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A new synthesis of α-methyl-L-tryptophan as the methyl ester derivative is described. This method is an improvement over previous methods.

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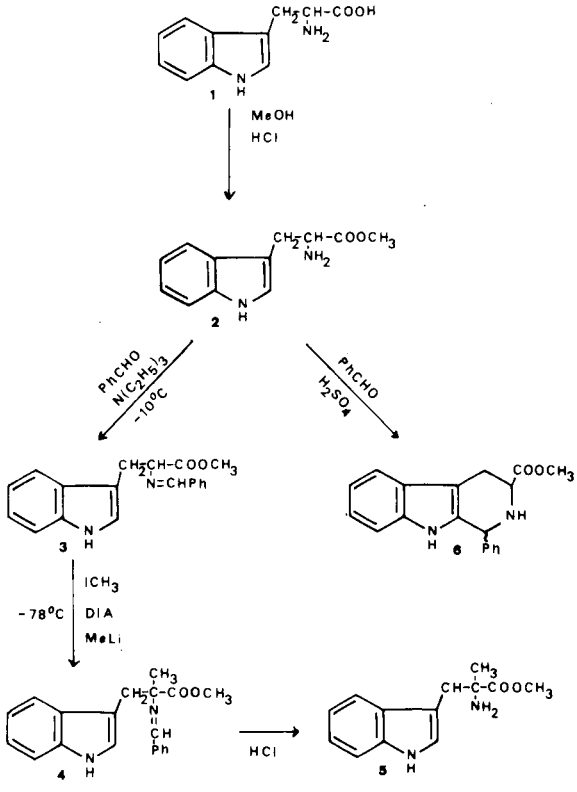
In some mental disturbances it is well known that the brain serotonin levels are abnormally low (1). For this reason a great deal of research has been devoted (2) to the chemical synthesis of α-alkyltroptophans, which might prove to be effective competitive inhibitors of the peripheric 5-hydroxytryptophan decarboxylase. This work is similar to research concerning other therapeutically interesting aminoacids such as L-Dopa (3). Although several techniques to synthetize α-alkyltryptophans have been described, all of these methods start from either difficult to obtain or expensive chemical raw materials, such as the gramines or other 3-indole derivatives (2,4a-b).

In 1977 two methods were described for the synthesis of α-alkylamino acids. The first of these methods was reported by Fitt and Gschend (5) and is based on the reaction between the amino acid and *N,N*-dimethylformamide dimethylacetal, followed by alkylation, *via* the carbanion, of the methyl ester of the newly formed formamide. The second method, described by Bey and Vevert (6), begins with the benzaldimine methyl ester of the amino acid, which is readily available *via* two steps. This ester, on reaction with methyl iodide in the presence of lithium diisopropylamidure, is alkylated. Both of these methods do not change the configuration of the chiral carbon due to the anchimeric assistance of the imine nitrogen (5). Nevertheless, none of the above mentioned authors makes use of their methods to synthetize α-methyltryptophan. We now report the application of the second method metnioned above, being somewhat less expensive than the first, to synthetize α-methyltryptophan according to the following scheme.



L-Tryptophan (**1**) was esterified, as described (7), with methanol in an acid medium. Thus, the corresponding methyl ester (**2**) was obtained. Benzaldimine (**3**) was obtained by treating **2** with benzaldehyde in a basic medium, and could be methylated by treating with diisopropylamine and methyl lithium followed by reaction with methyl iodide to give **4**. The α-methyl-L-tryptophan methyl ester (**5**) was obtained from **4** *via* mild acid hydrolysis. Starting from L-tryptophan, this technique gives the desired product in 40% overall yield. In this way, no formation of β-carboline (**6**), which is a mixture of the *SS* and *RS* diastereomers, can be chromatographically detected as a by-product. Only **3** is formed in an acid medium.

The α-methyltryptophan methyl ester (**5**) is a good pro-drug for pharmaceutical study. It is easily manageable due to its lacking of hygroscopicity *versus* free acid. This method provides a possible starting point for the synthesis of other α-alkylated tryptophan derivatives.

EXPERIMENTAL

The melting points were obtained on a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 257 spectrograph (potassium bromide discs). The nmr spectra were taken on a Varian T-60A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The mass spectra were run on a Varian Model MAT 7111 spectrometer; specific optic activity, [α], has been valued on a

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Perkin-Elmer Model 141 polarimeter. The elemental analysis were performed by "Centro Nacional de Química Orgánica", Madrid.

L-Tryptophane Methyl Ester (**2**).

This compound was obtained in 80% yield according to the literature reported method (7), m.p. 89-90°.

Method 1-Phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (**6**).

This compound was obtained in 33% yield according to the literature reported method (8), m.p. 190-192°.

Benzaldimine of L-Tryptophane Methyl Ester (**3**).

A mixture of compound **2** (3 g., 13 mmoles) in 20 ml. of triethylamine was cooled at -10°. A mixture of benzaldehyde (1.37 g., 13 mmoles) in 25 ml. of triethylamine was then slowly added while stirring. After the addition was completed the mixture was stirred, keeping the temperature between -10 and -5°, for an additional 4 hours. After warming to room temperature, the mixture was treated with solid potassium hydroxide and the solvent was removed *in vacuo* giving an oil, which on trituration with ethyl ether gave **3** (2.89 g., 66%), m.p. 124-126° (benzene-cyclohexane); nmr (deuteriochloroform): δ ppm 3.30 (m, 2, CH_2), 3.65 (s, 3, CH_3), 4.15 (m, 1, CH), 6.65-7.70 (m, 11, 10 ArH, 1 CH=N), 7.90 (s-broad, 1, NH); ir ν cm^{-1} 3160 (NH), 1740 (C=O), 1620 (N=C), 1580 (C=C); ms: m/e 306 (10, M^+), 130 (100).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.48; H, 5.92; N, 9.14. Found: C, 74.32; H, 5.99; N, 8.97.

α-Methyl-L-tryptophan Methyl Ester (**5**).

A mixture of diisopropylamine (1.31 g., 13 mmoles) in 15 ml. of dry tetrahydrofuran was cooled to -78° in a nitrogen atmosphere. Methyl lithium (6.5 g., 13 mmoles) in 20 ml. dry tetrahydrofuran was then slowly added and the mixture was stirred for 0.5 hour. Then, **3** (4 g., 13 mmoles) in 30 ml. of dry tetrahydrofuran was added and stirring was continued for an additional 0.5 hour. Methyl iodide (1.8 g., 13 mmoles) was then added and the mixture was left overnight at room temperature. The lithium iodide which formed was removed by filtration and the solvent was evaporated *in vacuo*. The resulting oil was treated with 25 ml. of 1*N* hydrochloric acid for 1 hour at room temperature. The reaction mixture was washed with ethyl ether, and the aqueous phase was made basic with sodium bicarbonate, extracted with chloroform and dried (anhydrous magnesium sulphate). The solvent was evaporated *in vacuo* providing an oil. Trituration with ethyl ether gave 2 g. (66%) of **5**, m.p. 135-137° (cyclohexane); nmr (deuteriochloroform): δ ppm 1.40 (s, 3, CH_3), 1.95 (s, 2, NH_2), 3.15 (d, 2, CH_2), 3.50 (s, 3, CH_3), 6.70-7.20 (m, 5, ArH), 7.00 (s-broad, 1, NH); ir: ν cm^{-1} 3320, 3290 (NH_2), 1720 (C=O), 1590 (C=C); ms: m/e 232 (0.2, M^+), 230 (7), 130 (100), 102 (16); $[\alpha]_D^{30}$ -3.8° (chloroform).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.21; H, 6.94; N, 12.06. Found: C, 66.93; H, 6.72; N, 11.99.

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