Anal. Calcd. for $C_{24}H_{32}ClNO_4$: Cl, 8.17. Found: Cl, 8.26.

The **propionate** melted at 171–173° and was converted to the **hydrochloride**, m. p. 260–262°.

Anal. Calcd. for $C_{25}H_{34}ClNO_4$: Cl, 7.92. Found: Cl, 7.81.

4-Phenyl-4-piperidinols.—A solution of 0.05 mole of the piperidone in ether was added to twice the calculated amount of an ether solution of phenylmagnesium bromide at 0°, and the mixture refluxed for one-half hour. The mixture was cooled to 0°, and a solution of 10 cc. of concentrated hydrochloric acid in 20 cc. of water was added slowly with stirring. The hydrochloride of the piperidinol crystallized and was removed by filtration, washed with ether, and crystallized from a suitable solvent. The free bases were prepared by adding aqueous ammonia to an alcohol solution of the hydrochloride, and were crystallized from methyl alcohol. The data on the individual compounds are summarized in Table II.

Summary

Twenty substituted 4-piperidones have been prepared by the Mannich reaction using acetic acid as a solvent. Two of the piperidones have been reduced to the 4-piperidinols, and the acetates, propionates and butyrates have been prepared. Five of the piperidones have been converted to 4-phenyl-4-piperidinols by reaction with phenylmagnesium bromide. All of the compounds are being tested for possible pharmacological activity.

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

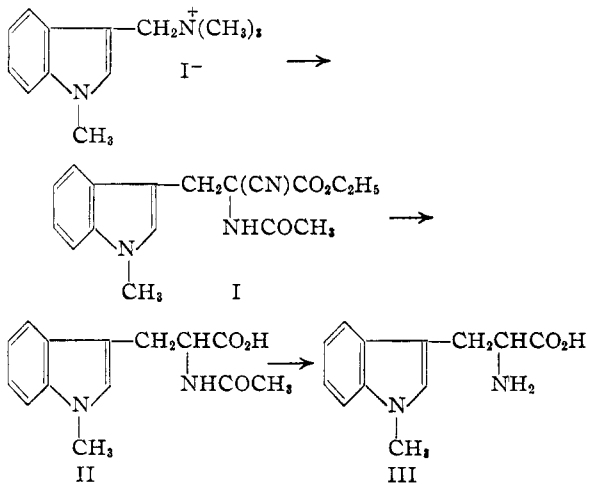
A Synthesis of 1-Methyltryptophan[1]

BY H. R. SNYDER AND ERNEST L. ELIEL[2]

In previous communications[3] the synthesis of 1-methylgramine and an alkylation reaction by its methiodide were described. The alkylating properties of 1-methylgramine methiodide have now been adapted to the synthesis of 1-methyltryptophan. This synthesis is of interest not only because it furnishes another instance of a facile alkylation by a quaternary salt which cannot react through an elimination mechanism,[3,4] but also because of the possible action of the product as an antimetabolite.

1-Methyltryptophan was obtained by alkylation of the sodium salt of ethyl acetamidocyanoacetate[5] with 1-methylgramine methiodide and hydrolysis of the alkylation product (I, 69% yield) with aqueous alkali. When 15% sodium hydroxide was employed in the hydrolysis, about half of the product was obtained as the free amino acid (III) and about half as the acetyl derivative (II). By subsequent hydrolysis of the acetyl derivative with 20% sodium hydroxide the conversion of the alkylation product to the free amino acid was brought to 92%. Hydrolysis of (I) with 10% alcoholic potassium hydroxide converted it only to the acetyl derivative (II).

A synthesis of 1-methyltryptophan has been reported in connection with investigations into the chemical nature of certain toad poisons.[6] The product, which was obtained by an azlactone synthesis from 1-methylindole-3-aldehyde, is stated to melt at 289° with decomposition. Our product melts at 223–225° with decomposition. Because of this discrepancy it was considered necessary to prove the structure of the 1-methyltryptophan obtained by the alkylation reaction. Accordingly, this amino acid was decarboxylated by heating in molten diphenylamine at 240–250° (a method which has been applied to the synthesis of tyramine from tyrosine).[7] The product was 1-methyltryptamine, identified as its hydrochloride, picrate and phthalimide. A by-product of the decarboxylation had the composition of a diketopiperazine related to 1-methyltryptophan.



We are at present unable to explain the difference in the melting points of the methyltryptophans obtained by the two different methods.

Experimental[8,9]

α-Carbethoxy-α-acetamido-β-3(1-methyl)-indolepropionitrile (I).—To the solution prepared from 1.15 g. of

(1) Presented before the Organic Division at the 113th meeting of the American Chemical Society, Chicago, Illinois, April, 1948.

(2) Present address: University of Notre Dame, Notre Dame, Indiana.

(3) Snyder and Eliel, THIS JOURNAL, **70**, 1703, 1857 (1948).

(4) Albertson, *ibid.*, **70**, 669 (1948).

(5) Tullar, U. S. Patent 2,393,723; *C. A.*, **40**, 2465[5] (1946).

(6) Wieland, Konz and Mittasch, *Ann.*, **513**, 1 (1934).

(7) Abderhalden and Gebelein, *Z. physiol. Chem.*, **152**, 125 (1926).

(8) All melting points are corrected.

(9) Microanalyses by Mr. Howard Clark.

sodium and 125 ml. of absolute alcohol[10] were added successively 8.5 g. of acetamidocyanoacetic ester[5] and 16.5 g. of methylgramine methiodide.[3] The reaction mixture was refluxed for forty-three hours, during which time trimethylamine was evolved steadily. At the end of the reaction period, a sample of the clear solution, freed of trimethylamine by bubbling air through it, was almost neutral to Universal indicator paper. About half of the alcohol was distilled and hot water was added to incipient cloudiness. The alkylation product crystallized on cooling. It was collected, washed with water, and dried *in vacuo* over calcium chloride. The tan solid was recrystallized from benzene, the yield of white crystals of m. p. 134.5–135.5° being 10.8 g. (69%). Attempts to work up the mother liquors yielded material of higher melting point. After two more recrystallizations the analytical sample melted at 135.5–136.5°.

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: N, 13.41. Found: N, 13.54.

N-Acetyl-1-methyltryptophan (II).—One gram of the above nitrile (I) was refluxed for seventeen hours with a solution of 1 g. of potassium hydroxide in 1 ml. of water and 9 ml. of 95% ethanol. There was a vigorous evolution of ammonia. After the addition of 9 ml. of water, the mixture was concentrated *in vacuo* to half volume. The solution was extracted with ether, boiled with Norite, filtered with suction, cooled, and acidified with 1 ml. of acetic acid. A scanty precipitate appeared and was collected; it did not melt up to 320° and was probably silicic acid. The filtrate was diluted with water and acidified with hydrochloric acid. Slightly yellowish platelets crystallized. These were collected, washed with water, and dried; weight, 0.59 g., m. p. 100–140° with effervescence. The product was apparently solvated; heating to 170° in an oil-bath followed by recrystallization from aqueous alcohol led to the material of the same wide melting range. However, recrystallization from benzene containing a little acetone yielded unsolvated material, of m. p. 171–172°, in the form of white crystalline aggregates.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: N, 10.76. Found: N, 10.86.

1-Methyltryptophan (III).—A mixture of 10.4 g. of the alkylation product (I) and a solution of 6 g. of sodium hydroxide in 40 ml. of water was refluxed for twenty-five hours. About thirty minutes before the end of the reflux period, Norite was added. Addition of 9 ml. of glacial acetic acid and 50 ml. of 95% alcohol to the filtered, cooled solution caused the separation of the amino acid (III). After the mixture had been allowed to stand in the refrigerator until crystallization was complete, the product (III) was collected, washed with alcohol and with ether, and dried in the air. It weighed 4.0 g. (55%). Concentration of the mother liquor and acidification of the residue to congo red by the addition of hydrochloric acid yielded 3.5 g. (40%) of the acetyl derivative (II), a sample of which melted at 170–172° after recrystallization from a mixture of acetone and benzene. This material was refluxed for forty hours with 10 ml. of 20% aqueous sodium hydroxide. Near the end of the reflux period the mixture was treated with Norite, as before, diluted with sufficient water to prevent the separation of the sodium salt, filtered, and acidified with 3 ml. of glacial acetic acid. The amino acid (III), collected as before, weighed 2.7 g. (92% based on the acetyl derivative). The total yield of material of m. p. 217.5–220.5° (dec). was 6.7 g. (92% based on I). The amino acid was recrystallized by dissolving one part in 150 parts of boiling water and adding 150 parts of 95% ethanol to the filtered, hot solution. Material so obtained melted at 223–225° (dec.)

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.38, 66.22; H, 6.56, —; N, 12.85.

(10) Manske, THIS JOURNAL, **53**, 1106 (1931); Fieser, "Experiments in Organic Chemistry," 2nd Edition, D. C. Heath and Company, Boston, Mass., 1941, p. 359.

1-Methyltryptophan gives a positive ninhydrin test, but no color with *p*-dimethylaminobenzaldehyde and hydrochloric acid (Ehrlich Reagent). In the Hopkins–Cole test it produces an olive-green to olive-brown color.

The hydrochloride was prepared by dissolving 1 g. of the amino acid in a solution of 1 ml. of concentrated hydrochloric acid in 9 ml. of water and evaporating to dryness *in vacuo* at a temperature not exceeding 45°. Recrystallization from acetone yielded large, white, fibrous needles of m. p. 239–242° (dec.) The hydrochloride is freely soluble in water, alcohol and acetone, but is not appreciably hygroscopic.

Decarboxylation of 1-Methyltryptophan.—One gram of 1-methyltryptophan and 20 g. of pure diphenylamine were heated to 240–250° under a slow current of nitrogen in a flask equipped with a nitrogen inlet and a reflux condenser. The exit gases were bubbled through a solution of barium hydroxide. At 240° the melt began to effervesce and a vigorous evolution of carbon dioxide was noted. Gas evolution slackened after about one-half hour. Heating was discontinued after forty minutes; the melt was allowed to cool and was taken up in ether. Some insoluble material (0.31 g.) was filtered off and washed with ether. The combined ether filtrate was extracted twice with 1 *N* hydrochloric acid and the acid extract was clarified by washing with a fresh portion of ether. It was then made alkaline with sodium hydroxide solution and the oil which separated was extracted with ether. The ether solution was dried over solid potassium hydroxide and divided into two parts.

One portion was treated with a saturated solution of hydrogen chloride in diisopropyl ether. The hydrochloride which separated was collected, washed with acetone and recrystallized four times from methanol–acetone–ether. It formed white needles of m. p. 199–202° (dec.) (lit.[11] 198°). Treatment of the aqueous solution of the hydrochloride with sodium picrate in water yielded the picrate which after recrystallization from ethanol melted at 179–180° (lit.[12] 180–181°).

Another portion of the amine was freed of solvent by distillation and treated with phthalic acid at 230° according to the method of Manske.[11] The phthalimide thus obtained melted at 177–177.5° (lit.[11] 177.5°) and showed no depression in melting point when mixed with a sample of 1-methyltryptamine phthalimide; the infrared absorption spectra of the two samples were identical.

3,6-bis-3-(1-Methylindolyl)-methyl-2,5-diketopiperazine.—The residue (weight 0.31 g.) remaining after the decarboxylation mixture was extracted with ether was washed with dilute hydrochloric acid and with water; it was then recrystallized once from 95% alcohol and twice from a mixture of acetone and alcohol to give a colorless solid melting at 258.5–260.5 (dec.). The analysis suggests that this substance is the diketopiperazine.

Anal. Calcd. for $C_{24}H_{24}N_4O_2$: C, 71.96; H, 6.04. Found: C, 72.02; H, 6.22.

Summary

1-Methyltryptophan has been synthesized by alkylation of ethyl acetamidocyanoacetate with 1-methylgramine methiodide followed by hydrolysis of the alkylation product. The over-all yield from 1-methylgramine methiodide is 63%, which corresponds to a yield of 48% from 1-methylindole. The melting point of 1-methyltryptophan thus obtained does not agree with that reported in the literature. Structure proof is afforded by decarboxylation to the known 1-methyltryptamine.

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(11) Manske, *Can. J. Research*, **5**, 597 (1931).

(12) Spaeth and Lederer, *Ber.*, **63**, 2106 (1930).