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

An Alkylation with the Methiodide of 1-Methyl-3-dimethylaminomethylindole (1-Methylgramine)[1]

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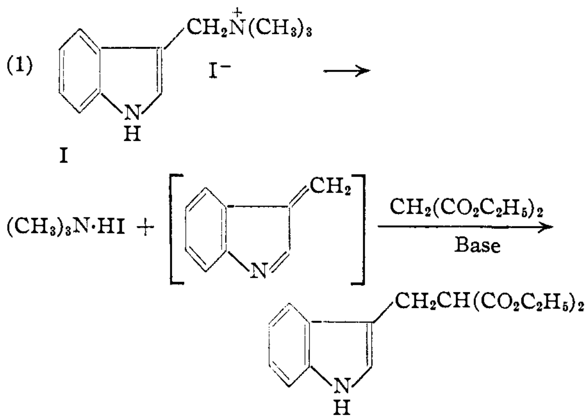
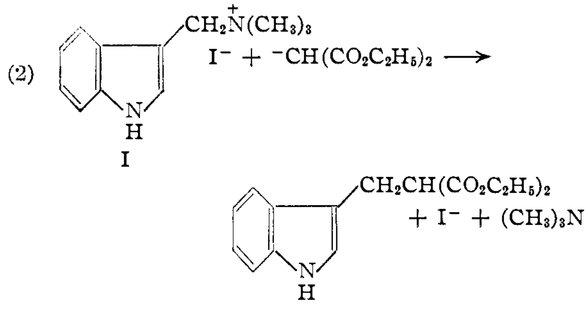
Alkylations with gramine[1,2] and its quaternary salts[3] proceed with such ease as to suggest that the mechanisms of the reactions differ from those of alkylations with simple amines and quaternary salts containing a radical of the benzyl type. Two possible mechanisms for reactions with gramine methiodide are shown in equations 1 and 2. The first, consisting in the elimination of trimethylamine hydriodide and a Michael-type addition, is patterned after that suggested by Mannich[4] for alkylations with salts from ketonic Mannich bases.





In the second mechanism it is assumed that the trimethylamine molecule is displaced from the quaternary ammonium ion by the anion of the substance being alkylated. Mechanisms similar to 1 and 2 can be written for reactions of the tertiary amine, gramine.

A consideration of the two mechanisms suggested that reactions of 1-methylgramine (III) and its quaternary salt (IV) be examined. This paper reports the preparation of these two substances and the reaction of the quaternary salt (IV) with aqueous sodium cyanide.

Application of the Mannich reaction to 1-methylindole[5] (II) gave the methylgramine (III) in about 80% yield. The methiodide (IV), obtained in nearly quantitative yield from the base and methyl iodide in ethanol, reacted readily with aqueous sodium cyanide. The expected 1-methylindoleacetonitrile (V) was obtained in about 50% yield, along with a much smaller amount of a more volatile isomer. The structure of this isomeric product is under investigation.

In the proof of the structure of the nitrile (V) the acid (VI) was prepared by hydrolysis. The product obtained melted slightly lower than that described in the literature,[6,7] and its picrate melted about twelve degrees lower than that previously reported.[6] However, reduction of the nitrile with sodium and ethanol gave 1-methyltryptamine (VIII), several derivatives of which had melting points identical with previously reported values. Also, 1,3-dimethylindole (VII) was produced in small quantity in the sodium–alcohol reduction,[8] and it proved to be identical with an authentic specimen made from skatyl sodium and methyl iodide. Decarboxylation of the acid produced the same 1,3-dimethylindole. The various samples of the dimethylindole were compared as pic-

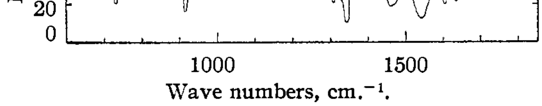


Fig. 1.—1, Infrared absorption spectrum of picrate of 1,3-dimethylindole from skatole. 2, Infrared absorption spectrum of picrate of 1,3-dimethylindole from 1-methylgramine (decarboxylation of 1-methylindole-3-acetic acid).

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[1] This is the seventh of a series of papers on quaternary ammonium salts; for the preceding paper, see Snyder and Katz, THIS JOURNAL, 69, 3140 (1947).

(2) Lyttle and Weisblat, *ibid.*, 69, 2118 (1947).

(3) Snyder, Smith and Stewart, *ibid.*, 66, 200 (1944); Snyder and Smith, *ibid.*, 66, 350 (1944); Albertson and Tullar, *ibid.*, 67, 502 (1945).

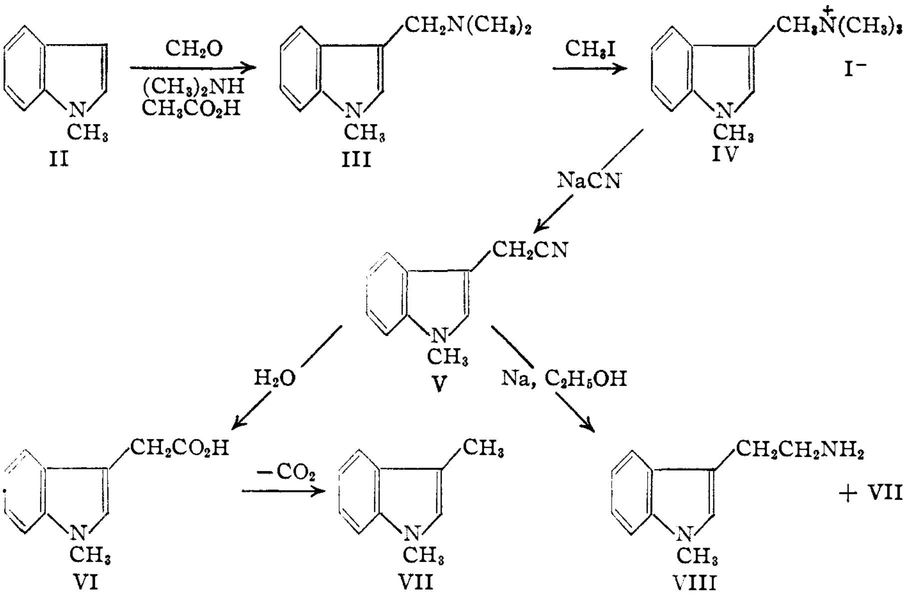
(4) Mannich, Koch and Barkousky, *Ber.*, 70, 355 (1937).

(5) This synthesis is believed to be the first application of the Mannich reaction to an N-alkylindole. Bauer and Andersag [U. S. Pat. 2,222,344 (*C. A.*, 35, 1807 (1941))] mention a somewhat similar reaction of N-methylindole with formaldehyde and an alkali cyanide to yield the β-acetonitrile, but no example is given.

(6) Piccini, *Atti acad. Lincei*, [5] 8, I, 315 (1899).

(7) King and L'Ecuyer, *J. Chem. Soc.*, 1901 (1934).

(8) Majuna and Hoshino [*Ber.*, 58, 2045 (1925)] observed the formation of skatole in a similar reduction of β-indoleacetonitrile.



rates by the aid of melting points, mixed melting points, and infrared absorption analyses[9] (see the figure). These observations prove that the methylindoleacetic acid obtained by hydrolysis of the nitrile had the structure VI.

The formation of the nitrile (V) from IV and sodium cyanide in water solution shows that the salt (IV), like gramine methiodide (I), is more reactive than simple quaternary salts containing benzyl groups. For example, benzylphenyldimethylammonium chloride is not cleaved by aqueous sodium cyanide.[3] It is probable that alkylations with gramine methiodide and the methylgramine methiodide proceed by the same mechanism, and that reactions of gramine methiodide do not proceed through a process of the Michael type (equation 1). The study of this problem is being continued.

Experimental[10,11]

1-Methylindole (II), prepared from N-methylphenylhydrazine and pyruvic acid by the method of Fischer and Hess[12] boiled at 134–135° (31 mm.) and had $n^{20}D$ 1.6062. Material prepared by the methylation of the sodium derivative of indole with methyl iodide[13] was unsatisfactory owing to contamination by -N-H compounds, the presence of which was revealed by infrared absorption analysis.

1-Methyl-3-dimethylaminomethylindole (III).—A mixture of 36 ml. of 25% aqueous dimethylamine and 40 ml. of glacial acetic acid was cooled in an ice-bath; when the temperature had fallen to 5°, 15 ml. of 40% aqueous formaldehyde was added. The resulting mixture was cooled to 5° and added in one lot to 23.7 g. of N-methylindole. The reaction mixture was shaken gently until it became homogeneous; during the shaking the temperature rose to about 50°. The mixture then was allowed to stand at room temperature for twenty-four hours.

The reaction mixture was poured into a solution of 40 g. of sodium hydroxide in 400 ml. of water, and the oil which separated was collected by extraction with one 300-ml. portion and one 200-ml. portion of ether. The ether extracts were washed exhaustively with 1 *N* hydrochloric acid (until the extracts no longer became turbid when made alkaline), about 500 ml. of the acid being required. The combined acid extract was made alkaline by the addition of an excess of 10% sodium hydroxide solution. The liberated base was collected by extraction with two 200-ml. portions of ether. The ether extract was washed, dried, and concentrated, and the residue distilled *in vacuo*. The main fraction, collected at 94–97° (0.2 mm.), weighed 26.3–26.9 g. (77.5–79.3% yield). The analytical sample was redistilled; b. p. 94–96° (0.2 mm.); $n^{20}D$ 1.5743.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.52; H, 8.57. Found: C, 76.64; H, 8.62.

The **picrate** crystallized from alcohol as yellow prisms melting at 145–146°.

Anal. Calcd. for $C_{18}H_{19}N_5O_7$: C, 51.81; H, 4.59. Found: C, 52.05; H, 4.55.

1-Methyl-3-dimethylaminomethylindole Methiodide (IV).—To a solution of 8.5 g. of the base (III) in 40 ml. of absolute ethanol was added in one portion 7.8 g. of methyl iodide. An exothermic reaction occurred, so the mixture was cooled to prevent the loss of methyl iodide. The mixture was allowed to stand for one hour at room temperature, during which period most of the product crystallized. Crystallization was completed by cooling, and the solid was collected and washed twice with absolute ethanol and thrice with anhydrous ether. After drying under nitrogen the salt weighed 14.3–14.6 g. (96–98%); the instantaneous decomposition point, determined on a Maquenne block, was 193°. The analytical sample, recrystallized three times from absolute ethanol, decomposed at 195°.

Anal. Calcd. for $C_{13}H_{19}N_2I$: C, 47.28; H, 5.84; N, 8.43. Found: C, 47.37; H, 5.84; N, 8.51.

1-Methylindole-3-acetonitrile (V).—To a solution of 10 g. of sodium cyanide in 100 ml. of water was added 16.5 g. of the crude methiodide (IV) and the mixture was boiled under reflux for two and one-fourth hours, during which period an oil separated from the aqueous solution and a solid appeared in the condenser. The oil and solid were collected from the cooled mixture by extraction with two 50-ml. portions of ether. The ether solution was washed three times with water, dried over sodium sulfate, filtered, and concentrated: the residue was distilled *in*

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(9) The authors are indebted to Mrs. Agatha Roberts Johnson for the absorption studies.

(10) All melting points are corrected.

(11) Microanalyses by Miss Theta Spoor and Miss Betty A. Snyder.

(12) Fischer and Hess, *Ber.*, **17**, 561 (1884)

(13) Weissgerber, *ibid.*, **43**, 3522 (1910)

vacuo. A small fraction (*ca.* 0.6 g.), which solidified in the receiver, was collected at 96–122° (0.15 mm.); it melted at 70–71° after three recrystallizations from petroleum ether (b. p. 30–60°). The main fraction, b. p. 123–131° (0.15 mm.), weighed 5.2–5.4 g. (60–64%); it solidified after standing in the ice-box and melted at 58–59° after an extraction with petroleum ether followed by two recrystallizations from a mixture of ether and petroleum ether (b. p. 30–60°).

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92. Found: (higher-melting product) C, 77.54; H, 6.16; (lower-melting product) C, 77.89; H, 5.95.

1-Methylindole-3-acetic Acid (VI).—A mixture of 2 g. of the lower-melting nitrile (V) with a solution of 5 g. of potassium hydroxide, 5 ml. of water, and 20 ml. of 95% ethanol was refluxed for seventeen hours. The solution was diluted with 50 ml. of water and distilled to remove most of the alcohol. The resulting clear solution was extracted three times with ether, heated with Norit, and filtered. The filtrate was very cautiously acidified with 3 *N* hydrochloric acid, and the first (dark-colored) solid which separated was removed by filtration. The acid (VI) was precipitated by acidification of the filtrate to congo red paper. It was collected on a filter, washed with ice-water, and dried in a vacuum desiccator. The material so obtained was a nearly white solid melting at 127–128.5°; wt. 2 g. (90%). Recrystallization from benzene improved the color but had no effect on the melting point; recrystallization from water and high-vacuum sublimation likewise had no effect on the melting point.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.81; H, 5.86; N, 7.40. Found: C, 70.03; H, 5.99; N, 7.41.

The **picrate** crystallized from benzene as red needles melting at 160.5–161.5°.

Anal. Calcd. for $C_{17}H_{14}N_4O_9$: C, 48.81; H, 3.37. Found: C, 48.91; H, 3.49.

1,3-Dimethylindole: From VI.—In the lower bulb of a two-bulb microdistillation apparatus 0.55 g. of the acid (VI) was heated at 200° until gas evolution ceased. The resulting brown oil was distilled into the upper bulb at 20 mm., with the bath temperature at 140–170°. The light-colored distillate ($n^{20}D$ 1.5920) was converted to the picrate which, after two recrystallizations from absolute ethanol, melted at 142.5–143.5° (lit., 143–144°).

From Skatole.—A modification of the method of Weissgerber[13] was employed. The product was fractionated at atmospheric pressure and the portion boiling at 220–240° was redistilled over sodium. The distillate from this treatment was fractionated *in vacuo* and the fraction boiling at 122–127° (20 mm.) was collected; $n^{20}D$ 1.5901. Infrared absorption analysis of this material showed the presence of appreciable amounts of —NH— compounds. The **picrate** obtained from this fraction melted at 141–142° after five recrystallizations from absolute ethanol, and the melting point was not changed by admixture of the picrate described in the previous paragraph.

1-Methyltryptamine (VIII).—To a hot solution of 3.4 g. of the nitrile (V) in 60 ml. of absolute ethanol was added, over a period of ten minutes, 4 g. of finely cut sodium. The mixture was refluxed until all the metal had dissolved; it was then diluted with 60 ml. of water and concentrated *in vacuo* to remove most of the alcohol. The residual solution was diluted with 40 ml. of water and extracted with two 100-ml. portions of ether. The base (*ca.* 2.4 g.) was recovered from the ether solution by extraction with 2 *N* hydrochloric acid (*ca.* 75 ml.), neutralization of the acid with an excess of aqueous sodium hydroxide, extraction of the alkaline solution with ether, drying of the ether solution, removal of the solvent, and distillation of the residue. It was obtained as a nearly colorless oil boiling at 108–110° at about 0.1 mm. The picrate melted at 178–179° (lit.[14] 180–181°), the hydrochloride at 199–201° (lit.[15] 198°), and the phthalimide at 176.5–177° (lit.[16] 177.5°).

The ether extract of the reaction mixture, after the extraction with 2 *N* hydrochloric acid described above, was concentrated. The resulting oil, wt. about 1.2 g., was distilled from a modified test-tube at about 0.1 mm. Two fractions, approximately equal in weight, were obtained, one boiling at a bath temperature of 90–100° and the other at 140–170°. The first fraction was identified as 1,3-dimethylindole by conversion to the picrate, m. p. 142–143°; the melting point of this picrate was not depressed by admixture with either of the samples described above, and its infrared absorption curve was identical with that shown in the figure. The higher-boiling fraction crystallized when seeded and was identified as 1-methylindole-3-acetonitrile by mixed melting point.

Summary

1-Methylindole reacts with formaldehyde and dimethylamine in the presence of acetic acid to give 1-methyl-3-dimethylaminomethylindole in good yield. The methiodide of this base reacts readily with aqueous sodium cyanide to give 1-methylindole-3-acetonitrile, along with a small amount of an isomeric substance. The structure of 1-methylindole-3-acetonitrile is proved by hydrolysis to 1-methylindole-3-acetic acid and by reduction to 1-methyltryptamine and 1,3-dimethylindole. The methiodide of 1-methyl-3-dimethylaminomethylindole and the methiodide of gramine (3-dimethylaminomethylindole) are more reactive as alkylating agents than simple quaternary ammonium salts containing benzyl groups.

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[14] Spaeth and Lederer, *Ber.*, **63**, 2106 (1930).

[15] Manske, *Can. J. Research*, **5**, 597 (1931).