A SYNTHESIS OF THE METHYLTRYPTAMINES AND SOME DERIVATIVES[1]

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Abstract

Because of the interest attached to N-methyltryptamine on account of its occurrence as an integral part of the calycanthine molecule, the free base and some of its derivatives have been synthesized. An account of the synthesis of N,N-dimethyltryptamine together with some carbolines derived from 1-methyltryptamine is also included. Finally, a detailed procedure for an improved preparation of tryptamine is given.

N-methyltryptamine has become of some interest because of its occurrence as an integral part of the alkaloid calycanthine. In a recent communication the author (5) recorded the degradation of calycanthine to benzoyl-N-methyltryptamine, but the free base was not obtained at that time and its preparation, together with some of its derivatives, is now placed on record.

Considerably more difficulty was encountered in the synthesis of N,N-dimethyltryptamine but sufficient was ultimately obtained for characterization. When tryptamine is treated with methyl iodide, all four possible products are obtained. The removal of the quaternary iodide is comparatively simple because of its sparing solubility in water or alcohol and the greater portion of the unchanged tryptamine can be separated from the mixture of bases on account of its sparing solubility in ether. Benzoylation of the residual mixture left the tertiary base intact and it was extracted from the crude product by means of dilute acid. The accumulated impurities were then removed by conversion to the picrate and the latter was recrystallized until pure. The picrate thus obtained consists of pale yellow needles sparingly soluble in water and melting at 168°C*. In melting point and composition this picrate closely resembles that of a base ($C_{12}H_{16}N_2$) isolated from *Withania somnifera* by Power and Salway (6, p. 496) but the question of identity was settled in the negative by the preparation of the free base which has the unexpectedly low melting point of 47°C. Furthermore, the hydrochloride could not be obtained crystalline although the pure base was used in its preparation. Aside from analysis the constitution of the base was proved by conversion to the previously described (5) quaternary iodide.

Another route which also led to the tertiary amine was via the quarternary chloride (from the iodide) by distillation *in vacuo*. The yield in this case as well as in the previous case was rather unsatisfactory and purification through the picrate was essential.

The physical properties of this series of bases are of some interest since the cases where all three representatives (primary, secondary and tertiary) have been obtained crystalline are extremely rare. Aside from a general effect in

All melting points are corrected.

[1] *Manuscript received October 29, 1931.*
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raising the melting point the indol nucleus is sufficiently removed from the nitrogen atom so that the effect of the successive introduction of methyl groups in lowering the melting point is probably not ascribable to any other cause. The melting points are: primary 117°, secondary 90°, tertiary 47°C. Parallel with the decrease in melting point a marked increase in solubility in organic solvents is observed. While tryptamine is soluble only with difficulty in boiling ether, the tertiary base dissolved rapidly in this solvent at 0°C.

In one attempt to methylate tryptamine with methyl iodide in acetone there was obtained, in addition to the quarternary iodide, a base or mixture of bases which yielded on benzoylation a beautifully crystalline product giving analytical figures in good agreement with $C_{20}H_{20}ON_2$. The substance gives a greenish blue color with Ehrlich's reagent, a fact which is indicative of substituents at positions 2 and 3 in the indol nucleus and probably also of ring closure. These properties and its mode of formation point to the substance being 2:2-dimethyl-3-benzoyl-2:3:4:5-tetrahydro-3-carboline, the gem-dimethyl group and the 2-carbon atom obviously originating in the acetone used as solvent. The mechanism of the synthesis recalls the usual isoquinoline synthesis, its facile occurrence being due to the great reactivity (3) of the 2-position in the indol nucleus.

Späth and Lederer (7) have described the synthesis of a number of carbolines from 1-methyltryptamine. The benzoyl derivative recently described by the author (5) has now been converted into the corresponding dihydro-carboline. Oxidation with chromic acid yields the carboline which exhibits the usual bluish fluorescence to a marked degree. Incidentally it may be pointed out that the phthalimido derivative of 1-methyltryptamine is admirably suited to the purification of the crude base owing to its ease of formation and sparing solubility even in boiling alcohol.

In view of the comparatively large amounts of tryptamine required for this investigation considerable attention was devoted to effecting improvements in yields at various stages, the final result being that the utility of the Ewin's (2) synthesis has been greatly enhanced.

The final condensation in the synthesis still leaves something to be desired in the matter of yields, but it must be kept in mind that in reality three reactions,—hydrolysis of the acetal, formation of the phenylhydrazone, and ring closure of the latter,—are carried out in one operation. The most serious obstacle heretofore has been the preparation of diethyl γ-aminobutyracetal from the difficultly accessible β-cyanoacetal (8). It has now been found that the comparatively simple preparation of the β-bromoacetal from acrolein has obviated much experimental difficulty in preparing the cyanide. The conversion of the bromide into the cyanide proceeds smoothly in boiling methanol, the troublesome autoclave conditions and the use of glycerol as solvent, essential in the case of chloroacetal, being entirely avoided. Furthermore, the yields are much better, and if the details given in the experimental section are observed the aminoacetal may be obtained in 85% yield from the cyanide.

The preparation of tryptamine is again detailed and finally attention may be

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directed to an error in the recorded melting point (given as 138°C.) of benzoyltryptamine. The correct value (174°C.) is that first recorded by Asahina and Mayeda (1) and the incorrect value (due to Ewins) was erroneously introduced in writing the manuscript. It may also be pointed out that Ewin's melting point for tryptamine (145-146°C.) could never be confirmed. If there are in reality two crystal forms the higher melting form must of necessity be the most stable. Nevertheless, the distilled base which crystallized while still hot, that recrystallized from chloroform, that from alcohol, and the resolidified melt, all melted at 118°C. Asahina records 120°C., while Majima and Hoshino (4 p. 2045) give 114.5-115.5°C. On the other hand the melting points of the picrate (242-243° C.) and the hydrochloride (246°C.) given by Ewins are substantially within experimental error.

Experimental

N-Methyltryptamine

A rapidly cooled solution of 32 gm. of tryptamine in 300 cc. of chloroform was treated with an equal weight of methyl iodide and the mixture kept in cold water. When the first appreciable evolution of heat had subsided and a considerable amount of colorless syrupy salt had separated, the mixture was placed in an ice chest and allowed to remain for 3 days, during which time the salt largely crystallized. The solvent was decanted off and the residue dissolved in 120 cc. of ethyl alcohol. On cooling, a copious yield of the quaternary iodide was obtained. This was recrystallized once and it then melted at 197°C.

The combined mother liquor was freed of alcohol, dissolved in water, basified and the mixture extracted with chloroform. A further small amount of the quaternary iodide was obtained at this stage. It was recrystallized from alcohol (m p. 197°C.) and together with the first amount weighed 12.1 gm. The chloroform extract was clarified with sodium sulphate, the solvent distilled, and the residue distilled *in vacuo*. While still warm the distillate was treated with a small volume of chloroform and as crystallization proceeded ether was added. The mixture was then thoroughly cooled and the tryptamine filtered off and washed with ether; recovery, 15.1 gm.

It is possible to isolate N-methyltryptamine from the mother liquor of the tryptamine by fractional precipitation with petroleum ether, but the procedure is so tedious and the yields so low that a description is felt to be of no value. The mixture of primary, secondary, and tertiary bases which weighed 9.3 gm. in the above experiment was benzoylated as already described and the chloroform solution extracted with dilute hydrochloric acid (*A*).

Recovery and purification of the benzoyl derivative and boiling under reflux for 24 hr. with an excess of alcoholic potassium hydroxide (methyl alcoholic potassium hydroxide is inadequate as a hydrolytic agent, presumably because of the lower temperature of boiling) yielded the crude base. It was isolated from the alcohol-free hydrolysate by extraction with ether and removal therefrom with dilute hydrochloric acid. Regeneration of the base, extraction and distillation *in vacuo* yielded a colorless viscous distillate which was dissolved

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in a little chloroform and cautiously treated with petroleum ether. Crystallization was rapid. After thorough chilling the base was filtered off, washed first with a little chloroform-petroleum ether and then with the latter solvent. N-methyltryptamine as thus obtained consists of stellate aggregates of needles, several isolated crystals showing rectangular form; m.p., 90°C.; yield, 4 gm. Analysis: Calcd. for $C_{11}H_{14}N_2$; C, 75.86; H, 8.05; N, 16.09%. Found: C, 76.07; H, 8.17; N, 15.90%.

The hydrochloride was obtained in colorless elongated plates with pyramidal terminations from alcohol-acetone or alcohol-ether; m.p., 180°C. Analysis: Calcd. for $C_{11}H_{15}N_2Cl$; Cl, 16.90%. Found: Cl, 16.96%.

It may finally be observed that hydrolysis of benzoyl N-methyltryptamine obtained from calycanthine yielded the base and hydrochloride identical with the above.

The picrate was obtained when an alcoholic solution of the base was treated with picric acid in the same solvent. Benzene was added and the solution evaporated to a small volume and the concentrate treated with much ether. The picrate then crystallized out in large plates closely resembling azobenzene in color. After thorough washing with ether it melted at 191°C. It is very sparingly soluble in hot water.

The phenylcarbamyl derivative of N-methyltryptamine was readily obtained by heating the base in chloroform with a slight excess of phenylisocyanate and evaporating to a small volume. Addition of ether caused the derivative in question to crystallize in large elongated hexagonal plates, which when recrystallized from methanol-ether melt sharply at 153°C. With Ehrlich's reagent it gives an immediate red color with a slight orange cast. Analysis: Calcd. for $C_{18}H_{19}ON_3$; N, 14.33%. Found: N, 14.47%.

N, N-Dimethyltryptamine Picrate

The acid extract (*A*) from the benzoylation of the tryptamines was basified and extracted with ether. Removal of the solvent and distillation of the residue yielded a pale yellow viscous oil which failed to crystallize under a variety of conditions; yield, 1.0 gm. It was therefore converted into the picrate which was twice recrystallized from alcohol, washed with ether, and then recrystallized from hot water in which it is sparingly soluble; m.p., 168°C. Analysis: Calcd. for $C_{18}H_{19}O_7N_5$; C, 51.80; H, 4.56; N, 16.78%. Found: C, 51.95; H, 4.75; N, 16.62, 16.53%.

N,N-Dimethyltryptamine

A hot aqueous solution of trimethyl-β-3-indolyl-ethylammonium iodide was treated with a 50% excess of freshly precipitated silver chloride and the mixture gently boiled for 15 min., during which time the larger lumps were frequently disintegrated with a stout glass rod. The silver halide was filtered off and the clear filtrate rapidly evaporated, preferably in a stream of air. The addition of a small amount of methanol and the cautious treatment of the solution with acetone yielded a copious crop of crystals of the quaternary chloride. The yield of crystalline product is well in excess of 80% if the procedure is rapidly carried out. Recrystallization by solution in a small

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volume of methanol and cautious addition of acetone yielded colorless many-sided stout crystals melting at 193°C. The chloride in contrast to the iodide is extremely soluble in water and alcohol, but only sparingly so in acetone. Analysis: Calcd. for $C_{13}H_{19}N_2Cl$; Cl, 14.87%. Found: Cl, 14.06%.

Methyl chloride was removed from the quaternary chloride by slowly heating 5 gm. in a distillation flask in a vacuum kept below 1 mm. Excessive heating caused much frothing so the operation was conducted very slowly. There was considerable deep-seated decomposition and an appreciable amount of non-volatile resin remained in the flask. The crude distillate was dissolved in a small volume of methanol and an excess of dilute aqueous nitric acid was added. After removal of the methanol the turbid mixture was filtered through a wet filter and the acid filtrate extracted several times with choloroform to remove non-basic material. The tertiary base was then liberated by the addition of an excess of sodium hydroxide and the base extracted with chloroform. The dried extract was freed of chloroform by repeated evaporation with ethyl alcohol and then poured into a hot dilute solution of picric acid. A small amount of insoluble resin was filtered off and the filtrate slowly cooled. The picrate was thus obtained in pale yellow slender needles melting at 167°C., which after one recrystallization melted alone or admixed with a specimen obtained from the methylation of tryptamine at 168°C.

The purified picrate from 5 gm. of the quaternary chloride was suspended in a small volume of boiling water and treated with an excess of sodium hydroxide. The cooled mixture was extracted with ether and the extract thoroughly washed with aqueous sodium hydroxide and dried over potassium carbonate. Removal of the ether yielded a pale yellow oil (1.6 gm.) which solidified completely in a short time. After pressing out on tile and washing with a mixture of ether and petroleum ether it melted sharply at 47°C. The free base was obtained only in very fine ill-defined needles. It is extremely soluble in all organic solvents with the exception of petroleum ether.

A small amount treated with an excess of methyl iodide in methanol yielded the characteristic micaceous plates of the quaternary iodide, which after one recrystallization from methanol melted at 197°C., alone or admixed with an authentic specimen.

The hydrochloride could be obtained only as a pale yellow resin, which when dried in a vacuum desiccator over potassium hydroxide became porous and brittle. Analysis: Calcd. for $C_{12}H_{17}N_2Cl$; Cl, 15.79%. Found: Cl, 15.44%.

2:2-Dimethyl-3-benzoyl-2:3:4:5-tetrahydro-3-carboline

A solution of 4 gm. of tryptamine in 40 cc. of dry acetone was treated with an excess of methyl iodide. Some heat was evolved but no precipitation occurred. After several hours the acetone was removed on the steam bath, water was added and the slightly turbid solution filtered through a layer of charcoal. The colorless filtrate was basified with excess KOH and the precipitated bases removed by extraction with a mixture of ether and chloroform. A small amount of insoluble crystalline material was obtained which proved to be the quaternary iodide, m.p., 197°C.

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The ether-chloroform extract was dried over sodium sulphate, evaporated somewhat and heated for four hours under reflux with an excess of benzoyl chloride and potassium carbonate. The chloroform solution was thoroughly washed with water and with dilute hydrochloric acid and dried over potassium carbonate. On evaporation and treatment with a little acetone and ether, the chloroform solution yielded about 0.7 gm. of very stout brilliant octahedra which after recrystallization from acetone, in which the substance is sparingly soluble, melted sharply at 285°C. Analysis: Calcd. for $C_{20}H_{20}ON_2$; C, 78.94; H, 6.58; N, 9.21%. Found: C, 78.77; H, 6.57; N, 9.25%.

3-(β-Phthalimidoethyl)-1-methylindol

A mixture of 7 gm. of crude 1-methyltryptamine and 12.5 gm. of phthalic acid was slowly heated to 230°C. in an oil bath. The somewhat cooled mixture was treated with 100 cc. of boiling alcohol and the solid broken up with a glass rod. The mixture was then heated under reflux for an hour, cooled, filtered and the solid washed with cold alcohol; yield, 10 gm. A small amount was recrystallized by solution in a large volume of hot acetone and rapidly evaporating the filtrate. On cooling, a solid mass of minute needles was obtained which after filtering, washing with alcohol, and drying melted sharply at 177.5°C. The substance is practically insoluble in cold alcohol and only sparingly in hot acetone. Analysis: Calcd. for $C_{19}H_{16}O_2N_2$; C, 75.00; H, 5.26; N, 9.21%. Found: C, 74.92; H, 5.36; N, 9.35%.

The phthalimido derivative when treated with hydrazine hydrate in the usual manner yielded 1-methyltryptamine quantitatively; b.p., 154°C./1 mm. All attempts to obtain the latter in a crystalline condition failed. Exposure in a sealed tube to the native climatic conditions for six months during which time the temperature frequently fell to -30°C. failed to cause crystallization.

The hydrochloride is readily obtained in colorless needles by neutralizing a solution of the base in alcohol with hydrochloric acid and cautiously adding acetone. Recrystallized from methanol-acetone the salt melts sharply at 198°C.

1-Methyl-2-phenyl-4:5-dihydro-3-carboline

A solution of 2.78 gm. of benzoyl-1-methyltryptamine in 35 cc. of chloroform was heated under reflux with 10 gm. of phosphorus oxychloride for one hour. The solvent and excess oxychloride were largely removed by evaporation in a current of air and the residue decomposed with ice. Some residual chloroform was then boiled off, and the turbid solution filtered through a layer of charcoal. The intensely yellow filtrate was basified and the base extracted with ether, the extract was dried over sodium sulphate, evaporated to a small volume and crystallization induced by cautious addition of petroleum ether. The microscopic crystalline base was filtered off and washed with ether-petroleum ether (1:1) and finally with petroleum ether; yield, 2.3 gm. The substance is colorless and melts sharply at 94°C. Alcohol readily dissolves it to a yellow solution with a pale greenish fluorescence. Analysis: Calcd. for $C_{18}H_{16}N_2$; C, 83.08, H. 6.15, N. 10.77%. Found: C, 83.02; H, 6.14; N, 10.88%.

The hydrochloride readily crystallizes from alcohol-ether or alcohol-acetone

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in golden yellow elongated plates, melting at 237°C. to an orange-colored liquid which resolidifies on cooling.

1-Methyl-2-phenyl-3-carboline

A small amount of the dihydro-base was dissolved in dilute sulphuric acid and treated while hot with a solution of chromic acid. A very sparingly soluble chromate was precipitated which gradually dissolved as oxidation proceeded. The filtered solution was basified and the mixture of chromium hydroxide and base filtered off, washed with water, dried and extracted with hot ethyl acetate. The base obtained from the extract did not crystallize. It was converted into the hydrochloride and the latter recrystallized from acetone by adding ether to the concentrated solution. The hydrochloride melts at 278°C. and is very soluble in water or alcohol, yielding a solution with an intense bluish fluorescence. Analysis: Calcd. for $C_{18}H_{15}N_2Cl$; C, 73.34; H, 4.75; Cl, 12.05%. Found: C, 73.02; H, 5.12; Cl, 12.05%.

The picrate is insoluble in water and was recrystallized from hot alcohol in which it is sparingly soluble; m.p., 234°C.

Diethyl β-Cyanopropionacetal

Six moles (275 gm.) of absolute alcohol contained in a flask provided with an inlet tube, a dropping funnel, and a calcium chloride tube, was treated with a stream of dry gaseous hydrogen bromide until 2.75 moles (220 gm.) had been absorbed. The mixture had to be kept cool during this addition since an elevation of temperature converts a portion of the alcohol into the bromide. The mixture was then cooled in salt and ice and 2.5 moles (140 gm.) of acrolein was slowly added, care being taken to prevent local superheating. The mixture was allowed to remain in ice overnight, neutralized with an excess of precipitated calcium carbonate, and about 300 cc. of dry ether was added. The mixture was again allowed to remain in ice overnight and the ethereal layer then decanted from the pasty calcium bromide solution. A small amount of calcium carbonate was added to the ether solution and the solvent then removed *in vacuo*. To the residue, dissolved in 300 cc. of methanol, there was then added 3 gm. of sodium iodide and 2.75 moles (138 gm.) of sodium cyanide dissolved in the minimum volume of water. The mixture was boiled under reflux for 15 to 16 hr., the solvent distilled off on a steam bath and the residue extracted with about 600 cc. of ether in several portions. The extract was freed of ether and the residue fractionally distilled *in vacuo*, through a good glass column. Two main fractions were obtained: (I) up to 97°C./15 mm. (II) 97 to 108°C./15 mm. (mostly at 104-106°C.). Each fraction was redistilled and the higher portion of the first added to the second. The second fraction consisted of the desired nitrile and was conveniently collected over a 2° range. Some boiling points (not corrected) with the corresponding pressures were: 84-85°C./7 mm.; 97°C./11 mm.; 105°C./15 mm. The lower fraction contained a considerable amount of unchanged bromide which may conveniently be added to a subsequent preparation. The yield of nitrile varied from 40 to 60%, depending upon the amount of unchanged bromide recovered.

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Diethyl γ-Aminobutyracetal

A solution of 79 gm. of β-cyanopropionacetal (0.5 mole) in 1000 cc. of absolute alcohol was treated with 70 gm. of sodium (3 moles) in large pieces, the mixture being cooled in running water. When the first vigor of the reaction had subsided, the flask was heated on a steam bath until all the sodium had dissolved. The somewhat cooled mixture was then treated with 200 cc. of water and as much alcohol as would distil was removed on a steam bath through a short column. The first distillate was discarded. The residue was distilled under reduced pressure until no more distillate could be obtained, and the distillate fractionated through a good column from a steam bath. The residue was then distilled through a long column *in vacuo*. With considerable care this distillation may be so carried out that a very sharp separation of the water is possible. The yield of a product of 3° boiling range was 67 to 68 gm. (85% of theory).

When methanol was substituded for ethyl alcohol the mean yield of four runs was 71%. The proportions were: nitrile, 157 gm.; methanol, 1500 cc.; sodium, 140 gm. The pure substance boils at 84°C./11 mm. or at 93°C./15 mm.

Tryptamine

The following procedure has been repeatedly followed after numerous trials using slightly different proportions or different conditions, and has been found to give the pure base in consistent yields.

A mixture of 80 gm. (0.5 mole) of γ-aminobutyracetal and 55 gm. of pure phenylhydrazine contained in a 1000-cc. round-bottomed flask is treated with 68 gm. of finely ground anhydrous zinc chloride. There is a moderate exothermal reaction and the mixture turns pale brown. An upright condenser is attached but no water is run into it. The flask is then gently heated by rotating it over a free flame and the greater portion of the alcohol formed in the reaction is distilled through the condenser. Further cautious heating is continued, preferably with a little local heating occasionally, until a rather vigorous exothermal reaction ensues. Water is then rapidly run into the condenser and the flask removed from the source of heat. When the reaction has subsided the fluid dark-brown mass is run onto the sides of the flask in order to present as great a surface as possible in the subsequent solution of the material. When sufficiently cooled, 60 cc. of acetic acid and 100 cc. of water is added and the mixture gently heated over a free flame until solution is complete. Water (about 600 cc.) is then added (the addition of the water precipitates a dark resinous material which need not be filtered off at this stage) and the zinc is precipitated with a stream of hydrogen sulphide. The zinc sulphide and resin are filtered off through a layer of charcoal and the pale yellow filtrate added to a concentrated solution of 100 gm. of sodium hydroxide. The oil which separates crystallizes on cooling or with great facility on seeding with a crystal of tryptamine. After remaining in the ice chest overnight the amine is filtered off, washed with cold water, and dried in a vacuum desiccator over potassium hydroxide. The yield of this product is 55 gm. (this and the subsequent yields are the average of four runs, the variation being less than

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5%). The crude product is distilled in a vacuum, preferably of 2 mm. or less, from an oil bath and is thus obtained as a pale yellow viscous liquid which rapidly solidifies; yield, 47.4 gm. Further purification is conveniently effected by solution in the minimum volume of hot chloroform and slow cooling. There is thus obtained an almost colorless product consisting of stout polyhedra melting at 118°C.; yield, 41 gm. (51% of theory). The mother liquor on removal of the solvent and distillation of the residue yields a further small amount of equally pure product.

Acknowledgment

The author acknowledges his indebtedness to Dr. G. S. Whitby, Director of the Division of Industrial Chemistry, National Research Laboratories, for his criticism of the manuscript and permission to publish the same.

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