[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Synthesis of 6-Methylindole and *dl*-6-Methyltryptophan

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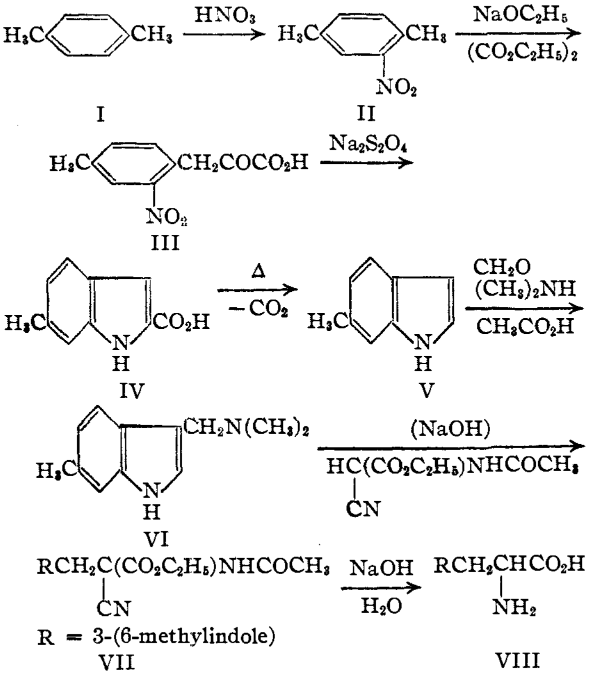
In connection with studies of possible antimetabolites related to the amino acids it was of interest to prepare *dl*-6-methyltryptophan,[1b] which apparently has not been previously reported. The synthesis has been accomplished as indicated in the accompanying diagram. The preparation of the intermediate 6-methylindole (V) by a method similar to that used here has been indicated previously,[1c] but the substance was not characterized.



p-Xylene (I) was mononitrated by a modification of the procedure of Brand and Mahr[2] to give 2-nitro-1,4-dimethylbenzene (II) in excellent yield (about 90%). The nitro compound condensed readily with ethyl oxalate in the presence of sodium ethoxide to give 2-nitro-4-methylphenylpyruvic acid (III).[1c] The general method of Reissert has been used by other investigators in similar condensations of ethyl oxalate with activated methyl groups.[3] Certain workers[3a,b,c,d,e,f,g,h] have preferred to use potassium ethoxide as the condensing agent for this reaction, but the use of this reagent possesses obvious disadvantages for large scale preparations.

Reduction of the nitro group and simultaneous ring-closure occurred when III was treated with hydrosulfite. The product thus formed, 6-methylindole-2-carboxylic acid (IV), was readily decarboxylated by heating at 230–240°. The decarboxylation product, 6-methylindole (V), was obtained in good yield (about 60%) only when very pure IV was used. A similar observation has been made in connection with the decarboxylation of indole-2-carboxylic acid.[3f] 6-Methylindole is a liquid at ordinary temperatures.

The Mannich reaction on 6-methylindole (V) by the method of Kühn and Stein[4] for the preparation of gramine led to the formation of 6-methylgramine [6-methyl-3-(dimethylaminomethyl)-indole, VI]. Alkylation of ethyl acetaminocyanoacetate[5] by 6-methylgramine (VI) in the presence of sodium hydroxide was found to occur readily and in good yield (about 80%). An aqueous suspension of the alkylation product, ethyl α-acetamino-α-cyano-β-[3-(6-methyl)-indole]-propionate (VII) was hydrolyzed by Albertson's procedure[6] to yield *dl*-6-methyltryptophan (VIII).

Experimental[7,8]

2-Nitro-1,4-dimethylbenzene II.—Three hundred and seventy-five grams of fuming nitric acid (sp. gr. 1.5) was added, dropwise, over a five-hour period to 150 g. of *p*-xylene (I). The rate of addition was regulated to maintain a temperature of 5–7° in the vigorously stirred reaction mixture which was cooled externally by an ice-salt-bath. The first few milliliters of nitric acid were added while the *p*-xylene was at 15° to prevent freezing of the reaction mixture (m. p. of *p*-xylene is 14°). Darkening of the reaction mixture and evolution of heat indicated that nitration had been initiated. Precautions were observed since the reaction frequently was slow in starting. When all the nitric acid had been added the dark mixture was poured onto 1 kg. of ice. Then 500 ml. of ether was added, and the spent acid was discarded. The ethereal solution was freed of acid by several water and bicarbonate extractions, dried over magnesium sulfate, treated with Norite and filtered. The ether was removed at atmospheric pressure and the yellow residual oil was fractionally distilled. The forerun, 14.5 g., b. p. 20–64° (0.35 mm.) consisted mainly of *p*-xylene. The main fraction, 191.0 g., b. p. 64–65° (0.35 mm.) consisted of pure II, yield 89.4%. A small amount of tarry residue (27 g.) remained in the distilling flask. Brand and Mahr[2] reported a yield of 62% for the preparation of II.

2-Nitro-4-methylphenylpyruvic Acid (III).—To a stirred solution prepared from 75 ml. of absolute ethanol and 4.6

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(1) (a) Present address: Chas. A. Pfizer and Co., Inc., Brooklyn, N. Y. (b) After this manuscript was submitted, a synthesis of 6-methyltryptophan was reported by Rydon (*J. Chem. Soc.*, 705 (1948)) from 6-methylgramine and acetaminomalonic ester; the 6-methylindole employed was prepared from formyl *p*-xylidine by the method of Marion and Oldfield [*Can. J. Research*, **25B**, 1 (1947)]; (c) Reissert, *Ber.*, **30**, 1030 (1897).

(2) Brand and Mahr, *J. prakt. Chem.*, [2] **142**, 163 (1935).

(3) (a) Mayer and Balle, *Ann.*, **403**, 188 (1914); (b) Wislicenus and Thoma, *ibid.*, **436**, 45 (1924); (c) Maurer and Moser, *Z. physiol. Chem.*, **161**, 131 (1926); (d) Cornforth and Robinson, *J. Chem. Soc.*, 681 (1942); (e) Harvey and Robson, *ibid.*, 97 (1938); (f) Elks, Elliot and Hems, *ibid.*, 630 (1944); (g) Di Carlo, THIS JOURNAL, **66**, 1420 (1944); (h) Snyder, Parmerter and Katz, *ibid.*, **70**, 222 (1948).

(4) Kühn and Stein, *Ber.*, **70**, 567 (1937).

(5) (a) Albertson and Tullar, THIS JOURNAL, **67**, 502 (1945); (b) Tullar, U. S. Patent 2,393,723.

(6) Albertson, THIS JOURNAL, **68**, 450 (1946).

(7) All melting and boiling points are corrected.

(8) Microanalyses by Mr. Howard Clark, Miss Emily Davis and Mrs. Jane Wood.

g. of sodium was added 29.2 g. of ethyl oxalate and, after ten minutes, 30.0 g. of II. The mixture was boiled for ten minutes and then allowed to stand at 30° for twelve hours. The reaction mixture was cooled to 0°, acidified (to *p*H 3) with 1:1 hydrochloric acid at 0–5°, and the ethanol was removed by distillation under reduced pressure (bath temperature below 40°). The residual oil was treated with 500 ml. of ether, and the ethereal solution was extracted with two 200-ml. portions of 5% sodium hydroxide solution, the combined alkaline extracts were washed with 100 ml. of ether and the combined, dried ether solutions were distilled to yield 14.4 g. of unchanged II. The sodium hydroxide solution was acidified (to *p*H 3) at 10° by 1:1 hydrochloric acid, and the acid solution was extracted with 400 ml. of ether. The ethereal extract was dried over magnesium sulfate, the ether was removed by distillation at atmospheric pressure, the dark oily residue was triturated with 100 ml. of dry benzene, and the benzene suspension was filtered to yield 14.7 g. of crude III, m. p. 144–146° (66.3%, based on II used). The crude material was suitable for conversion to IV.

A sample of III, prepared for analysis by recrystallization from absolute alcohol, was found to melt at 146–147° (lit.,[1c] 145°).

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.81; H, 4.04. Found: C, 53.95; H, 4.22.

6-Methylindole-2-carboxylic Acid (IV).—Crude III (100.5 g.) was dissolved in a solution of 30.3 g. of sodium hydroxide in 830 ml. of water and 284 g. of sodium hydrosulfite was added, portionwise, to the vigorously stirred alkaline solution over a one-hour period (temperature not allowed to exceed 70°). The reaction was considered to be complete when a drop of sodium hydroxide solution, added to the reaction mixture, produced no color change. The reaction mixture was treated with Norite, filtered, acidified (to *p*H 3–3.5) with 1:1 hydrochloric acid and cooled to 5°. Crude IV (49.0 g., m. p. 212–214°) was separated from the reaction mixture by filtration. When the filtrate was heated on the steam cone for twelve hours, an additional 7.0 g. (m. p. 212–214°) of crude product separated and was removed by filtration. From an ether extract of the mother liquor there was obtained an additional 4.0 g. of crude IV. The over-all yield of crude IV was 60.0 g. (76%). When this material was recrystallized three times from 70% ethanol, 31.0 g. of pure IV, m. p. 216–217° (yield, 39.2%) was obtained.

Anal. Calcd. for $C_{10}H_9NO_2$: N, 8.00. Found: N, 7.84.

Reissert[1c] reported a melting point of 217° for IV prepared by treatment of III with zinc and acetic acid.

6-Methylindole (V).—When 31.0 g. of pure IV (m. p. 216–217°) was heated in a small distilling flask at a bath temperature of 230–240°, decarboxylation took place smoothly and 14.0 g. of 6-methylindole (V) was obtained (yield, 60.1%). The product, [b. p. 112° (5 mm.), m. p. 13.5–14°, n^{20}_D 1.6042] was a viscous oil at room temperature and possessed a characteristic odor similar to that of indole.

Anal. Calcd. for C_9H_9N: C, 82.44; H, 6.87. Found: C, 83.11; H, 6.97.

The picrate crystallized from ethanol as deep red needles of m. p. 157°.

Anal. Calcd. for $C_{15}H_{12}N_4O_7$: C, 50.00; H, 3.33. Found: C, 50.30; H, 3.67.

6-Methyl-3-(dimethylaminomethyl)-indole (6-Methylgramine) (VI).—6-Methylindole (12.5 g.) was added, at 5°, to a well-stirred solution consisting of 12.8 g. of 35% dimethylamine, 13.4 g. of glacial acetic acid and 7.2 g. of 40% formaldehyde. During the addition the temperature of the reaction mixture rose to about 60°. The reaction mixture, after a twelve-hour period at 30°, was poured into a stirred solution of 13.8 g. of sodium hydroxide and 150 ml. of water; the mixture was stirred for one hour at 30° and then was cooled to 5° and maintained at that temperature for two hours. The crude product was separated by filtration, washed on the filter with cold water, dried and recrystallized from ether. The product (VI) melted at 120–122°.

A sample of VI, prepared for analysis by recrystallization from ether, melted at 124–125°.

Anal. Calcd. for $C_{12}H_{16}N_2$: N, 14.89. Found: N, 15.01.

Ethyl α-Acetamino-α-cyano-β-(3-[6-methyl]-indole)-propionate (VII).—In a 500-ml. three-necked flask fitted with mechanical stirrer, reflux condenser and nitrogen inlet tube were placed 125 ml. of dry xylene and 0.52 g. of powdered sodium hydroxide. The mixture was heated to 90°, and a well-pulverized mixture of 5.00 g. of VI and 4.52 g. of ethyl acetaminocyanoacetate was added; the mixture was heated to boiling and was refluxed for seven hours. The evolution of dimethylamine which was vigorous at first had practically ceased after six hours heating. The reaction mixture was cooled at 5° for twelve hours and filtered to yield 9.0 g. of crude product. The crude material was treated with a warm solution of benzene and ethanol, the resulting suspension was filtered from insoluble material, and the filtrate was allowed to cool to 5°. The crystals of VII which separated were collected on a Buchner funnel and dried. The yield of VII was 6.3 g. (76%) m. p. 165–167°.

A sample of VII, prepared for analysis by recrystallization from ether, melted at 167–168°.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.18; H, 6.07; Found: C, 65.36; N, 6.32.

***dl*-6-Methyltryptophan (VIII).**—To a solution of 4.2 g. of sodium hydroxide in 25 ml. of water was added 5.8 g. of pure VII and the mixture was boiled for twenty-four hours. During this period the solid material dissolved in the alkaline solution and ammonia was evolved. The hot reaction mixture was filtered at the end of the reflux period and the cooled, light yellow solution was made neutral (litmus) with 50% acetic acid. White crystals of VIII separated and were filtered and dried. The yield of *dl*-6-methyltryptophan was 3.9 g. (96.3%), m. p.[9] 298–300°.

A sample of VIII, prepared for analysis by recrystallization from water and alcohol, melted[9] at 298–300°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.06; H, 6.42; N, 12.84. Found: C, 66,16; H, 6.94; N, 12.99.

Summary

dl-6-Methyltryptophan [[α-amino-β-[3-(6-methyl)-indole]-propionic acid]] has been synthesized *via* the sequence: *p*-xylene, 2-nitro-1,4-dimethylbenzene, 2-nitro-4-methylphenylpyruvic acid, 6-methylindole-2 carboxylic acid, 6-methylindole, 6-methyl-3-(dimethylaminomethyl)-indole (6-methylgramine), ethyl-α-acetamino-α-cyano-β-[3-(6-methyl)-indole]-propionate, *dl*-6-methyltryptophan.

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[9] The melting point was observed by inserting the tube in an air bath (aluminum block) at 295° and raising the temperature rapidly. The substance decomposed at about 260° (*cf.* ref. 1a) when the determination was made in the usual way. In our experience the higher value obtained with the preheated bath is the more reproducible.