

α -ALKYLTRYPTOPHANS

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Abstract- A study of three direct methods for the synthesis of α -alkyl α -amino acids has been applied to the preparation of α -alkyltryptophan esters. Reaction of N_b -benzylidene-L-tryptophan methyl esters **3** with tetrabutylammonium hydrogen sulfate and methyl or ethyl iodide (phase-transfer method) gives α -methyl and α -ethyltryptophan methyl esters **6a,b** in poor yield with complete racemization. Reaction of L-tryptophan **1** with dimethylformamide dimethyl or diethyl acetal followed by treatment of **8a,b** with LDA and methyl iodide (Fitt and Gschwend method) gives rise to the formation of α, N_a -dimethyl- N_b -dimethylaminomethylenetryptophan methyl or ethyl esters hydriodide **9a,b**. Treatment of **9a** or **9b** with aqueous acid, under mild conditions, fails to hydrolyze the imine functionality. Reaction of **3** with LDA and methyl or ethyl iodide (Bey and Veveret method) followed by hydrolysis provides α -methyl and α -ethyltryptophan methyl esters **6a,b**. By carrying out this procedure with isopropyl, benzyl and allyl iodide or bromide the corresponding α -alkyl esters are not obtained.

In the course of a continuing study of the biological effects of various types of tryptophan derivatives we undertook the preparation of some α -alkyltryptophans, which could conceivably act as serotonin antagonists¹ or as competitive inhibitors of monoamine oxidase¹ by acting as precursors capable of crossing the blood-brain barrier.

The only derivative of α -alkyltryptophans reported to date is α -methyltryptophan. Although several techniques to synthesize this amino acid have been described¹⁻³, all of these methods start from either difficult to obtain or expensive chemical raw materials, such as gramines or other 3-indole derivatives. Recently, Schöllkopf et al.⁴ have reported on the asymmetric synthesis of the methyl (R)- α -methyltryptophanate via lithiated bislactim ethers. By this procedure these authors have described

the asymmetric synthesis of several non-proteinogenic amino acid⁵.

On the other hand, Seebach et al.^{6,7} have developed a stereoselective method of α -alkylations of amino acids through heterocyclic enolates.

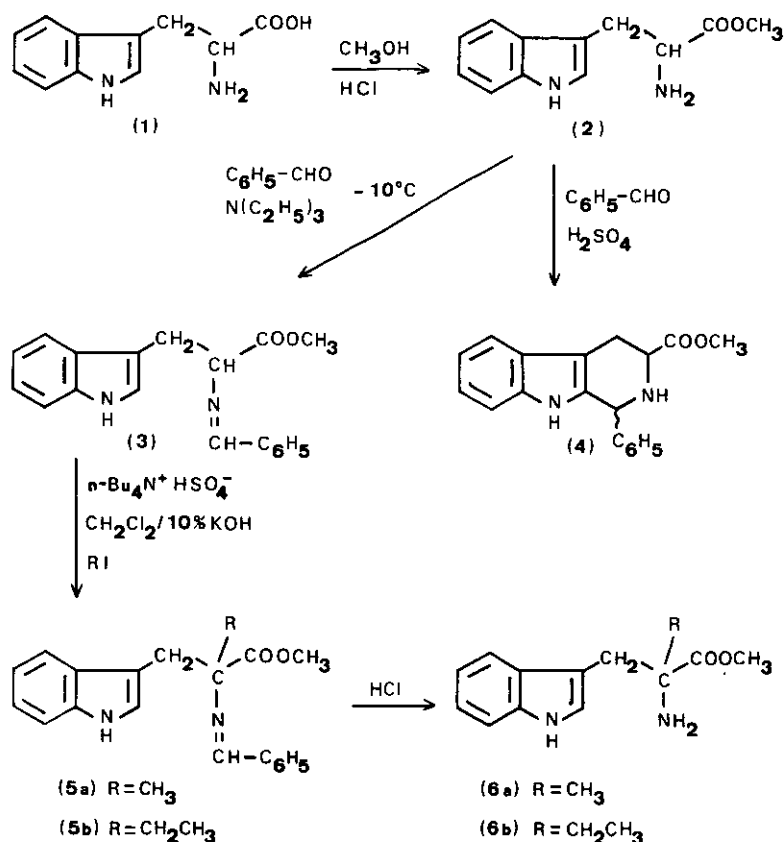
There are three direct methods for the synthesis of α -alkyl α -amino acids in the literature. The procedure reported by Bey and Vever⁸ is based on the direct alkylation of the benzalimine methyl ester of the amino acid. The Fitt and Gschwend⁹ method consists of the reaction between the amino acid and N,N-dimethylformamide dimethyl acetal, followed by alkylation, via carbanion of the methyl ester of the newly formed formamide and imine hydrolysis. The Fitt procedure, described by O'Donnell and coworkers¹⁰, is based on the alkylation of a stable Schiff base of α -amino acid esters by phase transfer reactions. Nevertheless, none of the above mentioned authors utilize their methods to synthesize α -alkyltryptophans.

In a previous work we reported¹¹ on the direct methylation of the lithium derivative of N-benzylidenetryptophan methyl ester. In this work we made the mistake of expecting that the reaction would take place with change of configuration at the chiral center- α -methyltryptophanate, $[\alpha]_D^{20} = -3.89$ (c 0.7, CHCl_3). However, several authors^{4,6,12} have carried out our method and in their hands our procedure gave essentially racemic material. Due to this discrepancy we have repeated the reaction and we have found erratic values of α which evidence that the reaction proceeds with 95% of racemization. In spite of the fact that the synthesis of α -methyltryptophan methyl ester by using the Bey and Vever method⁸ is not stereospecific, it is interesting due to the simplicity of the procedure.

We present in this paper a comparative study of the above mentioned methods in order to ascertain which of them could give the most satisfactory results for the preparation of α -alkyltryptophans.

We first considered the utilization of the phase-transfer method¹⁰. The synthesis (Scheme 1) commenced with the preparation of L-tryptophan methyl ester **2** from L-tryptophan **1** by esterification in methanolic HCl. Treatment of **2** with benzaldehyde in a basic medium provides the N_B-benzylidene-L-tryptophan methyl ester **3**^{11,14}. In this way, no formation of the SS and RS diastereomers of methyl 1-phenyl-1,2,3,4-tetrahydro- β -carboline-3-carboxylate **4**^{14,15} can be chromatographically detected as a byproduct. Only **4** is formed in an acidic medium. The alkylation of **3** is accomplished in a two-phase solvent system (CH_2Cl_2 /10% aqueous KOH) with tetrabutylammonium hydrogen sulfate as the phase-transfer reagent and methyl or ethyl iodide as the alkylating agents. The alkylated Schiff base products **5a,b** are not isolated

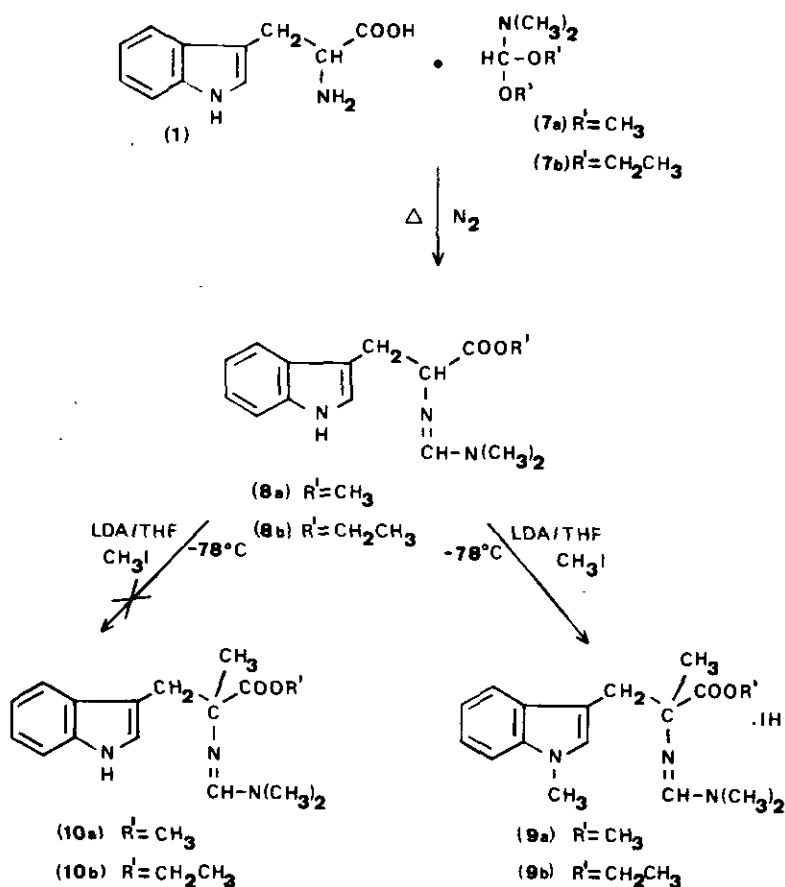
but are hydrolyzed under mild conditions to the α -methyl and α -ethyltryptophan methyl esters **6a,b** in poor yield (procedure A).



Scheme 1

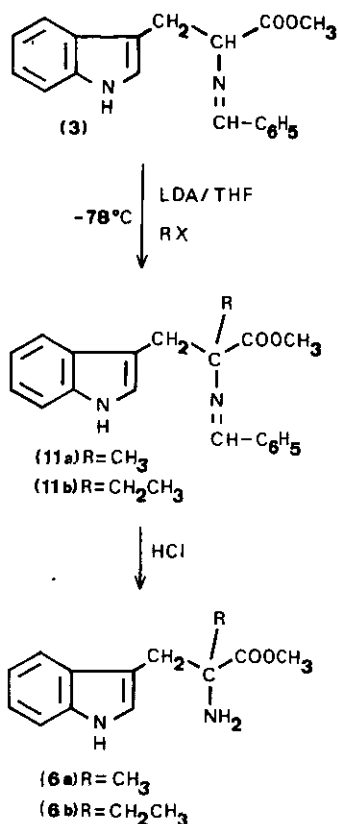
We then considered the Fitt and Gschwend procedure⁹ which permits α -alkylation of the α -amino acid in three steps: (a) simultaneous protection of acid and amine groups with dimethylformamide dialkyl acetal, (b) α -alkylation, and (c) acidic hydrolysis.

Reaction of L-tryptophan **1** with dimethylformamide dimethyl or diethyl acetal **7a,b** leads to the formation of N_b -dimethylaminomethylene-L-tryptophan methyl or ethyl esters **8a,b**. The treatment of this intermediates with lithium diisopropylamide (LDA) and methyl iodide gives rise to the formation of α, N_a -dimethyl- N_b -dimethylaminomethylenetriptophan methyl or ethyl esters hydrogen iodides **9a,b**. No α -methyl- N_b -dimethylaminomethylenetriptophans esters **10a,b** are formed (Scheme 2). Mild acidic hydrolysis of **9a,b** does not lead cleavage of the imine to release the amine functionality.



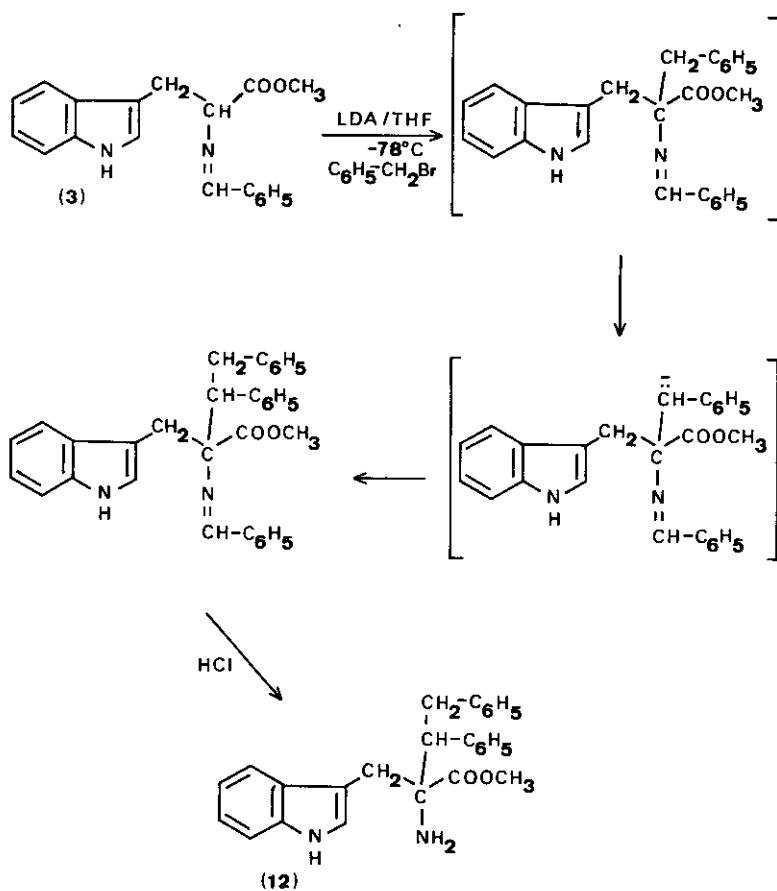
Scheme 2

Finally, we have carried out the method described by Bey and Vever⁸ (Scheme 3). The reactions of N_b -benzylidene-L-tryptophan methyl ester **3** which LDA in THF and methyl or ethyl iodide as alkylating agents provide the intermediates **11a,b**. The α -methyl and α -ethyltryptophan methyl esters **6a,b** are obtained in good yield from **11a,b** via mild acidic hydrolysis (procedure B).



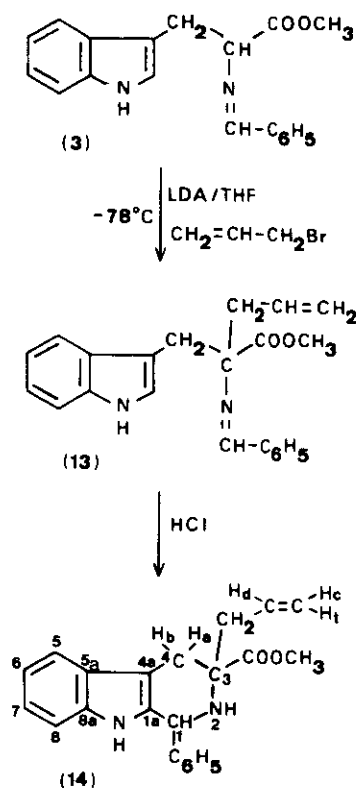
Scheme 3

Because of the promising results obtained in the synthesis of 6a,b by using the Bay Vevert method, other reactions have been carried out in order to prepare the α -isopropyl, α -benzyl and α -allyltryptophan methyl esters. However, in the reaction of 3 with LDA and isopropyl iodide or bromide, the L-tryptophan methyl ester 2 is recovered after treatment with aqueous hydrochloric acid. This is presumably due to the tendency of the isopropyl iodide or bromide to undergo elimination products¹⁶. Treatment of 3 with LDA and benzyl bromide provides α -(1,2-diphenylethyl)tryptophan methyl ester (48%). No α -benzyltryptophan methyl ester is formed (Scheme 4). The formation of 12 could be explained considering the large difference in pK_a values between the indolic and benzylic hydrogens (~ 16 ¹⁷ for acidic NH and ~ 35 ¹⁸ for methylene). Bases such as LDA with high pK_b values act under kinetic control, without discrimination of relative acidities.



Scheme 4

Treatment of 3 with LDA and allyl bromide affords 3-allyl-3-methoxycarbonyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline 14 via intramolecular cyclization of the intermediate 13 in the acidic medium of hydrolysis (Scheme 5). None of the expected α-allyl-tryptophan methyl ester is formed in this reaction.



Scheme 5

EXPERIMENTAL

Melting points were determined on a Büchi apparatus in open capillaries and are uncorrected. Ir spectra were measured on a Perkin-Elmer 781 spectrophotometer. ¹H nmr spectra were recorded on a Varian T-60A (60 MHz) and Varian XL-300 (300 MHz) spectrometers using Me₄Si as an internal standard. ¹³C nmr spectra were obtained on a Varian FT-80A spectrometer. Mass spectra were determined on a Varian MAT-711 spectrometer. The elemental analyses were performed by "Centro Nacional de Química Orgánica", Madrid.

L-Tryptophan Methyl Ester¹³ **2** and N_B-Benzyldiene-L-tryptophan Methyl Ester^{11,14} **3**

Both compounds (**2**, **3**) were obtained according to literature methods.

Methyl 1-Phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate **4**

This compound was obtained in 33% yield according to the reported method¹⁵. mp 190-192 °C (ethanol-water).

General Procedures for the Preparation of α -Alkyltryptophans

Procedure A

A mixture of **3** (3g, 0.01 mol), tetrabutylammonium hydrogen sulfate (3.99g, 0.012 mol), alkyl iodide (0.04 mol) in methylene chloride (25 ml) and 10% aqueous potassium hydroxide (25 ml) was stirred at 50 °C for 4 h. The layers were separated and the organic layer was washed with saturated aqueous NaCl and dried (MgSO_4). The solvent was removed under reduced pressure and the resulting oil was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was made basic with NaHCO_3 , extracted with chloroform and dried (MgSO_4). The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl ether gave the compounds.

Procedure B

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78 °C in a nitrogen atmosphere. Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and the mixture was stirred for 0.5 h. A solution of **3** (4g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Alkyl iodide (0.013 mol) was then added and the mixture was left overnight at room temperature. The lithium iodide was filtered and the solvent was evaporated under reduced pressure. The resulting oil was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was made basic with NaHCO_3 , extracted with chloroform and dried (MgSO_4). The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl ether gave the compounds.

α -Methyltryptophan Methyl Ester **6a**

Procedure A. (0.5g, 16%). Procedure B. (2g, 66%); mp 135-137 °C (cyclohexane); ν (cm^{-1}) (KBr): 3340, 3290 (NH_2), 3140 (NH), 1720 (C=O), 1590 (ArC=C); ^1H nmr (CDCl_3) (δ , ppm): 1.4 (s, 3H, CH_3), 1.9 (s, 2H, NH_2), 2.7 (part A, AB system, $J_{\text{AB}} = 14$ Hz, 1H, CH_2), 3.1 (part B, AB system, $J_{\text{AB}} = 14$ Hz, 1H, CH_2), 3.5 (s, 3H, OCH_3), 6.7-7.2 (m, 5H, ArH), 7.9 (s, 1H, NH); ^{13}C nmr (CDCl_3) (δ , ppm): 26.8 (CH_2), 36.5 ($\alpha\text{-CH}_3$), 52.1 (OCH_3), 59.2 (C_α), 110.8, 111.1, 119.2, 119.5, 122.0, 123.3, 128.2, 136.1 (indole), 178.0 (C=O); MS m/z (rel. intensity %): 232 (M^+ , 0.2), 230 ($\text{M}^+ - \text{H}_2$, 7), 173 ($\text{M}^+ - \text{C}_2\text{H}_3\text{O}_2$, 5), 130 ($\text{M}^+ - \text{C}_4\text{H}_8\text{NO}_2$, 100), 102 ($\text{M}^+ - \text{C}_9\text{H}_8\text{N}$, 17); Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$: C, 67.21; H, 6.94; N, 12.06. Found: C, 66.93; H, 6.72; N, 11.99.

α -Ethyltryptophan Methyl Ester 6b

Procedure A. (0.45g, 14%). Procedure B. (1.45g, 45%); mp 105-106 °C (cyclohexane); ir (ν , cm^{-1}) (KBr): 3340, 3300 (NH_2), 3160 (NH), 1720 (C=O), 1600 ($\text{ArC}=\text{C}$); ^1H nmr (CDCl_3) (δ , ppm): 0.9 (t, 3H, CH_3), 1.4-2.3 (m, 4H, CH_2 , NH_2), 2.9 (part A, AB system, $J_{\text{AB}} = 14$ Hz, 1H, CH_2), 3.3 (part B, AB system, $J_{\text{AB}} = 14$ Hz, 1H, CH_2), 3.7 (s, 3H, OCH_3), 6.9-7.5 (m, 5H, ArH), 8.5 (s, 1H, NH); ^{13}C nmr (CDCl_3) (δ , ppm): 8.6 (CH_3), 33.2 (CH_2), 35.4 ($\alpha\text{-CH}_2$), 52.0 (OCH_3), 63.0 (C_α), 110.2, 111.2, 119.0, 119.4, 121.9, 123.4, 128.1, 136.1 (indole), 177.5 (C=O); Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$: C, 68.26; H, 7.36; N, 11.37. Found: C, 67.97; H, 7.53; N, 11.12.

 N -Dimethylaminomethylene-L-tryptophan Methyl Ester 8a

A suspension of L-tryptophan **1** (4g, 0.02 mol) in dimethylformamide dimethyl acetal **7a** (30 ml) was refluxed under N_2 for 6 h. Methanol was removed by distillation and the reflux continued for an additional 1 h. Excess reagent was distilled and the residue was evaporated under reduced pressure to dryness. Column chromatography (ethyl ether) afforded **8a** (4.2g, 78%); mp 112-115 °C (ethyl ether); ir (ν , cm^{-1}) (KBr): 3340 (NH), 1730 (C=O), 1640 (C=N); ^1H nmr (CDCl_3) (δ , ppm): 2.6 (s, 6H, $\text{N}(\text{CH}_3)_2$), 2.9-3.3 (m, 2H, CH_2), 3.5 (s, 3H, OCH_3), 3.7-4.0 (m, 1H, CH), 6.7-7.5 (m, 6H, 5ArH, $\text{N}=\text{CH}$), 8.2 (s, 1H, NH); ^{13}C nmr (CDCl_3) (δ , ppm): 30.8 (CH_2), 37.1 (NCH_3), 51.7 (OCH_3), 69.3 (CH), 111.3, 111.8, 118.8, 118.9, 121.4, 123.4, 127.6, 136.3 (indole), 156.5 ($\text{CH}=\text{N}$), 174.7 (C=O); Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 66.04; H, 7.14; N, 15.43.

 N -Dimethylaminomethylene-L-tryptophan Ethyl Ester 8b

A suspension of L-tryptophan **1** (4g, 0.02 mol) in dimethylformamide diethyl acetal **7b** (30 ml) was refluxed under N_2 for 6 h. Ethanol was removed by distillation and the reflux continued for an additional 1 h. Excess reagent was distilled and the residue was evaporated under reduced pressure to dryness. Column chromatography (ethyl ether) afforded **8b** (4.7g, 84%); mp 112-114 °C (ethyl acetate); ir (ν , cm^{-1}) (KBr): 3140 (NH), 1720 (C=O), 1640 (C=N); ^1H nmr (CDCl_3) (δ , ppm): 1.2 (t, 3H, CH_3), 2.7 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.1-3.4 (m, 2H, CH_2), 3.9-4.4 (m, 3H, OCH_2 , CH), 6.9-7.7 (m, 7H, 5ArH, $\text{N}=\text{CH}$, NH); ^{13}C nmr (CDCl_3) (δ , ppm): 14.1 (CH_3), 30.8 (CH_2), 37.0 (NCH_3), 60.5 (OCH_2), 69.3 (CH), 111.3, 111.8, 118.7, 118.9, 121.3, 123.4, 127.7, 136.3 (indole), 156.4 ($\text{CH}=\text{N}$), 174.3 (C=O); Anal. Calcd. for $\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_2$: C, 66.87; H, 7.31; N, 14.26. Found: C, 66.67; H, 7.56; N, 14.44.

α ,N_a-Dimethyl-N_b-dimethylaminomethylenetriptophan Methyl Ester Hydriodide 9a

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78 °C under N₂. Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and stirred for 0.5 h. A solution of 8a (3.15g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Methyl iodide (1.8g, 0.013 mol) was then added and the mixture was left overnight at room temperature. The lithium iodide was removed by filtration and the solvent was evaporated under reduced pressure. The resulting oil was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The mixture was neutralized with NaHCO₃, extracted with chloroform and dried over MgSO₄. The solvent was evaporated under reduced pressure providing an oil. Trituration with chloroform gave 9a (0.89g, 18%); mp 150-151 °C (methanol-ethyl ether); ir (ν, cm⁻¹)(KBr): 1730 (C=O), 1690 (C=N), 1610 (ArC=C); ¹H nmr (CDCl₃)(δ, ppm): 2.0 (s, 3H, α-CH₃), 2.8 (s, 3H, NCH₃), 3.1 (s, 3H, NCH₃), 3.5 (s, 2H, CH₂), 3.7 (s, 3H, NCH₃-indole), 3.8 (s, 3H, OCH₃), 6.8-7.9 (m, 6H, 5ArH, N=CH); ¹³C nmr (CDCl₃)(δ, ppm): 24.9 (CH₂), 33.3, 35.2, 38.8 (N(CH₃)₂ and α-CH₃), 44.1 (NCH₃-indole), 53.7 (OCH₃), 65.7 (C_α), 106.8, 109.7, 119.0, 119.7, 122.1, 128.2, 128.9, 136.7 (indole), 154.1 (CH=N), 172.8 (C=O); MS m/z (rel. intensity %): 301 (M⁺ -IH, 2), 242 (M⁺ - C₂H₄O₂I, 15), 157 (M⁺ - C₁₀H₁₁NI, 43), 144 (M⁺ - C₇H₁₄N₂O₂I, 100), 130 (M⁺ - C₈H₁₆N₂O₂I, 28); Anal. Calcd. for C₁₇H₂₄N₃O₂I: C, 47.55; H, 5.59; N, 9.79. Found: C, 47.75; H, 5.81; N, 9.81.

α ,N_a-Dimethyl-N_b-dimethylaminomethylenetriptophan Ethyl Ester Hydriodide 9b

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78 °C under N₂. Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and stirred for 0.5 h. A solution of 8b (3.7g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Methyl iodide (1.8g, 0.013 mol) was then added and the mixture was left overnight at room temperature. The lithium iodide was removed by filtration and the solvent was evaporated under reduced pressure. The resulting oil was treated with 1N-hydrochloric acid (25 ml) for 1h at room temperature. The mixture was neutralized with NaHCO₃, extracted with chloroform and dried over MgSO₄. The solvent was evaporated under reduced pressure providing 9b (2.1g, 37%); mp 156-158 °C (methanol-ethyl acetate); ir (ν, cm⁻¹)(KBr): 1740 (C=O), 1700 (C=N), 1600 (ArC=C); ¹H nmr (Me₂SO-d₆)(δ, ppm): 1.2 (t, 3H, CH₃), 1.9 (s, 3H, α-CH₃), 3.0 (s, 3H, NCH₃), 3.1 (s, 3H, NCH₃), 3.3-3.5 (m, 2H, CH₂), 3.7 (s, 3H, NCH₃-indole), 4.2 (q, 2H, OCH₂), 7.0-8.1 (m, 6H, 5ArH, N=CH); ¹³C nmr (Me₂SO-d₆)(δ, ppm): 13.8 (CH₃),

27.4 (CH_2), 36.4, 41.6, 42.8 ($\text{N}(\text{CH}_3)_2$ and $\alpha\text{-CH}_3$), 44.8 ($\text{NCH}_3\text{-indole}$), 60.1 (OCH_2), 61.4 (C_α), 108.3, 111.4, 118.0, 118.5, 121.1, 124.1, 126.9, 136.0 (indole), 156.3 (CH=N), 170.0 (C=O); MS m/z (rel. intensity %): 315 ($\text{M}^+ - \text{IH}$, 2), 156 ($\text{M}^+ - \text{C}_{11}\text{H}_{14}\text{NI}$, 100), 144 ($\text{M}^+ - \text{C}_8\text{H}_{16}\text{N}_2\text{O}_2\text{I}$, 3), 130 ($\text{M}^+ - \text{C}_9\text{H}_{18}\text{N}_2\text{O}_2\text{I}$, 14); Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_3\text{O}_2\text{I}$: C, 48.76; H, 5.91; N, 9.47. Found: C, 48.55; H, 5.65; N, 9.73.

α -(1,2-Diphenylethyl)tryptophan Methyl Ester 12

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78°C under N_2 . Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and stirred for 0.5 h. A solution of **3** (4g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Benzyl bromide (2.23g, 0.013 mol) was then added and the mixture was left overnight at room temperature. The mixture was evaporated under reduced pressure and the residue was dissolved in chloroform, washed with H_2O twice, dried over MgSO_4 , and evaporated to yield an oil which, was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was neutralized with NaHCO_3 , extracted with chloroform and dried over MgSO_4 . The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl acetate-carbon tetrachloride gave **12** (2.5g, 48%); mp $176\text{--}178^\circ\text{C}$ (ethyl acetate); ir (ν , cm^{-1}) (KBr): 3400, 3320 (NH_2), 1720 (C=O), 1590 (ArC=C); ^1H nmr (CDCl_3) (δ , ppm): 2.4 (s, 2H, NH_2), 2.8–3.3 (m, 4H, 2CH_2), 3.4 (s, 3H, OCH_3), 5.3 (m, 1H, CH), 6.8–7.7 (m, 16H, 15ArH, NH). ^{13}C nmr (CDCl_3) (δ , ppm): 29.8 (t, CH_2), 47.2 (t, $\text{CH}_2\text{-C}_6\text{H}_5$), 51.5 (q, CH_3), 55.4 (d, CH), 64.0 (s, C_α), 107.3 (s), 110.6 (d), 118.1 (d), 119.0 (d), 121.4 (d), 126.8 (d), 126.9 (d), 127.9 (d), 128.2 (d), 128.4 (d), 128.5 (d), 129.7 (d), 134.1 (s), 135.5 (s), 136.2 (s), 142.3 (s) (aromatics), 175.2 (s, C=O); MS m/z (rel. intensity %): 398 (M^+ , 40), 339 ($\text{M}^+ - \text{C}_2\text{H}_3\text{O}_2$, 18), 307 ($\text{M}^+ - \text{C}_7\text{H}_7$, 100), 247 ($\text{M}^+ - \text{C}_9\text{H}_{11}\text{O}_2$, 29), 218 ($\text{M}^+ - \text{C}_{14}\text{H}_{12}$, 48), 169 ($\text{M}^+ - \text{C}_{11}\text{H}_7\text{NO}$, 34), 91 ($\text{M}^+ - \text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_2$, 24); Anal. Calcd. for $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_2$: C, 78.30; H, 6.58; N, 7.03. Found: C, 78.29; H, 6.25; N, 7.05.

3-Allyl-3-methoxycarbonyl-1-phenyl-1,2,3,4-tetrahydro- β -carboline 14

A mixture of diisopropylamine (1.3g, 0.013 mol) in dry THF (20 ml) was cooled to -78°C under N_2 . Methyl lithium (6.5 ml, 0.013 mol) in THF (20 ml) was added and stirred for 0.5 h. A solution of **3** (4g, 0.013 mol) in THF (30 ml) was added and stirred for an additional 0.5 h. Allyl bromide (1.07g, 0.013 mol) was then added and the mixture was left overnight at room temperature. The mixture was evaporated under reduced pressure and the residue was dissolved in chloroform, washed with

H₂O twice, dried over MgSO₄, and evaporated to yield an oil which, was treated with 1N-hydrochloric acid (25 ml) for 1 h at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was neutralized with NaHCO₃, extracted with chloroform and dried over MgSO₄. The solvent was evaporated under reduced pressure providing an oil. Trituration with ethyl acetate-petroleum ether gave 14 (1g, 22%); mp 135-137 °C (ethyl acetate); ir (ν, cm⁻¹)(KBr): 3220, 3160 (NH), 1700 (C=O), 1670 (C=C), 1590, 1550, 1520, 1480 (ArC=C); ¹H nmr (CDCl₃, 300 MHz)(δ, ppm): 2.45 (m, 1H, NH, overlaped with the signal at 2.47), 2.47 (q, 1H, allylic CH, J= 13.6 and 6.5 Hz), 2.67 (q, 1H, allylic CH, J= 13.6 and 6.5 Hz), 2.88 (q, 1H, H_a, J= 15.2 and 2.5 Hz), 3.49 (q, 1H, H_b, J= 15.2 and 1.6 Hz), 3.57 (s, 3H, CH₃), 5.13 (d, 1H, H_c, J= 11.4 Hz), 5.14 (d, 1H, H_t, overlaped with the signal at 5.13, J= 15.7 Hz), 5.36 (s, 1H, CH-C₆H₅), 5.77 (m, 1H, H_d), 7.02-7.53 (m, 10H, ArH, NH-indole); ¹³C nmr (CDCl₃)(δ, ppm): 29.3 (t, C₄), 45.0 (t, allylic CH₂), 51.7 (q, CH₃), 55.4 (d, C₁), 62.7 (s, C₃), 107.4 (s, C_{4a}), 110.6 (d, C₈), 118.0 (d, C₅), 119.0 (t, =CH₂), 119.3 (d, C₆), 121.4 (d, C₇), 126.8 (s, C_{5a}), 127.9 (d, C_p-phenyl), 128.4 (d), and 128.5 (d)(C_o and C_m-phenyl), 131.9 (d, =CH), 134.1 (s, C_{1a}), 136.2 (s, C_{8a}), 142.2 (s, C₁-phenyl), 175.5 (s, C=O); MS m/z (rel. intensity %): 346 (M⁺, 78), 305 (M⁺-C₃H₅, 94), 246 (M⁺-C₅H₈O₂, 53), 219 (M⁺-C₆H₉NO₂, 64), 218 (M⁺-C₆H₁₀NO₂, 100), 169 (M⁺-C₁₁H₁₅NO, 72); Anal. Calcd. for C₂₂H₂₂N₂O₂: C, 76.27; H, 6.70; N, 8.08. Found: C, 76.46; H, 6.54; N, 7.96.

ACKNOWLEDGEMENT

We thank the Comisión Asesora de Investigación Científica y Técnica (CAICYT) for financial support.

REFERENCES

1. R.V. Heinzelman, W.C. Anthony, D.A. Lyttle, and J. Szmuszkowicz, J. Org. Chem., 1960, 25, 1548.
2. K. Pfister and W.J. Leanza, U.S. Patent, 1956, 2,766,255. Chem. Abstr., 1956, 51, 6702.
3. M. Suzuki, T. Miyahara, R. Yoshika, M. Miyoshi, and K. Matsumoto, Agr. Biol. Chem., 1974, 38, 1709.
4. U. Schöllkopf, R. Lonsky, and P. Lehr, Liebigs Ann. Chem., 1985, 413.
5. U. Schöllkopf, W. Hartwig, and U. Groth, Angew. Chem., 1979, 91, 922; Angew. Chem. Int. Ed. Engl., 1979, 18, 863; U. Schöllkopf, W. Hartwig, U. Groth, and K.O. Westphalen, Liebigs Ann. Chem., 1981, 696; U. Schöllkopf, U. Groth, K.O. Westpha-

- len, and C. Deng, Synthesis, 1981, 969; U. Schöllkopf, H.J. Neubauer, and M. Hauptreif, Angew. Chem., 1985, 97, 1065; Angew. Chem. Int. Ed. Engl., 1985, 24, 1066; U. Schöllkopf, D. Pettig, U. Busse, E. Egert, and M. Dyrbusch, Synthesis, 1986, 737.
6. D. Seebach and D. Wasmuth, Angew. Chem., 1981, 93, 1007.
 7. D. Seebach, J.D. Aebi, R. Naef, and Th. Weber, Helv. Chim. Acta, 1985, 68, 144; D. Seebach, D.D. Miller, St. Müller, and Th. Weber, Helv. Chim. Acta, 1985, 68, 949; J.D. Aebi and D. Seebach, Helv. Chim. Acta, 1985, 68, 1507; R. Fitzi and D. Seebach, Angew. Chem., 1986, 98, 363; Angew. Chem. Int. Ed. Engl., 1986, 25, 345.
 8. P. Bey and J.P. Vever, Tetrahedron Lett., 1977, 17, 1455.
 9. J.J. Fitt and H.W. Gschwend, J. Org. Chem., 1977, 42, 2639.
 10. M.J. O'Donnell, J.M. Boniece, and S.E. Earp, Tetrahedron Lett., 1978, 30, 2641; M.J. O'Donnell, B. LeClef, D.B. Rusterholz, L. Ghosez, J.P. Antoine, and M. Navarro, Tetrahedron Lett., 1982, 23, 4259.
 11. M.F. Braña, M. Garrido, M.L. López, and A.M. Sanz, J. Heterocyclic Chem., 1980, 17, 829.
 12. G.M. Anantharamaiah and R.W. Roeske, Tetrahedron Lett., 1982, 23, 3335.
 13. Y. Kanoaka, E. Sato, and Y. Ban, Chem. Pharm. Bull., 1967, 15, 101.
 14. J. Sandri, D. Soerens, L. Hutkins, E. Richfield, F. Ungemach, and J.M. Cook, Heterocycles, 1976, 4, 1101; R. Grigg, H.Q.N. Gunaratne, and E. McNaghten, J. Chem. Soc. Perkin Trans. 1, 1983, 185; M. Jawdosiuk and J.M. Cook, J. Org. Chem., 1984, 49, 2699.
 15. H.R. Snyder, C.H. Hansch, L. Katz, S.M. Parmerter, and E.C. Spaeth, J. Am. Chem. Soc., 1948, 70, 219.
 16. T.H. Lowry and K.S. Richardson, "Mechanism and Theory in Organic Chemistry". Harper and Row, Publishers. New York, 1981, chapter 7, p. 554.
 17. R.E. Dessy, W. Kitching, T. Psarras, R. Salinger, A. Chem, and T. Chivers, J. Am. Chem. Soc., 1966, 88, 460; R. Streitwieser, S. Granger, R. Mares, and P. Wolf, J. Am. Chem. Soc., 1973, 95, 4257.
 18. N.L. Allinger, M.P. Cava, D.C. Jongh, C.R. Johnson, N.A. Lebel, and C.L. Stevens, "Química Orgánica" Ed. Reverté. Barcelona, 1975, p. 375.

Received, 23rd March, 1987