25 (m, ArH and -CH=CH-), 8.1 (d, J = 8, ArH) and 9.3 (bs, NH) |
| **7h** | $C_6H_5CH_2CH_2$ | $C_{22}H_{20}N_2O_2$ | 76.74<br>76.44 | 5.81<br>5.83 | 8.13<br>8.07 | (deuteriochloroform): 3.05 (s, $C_4$-$CH_3$), 3.1-3.4 (m, -$CH_2$-$CH_2$-), 3.92 (s, -$OCH_3$), 6.9-7.2 (m, ArH), 7.2-7.5 (m, ArH), 8.23 (d, J = 8, ArH) and 8.56 (bs, NH) |
| **7i** | $CH_3C=O$ | $C_{16}H_{14}N_2O_3$ | 68.07<br>67.97 | 5.00<br>4.81 | 9.92<br>9.8 | (deuteriochloroform): 2.86 (s, $CH_3CO$), 3.1 (s, $C_4$-$CH_3$), 4.02 (s, -$OCH_3$), 7.1-8.1 (m, ArH), 8.18 (d, J = 8, ArH), and 10.22 (bs, NH) |

95-105° for 10 hours. The toluene solution was washed with 5% hydrochloric acid solution (3 × 100 ml), then with water (5 × 100 ml) and was then dried (magnesium sulfate). Evaporation of the solvent on a rotoevaporator and then on a vacuum pump at 60° overnight gave 12.2 g (93%) of a brown solid. $^1$H nmr analysis showed it to contain two isomers [2*RS*,3*SR* (**5A**) and 2*RS*,3*RS* (**5B**)] in the ratio of 2:1 [12]. Recrystallization of this mixture from chloroform-hexane (60:40) gave 11.34 g (86% overall, mp 107.5-109°) of pure **5A**; ir (chloroform): ν 3475, 3120, 3020, 1758, 1560 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.54 (d, 3H, J = 7 Hz), 3.5 (s, 3H), 4.15 (m, 1H), 5.37 (d, 1H, J = 9 Hz), 6.9-7.3 (m, 4H), 7.37-7.67 (m, 1H), 8.07 (bs, 1H). The nmr signals of **5B** are nearly superimposable on those of **5A** except for its methoxy singlet and α-H doublet signals which appear at 3.75 and 5.44 ppm respectively; ms: m/e 262, 216, 188, 170, 160, 156, 144, 130, 115.

*Anal.* Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.32; H, 5.19; N, 10.92.

Methyl 2-Amino-3-(3-indolyl)butanoate, β-Methyltryptophan Methyl Ester (**2A**; 2*RS*,3*SR* isomer).

In a 500 ml heavy-walled flask containing a magnetic bar, 75 ml of an ice-cooled solution of 5.2 g (45.6 mmoles) of trifluoroacetic acid in absolute ethanol was placed and then ground nitroester **5A** (3.00 g, 11.4 mmoles) was added. The mixture was stirred for 30 minutes until all or nearly all of the solid was dissolved. The magnetic bar was removed and then 9 g of freshly prepared Ra-Ni (W-4) [27] or commercial Raney nickel was added and hydrogenation was carried out at 40 psi (~ 2.75 atm) at room temperature until hydrogen absorption ceased (~ 1 hour) [28]. The reaction mixture was filtered through a layer of celite, washed with 3 × 50 ml of absolute ethanol [29] and the filtrate was evaporated under vacuum. To the resulting material 100 ml of ether and 100 ml of water containing 3.5 g of sodium carbonate were added. After stirring for 30 minutes the ether layer was separated and the aqueous layer extracted with 4 × 50 ml of ether. The combined ether extract was washed with 50 ml of water, 50 ml of 10% ammonium chloride solution, dried (magnesium sulfate), and evaporated to give 2.530 g (96%) of nearly pure amino ester **2A** (**2A**:**2B** = 97:3). Recrystallization with ethyl acetate gave pure **2A**, mp 118-120; ir (chloroform): ν 3475, 3380, 3120, 2990, 1738 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.28 (d, 3H, J = 6.5 Hz), 1.41 (br s, 2H), 3.58 (m, 1H), 3.63 (s, 3H), 3.85 (d, 1H, J = 4 Hz), 6.7-7.2 (m, 4H), 7.3-7.7 (m, 1H), 8.17 (bs, 1H); ms: m/e 232, 144.

*Anal.* Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.31; H, 6.64; N, 12.29.

Methyl Esters of Isomers **A** (2*RS*,3*SR*) and **B** (2*RS*,3*RS*) of β-Methyltryptophan (**2A** and **2B**).

β-Methyltryptophan [7] isomer **A** or **B** (0.510 g, 2.35 mmoles) was dissolved in 60 ml of saturated methanolic hydrogen chloride solution and refluxed under nitrogen for 10 hours. The reaction mixture was allowed to cool to room temperature, concentrated to about 3 ml, basified with 14% aqueous ammonium hydroxide (*p*H ~ 9) and extracted with ethyl acetate (5 × 25 ml). The combined extracts were dried (magnesium sulfate) and then evaporated to give a brown solid (0.503 g, 93%). This

material was recrystallized with ethyl acetate. Isomer **A** ester had mp 121-122°, mixed mp with **2A**, 118-120°. The $^1$H nmr was the same as that of **2A**. Isomer **B** ester had mp 115-118°, mixed mp with **2A**, 102-112°; $^1$H nmr (deuteriochloroform): δ 1.41 (d, 3H, J = 6.5 Hz), 1.58 (br s, 2H), 3.3-3.8 (m, 2H), 3.58 (s, 3H), 6.86-7.27 (m, 4H), 7.33-7.67 (m, 1H), 8.2 (bs, 1H).

Method I. β-Carbolines from β-Methyltryptophan Methyl Ester in Aprotic Conditions.

β-Carbolines described in Table I were synthesized according to the following procedures used for the synthesis of **6d** and **7d** [21a,b].

3-Carbomethoxy-4-methyl-1-(2-pyridyl)-1,2,3,4-tetrahydro-β-carboline (**6d**).

To a magnetically stirred solution of β-methyltryptophan methyl ester (**2A**, 1.0 g, 4.3 mmoles) in 50 ml of warm (60°) dry xylene under nitrogen freshly distilled pyridine-2-carboxaldehyde (0.92 g, 8.6 mmoles) was added and the mixture was refluxed for 4 hours. Evaporation of the solvent gave 1.31 g (95%) of a yellow oily material. Tlc analysis (silica gel, petroleum ether-ethyl acetate, 1:1) showed two spots ($R_f$ = 0.56 and (0.60) corresponding to the two diastereomers of tetrahydro-β-carboline **6d**.

3-Carbomethoxy-4-methyl-1-(2-pyridyl)-β-carboline (**7d**).

To a solution of 1.31 g (4.08 mmoles) of crude mixture **7d** in 50 ml dry xylene 1.5 g 10% Pd/C was added and the mixture refluxed for 3 hours under nitrogen. The reaction mixture was filtered off, the black mass was washed with 50 ml of hot xylene and the filtrate evaporated to give 1.21 g (94%) of **7d** as a yellow oil. Trituration of this material with a mixtue of benzene-methanol (1:50) gave a solid material which was recrystallized with methanol-ethyl acetate, mp 168-169°; ir (chloroform): ν 3360, 3010, 2960, 1710 cm$^{-1}$; ms: m/e 317, 285, 259, 258, 257, 229, 78, 77, 52. Elemental analysis and the $^1$H nmr data are given in Table III.

Method II. β-Carbolines from β-Methyltryptophan in Aqueous Acidic Conditions.

β-Carbolines **7a,b,i** (Table II) were prepared according to the following procedures described for the synthesis of **8a**, **6a**, and **7a**. β-Carboline **7i** was obtained in the esterification step and consequently the dehydrogenation step was not necessary.

3-Carboxy-1,4-dimethyl-1,2,3,4-tetrahydro-β-carboline, (Zwitter ion **8a**).

To a stirred suspension of 0.982 g (4.5 mmoles) of β-methyltryptophan (isomer **A**) in 20 ml of 0.005 *M* aqueous sulfuric acid solution under nitrogen, 0.91 g (20.7 mmoles) of acetaldehyde was added *via* a syringe. The resulting solution was stirred at 25° for 14-18 hours. The light grey precipitate was filtered off and dried under vacuum at 60° to give 8.12 g (74%, mp 272-278°) of **8a**.

3-Carbomethoxy-1,4-dimethyl-1,2,3,4-tetrahydro-β-carboline (**6a**).

A solution of **8a** (0.7 g, 2.86 mmoles) in 60 ml of saturated methanolic hydrogen chloride was refluxed under nitrogen for 7½ hours. The reaction mixture was allowed to cool to room temperature and concentrated to approximately 2 ml. The oily residue was basified (*p*H 9) with 14% aqueous ammonia, extracted with ethyl acetate (5 × 25 ml), dried (magnesium sulfate) and evaporated to give 0.604 g (82%) of **6a**) as a dark brown solid.

3-Carbomethoxy-1,4-dimethyl-β-carboline (**7a**).

To a solution of crude **6a** (0.604 g, 2.34 mmoles) in 50 ml of dioxane, 500 mg of 10% Pd/C was added and refluxed under nitrogen for 3½ days. The black suspension was filtered through a layer of celite, washed with 50 ml of hot dioxane and then filtered through a layer of silica gel followed by 50 ml of hot dioxane. The resulting solution was evaporated and dried at 50° overnight under vacuum to give 0.52 g (87%) of **7a**. Thin layer chromatography (silica gel, ethyl acetate-petroleum ether 1:1) showed a predominant fluorescent spot ($R_f$ = 0.21). Flash chromatography (ethyl acetate-petroleum ether, 1:1) afforded 0.44 g (74%) of pure **7a**. Recrystallization with chloroform-petroleum ether gave a white solid (mp 213-214.5°); ir (dichloromethane): 3340, 3075, 2990, 1710 cm$^{-1}$; ms: m/e 254, 222, 196, 194, 168, 98; $^1$H nmr and elemental analysis data are given in Table III.

Methyl 2-(2-Hydroxybenzaldimino)-3-(3-indolyl)butanoate (**10**).

To a magnetically stirred solution of **2A** (1.0 g, 4.3 mmoles) in 250 ml of dry xylene under nitrogen 0.52 g (4.3 mmoles) of freshly distilled salicylaldehyde was added and the mixture refluxed for 3 hours. Evaporation of the solvent and trituration of the green-yellow oil with a mixture of hexane-petroleum ether (5:2) gave a green-yellow crystalline material (1.39 g, 97%). Thin layer chromatography analysis (silica gel, petroleum ether-ethyl acetate, 3:1) showed a single spot ($R_f$ = 0.54). An analytical sample was obtained by recrystallization with ethyl acetate, mp 138-140°; ir (paraffin oil): 3363, 1730, 1626 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 1.39 (d, 3H), 3.69 (s, 3H), 3.8-4.08 (m, 1H), 4.2 (d, 1H), 6.66-7.43 (m, 9H), 7.43-7.73 (m, 1H), 7.6 (s, 1H), 7.87 (bs, 1H); ms: m/e 336, 219, 144, 132, 117, 115, 78.

*Anal.* Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.48; H, 6.02; N, 8.43.

Acknowledgements.

The financial support of this work by the National Institute of Health (GM 37491), the Research Corporation, ACS-PRF and the Indiana Academy of Science is gratefully acknowledged. We are indebted to Professor James M. Cook of the University of Wisconsin at Milwaukee and Professors Lynn R. Sousa and Terry L. Kruger of Ball State University for their helpful discussions.

## REFERENCES AND NOTES

[1] Presented in part at the "194th ACS National Meeting", New Orleans, Louisiana, August 30-September 4, 1987.

[2] Ball State University Honors College Undergraduate Fellows.

[3] J. C. Sheehan, J. D. Mania, S. Nakamura, J. A. Stock, and K. Maeda, *J. Am. Chem. Soc.*, **90**, 462 (1968).

[4] S. J. Gould, C. C. Chang, D. S. Darling, J. D. Roberts, and M. Squillacote, *J. Am. Chem. Soc.*, **102**, 1707 (1980)

[5] T. W. Doyle, D. M. Balitz, R. E. Glurich, D. E. Nettleton, S. J. Gould, Chou-hong Tann, and A. E. Moews, *Tetrahedron Letters*, **26**, 4595 (1981).

[6] K. F. Turchin, M.N. Preobrazhenskaya, L. A. Savel'eva, E. S. Belen'kaya, N. P. Kostyuchenko, Yu. N. Sheinker, and N. N. Suvorov, *Zh. Org. Khim.*, **7**, 1290 (1971).

[7] H. Snyder and D. Matteson, *J. Am. Chem. Soc.*, **79**, 2217 (1957).

[8] D. A. Lyttle and D. I. Weisblat, *J. Am. Chem. Soc.*, **69**, 2118 (1947).

[9] Y. V. Erofeev, V. S. Velezheva, N. K. Genkina, and N. N. Suvorov, *Khim. Geterosikl. Soedin.*, 780 (1978).

[10] A. V. R. Rao, S. P. Chavan, and L. Sivadsan, *Indian J. Chem.*, **23B**, 496 (1984).

[11] For the preparation of **3** the only modification to the literature procedure [7] is to basify the aqueous extract to *p*H ~11 and after the addition of methylcyclohexane allow the mixture to cool for 48 hours in a refrigerator.

[12] In some experiments isomer ratios of 3:1 or even 9:1 are obtained for **5A**:**5B**. Regardless of the isomer ratios recrystallization of the mixtures always produces pure **5A**. The isomer ratios are based on the relative areas of nmr signals of the methoxy protons of **5A**; δ = 3.5 and **5B**; δ = 3.75 ppm.

[13] When a solution of pure **5A** in deuteriochlorform was allowed to stand at room temperature for 11 days, no isomerization of **5A** to **5B** was observed by nmr spectroscopy. However, addition of an equimolar amount of triethylamine to this solution caused an immediate equilibration of the isomers (**5A**:**5B** = 54:46). The interconversion occurs very slowly in the presence of acids. No isomerization was observed when an equimolar amount of trifluoroacetic acid was added to a deuteriochloroform solution of **5A** and allowed to stand at room temperature for two

days. However, after six days some epimerization occurred (**5A**:**5B** = 1/18).

[14] When the hydrogenation was carried out in the absence of acid, the ratio of **2A**:**2B** was 77:23. This indicated that during the reduction as **2A** was formed, it catalyzed the epimerization of the unreacted **5A**.

[15a] R. A. Abramovitch and D. I. Spenser, "Advances in Heterocyclic Chemistry", Vol **3**, Academic Press, New York, 1964, p 79; [b] R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970, p 236; [c] K. Stuart, R. Woo-Ming, *Heterocycles*, **3**, 223 (1975).

[16] J. Toreilles, M.-G. Guerin, and A. Previero, *Biochimie*, **67**, 929 (1985) and references therein.

[17] G. Biggio and E. Costa, *Adv. Biochem. Psychopharmacol.*, **41** 67-106 (1986) and references therein.

[18] W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 151 (1951), also see p 83 ref [15a] and p 236 ref [15b].

[19] F. Ungemach and J. M. Cook, *Heterocycles*, **9**, 1089 (1978).

[20] M. Cain, R. W. Weber, F. Guzman, J. M. Cook, S. A. Baker, R. C. Rice, J. N. Crawley, S. M. Paul and P. Skolnick, *J. Med. Chem.*, **25**, 1081 (1982).

[21a] J. Sandrin, D. Soerens, L. Huchins, F. Ungemach, and J. M. Cook, *Heterocycles*, **4**, 1101 (1976); [b] D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, S. G. Wu, E. Yamanaka, L. Huchins, M. DiPierro, and J. M. Cook, *J. Org. Chem.*, **44**, 535 (1979); [c] F. Ungemach, D. Soerens, R. W. Weber, M. DiPierro, O. Campas, R. Mokry, J. M. Cook, and J. V. Silverton, *J. Am. Chem. Soc.*, **102**, 6976 (1980).

[22] N. Fukuda, M. L. Trudell, B. Johnson, and J. M. Cook, *Tetrahedron Letters*, 2139 (1985).

[23] G. Neef, U. Eder, A. Huth, D. Rahtz, R. Schmiechen, and D. Seidelmann, *Heterocycles*, **20**, 1295 (1983).

[24a] A. S. Kende and F. H. Ebetino, *Tetrahedron Letters*, 923 (1984); [b] S. Hibino, M. Okazaki, M. Iichikawa, K. Sato, and T. Ishizur, *Heterocycles*, **23**, 261 (1985); [c] D. L. Boger, R. S. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.*, **50**, 5790 (1985).

[25] F. Faini, M. Castillo, and R. Torres, *Phytochemistry*, **17**, 338 (1978).

[26] H. Feuer, H. B. Hass, and K. S. Warren, *J. Am. Chem. Soc.*, **71**, 3078 (1949).

[27] A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

[28a] To minimize the amount of water the aqueous suspension of the Commercial Raney nickel was washed with 3 × 10 ml (decanted) of absolute ethanol; [b] The hydrogen pressure drops 1 psi for each gram of **5A**.

[29] To avoid catalyst fire, keep it wet during the filtration and washing steps.