

7-(*N,N*-Trimethyl)-5-methoxytryptamine

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Synthesis of 7-(*N,N*-trimethyl)-5-methoxytryptamine from 2,5-dimethylpyrone via 4-methoxy-2,6-dimethylnitrobenzene and 5-methoxy-7-methylindole is described.

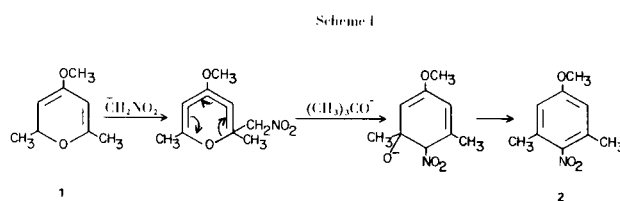
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*N,N*-Dimethyltryptamine and its 5-methoxy derivative are well known hallucinogenic substances (1,2,3,4). In the course of current work in this laboratory on structure-activity relationships among other potential hallucinogenic ring-substituted tryptamines, we undertook the synthesis of the title compound since it contains a non-polar 7-methyl substituent in conjunction with the 5-methoxy group, which enhances the psychotomimetic activity of *N,N*-dimethyltryptamine (4). We wish to report the synthesis of this new indolealkylamine here and will present details concerning its psychopharmacological activity elsewhere.

A key intermediate in our projected synthesis of 7-(*N,N*-trimethyl)-5-methoxytryptamine was 4-nitro-3,5-dimethylphenol, which has been reported to be formed as a minor product from the nitration of 3,5-dimethylphenol by Adams and Stewart (5). Because this nitration with mixed acid gave principally 2-nitro-3,5-dimethylphenol, other preparative approaches to the desired isomer were sought. Nitration of *O*-benzenesulfonyl-3,5-dimethylphenol with mixed acid (6) gave a nitration product which contained three nitro groups. Alkaline saponification of this substance yielded only 2,4-dinitro-3,5-dimethylphenol in 87% yield, indicating the presence of the third nitro group in the second aromatic ring. The same *O*-benzenesulfonyl derivative when dissolved in concentrated sulfuric acid and nitrated with solid potassium nitrate (7) gave a mixture of polynitration products which could not be separated by repeated fractional crystallization. In still an additional attempt to obtain the desired 4-nitro compound, 3,5-dimethylphenol was first 4-nitrosated by the procedure of Klages (8), and this intermediate was oxidized with 30% hydrogen peroxide in acetic acid solution. Only a small

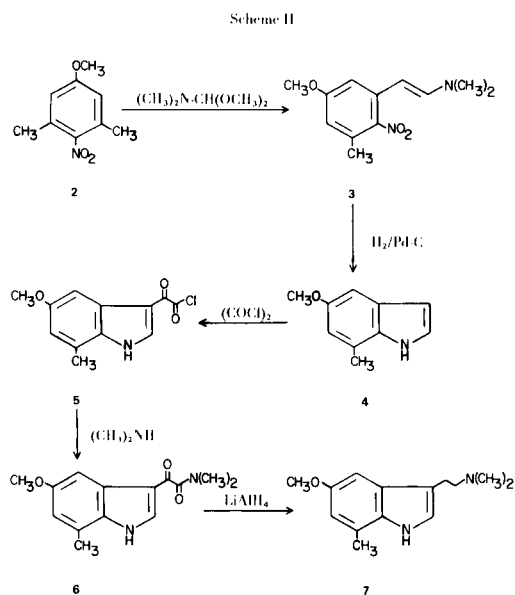
From an examination of Dreiding models of various esters of 3,5-dimethylphenol with sterically bulky acids, it appeared that the pivaloyl ester might provide sufficient steric shielding of the 2- and 6- positions from attack by nitronium ion. However, when this ester was subjected to the action of mixed acid at 0°, only 2,4,6-trinitro-3,5-dimethylphenol was obtained, indicating that acid hydrolysis may have occurred prior to nitration.

Because direct nitration procedures were unsuccessful in producing significant amounts of the required intermediate 2, an alternative synthetic route was sought. Ohta and Kato (9) have reported an indirect small-scale preparation of 4-methoxy-2,6-dimethylnitrobenzene (2) by means of reaction Scheme I. Since 2 was deemed an ideal



starting material for the preparation of the title compound in which the potential 5-methoxy group is already present, we undertook a larger scale preparation of this substance. Available 2,5-dimethylpyrone was first converted to the 4-methoxy compound by means of dimethyl sulfate and alkali, and this, in turn, was treated with 20% perchloric acid to form the perchlorate salt in 85% yield (10). Conversion of 1 to the required nitro compound (2) was carried out on a preparative scale in 72% yield.

The facile synthesis of numerous ring-substituted indoles from appropriately substituted 2-nitrotoluenes as shown



(11). Following this reaction sequence, compound **2** was reacted with a slight molar excess of *N,N*-dimethylformamide dimethylacetal in refluxing *N,N*-dimethylformamide to give a 54% yield of the intermediate enamine **3**. This underwent a rapid reductive cyclization which resulted in a 66% yield of the desired 5-methoxy-7-methylindole (**4**). Introduction of the 3-( $\beta$ -*N,N*-dimethylaminoethyl) side chain was accomplished by the general method of Speeter and Anthony (12) in which **4** was first reacted with oxalyl chloride in ether to give the corresponding 3-glyoxalyl chloride (**5**), and this was converted to the *N,N*-dimethylglyoxalamide (**6**) by the action of anhydrous dimethylamine. The final reduction of **6** to 7-(*N,N*-trimethyl)-5-methoxytryptamine (**7**) was accomplished with lithium aluminum hydride in ether solution.

#### EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined on either Nujol mulls or as neat compounds using a Beckman Acculab 2 spectrophotometer. All spectra were consistent with the proposed structures. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana.

##### *O*-Benzenesulfonyl-3,5-dimethylphenol.

A solution of 3,5-dimethylphenol (48.9 g., 0.4 mole) in pyridine (150 ml.) was stirred vigorously during the addition of benzenesulfonyl chloride (77.7 g., 0.44 mole) at such a rate that the internal temperature was kept below 45°. When the slurry of pyridine hydrochloride became too thick for efficient stirring, 75 ml. of pyridine was added, and stirring was continued for 2 hours at room temperature. The mixture was then heated to just below reflux for 25 minutes, cooled and poured into 1 l. of ice and water. The crystalline ester was collected on a filter and

the crude product amounted to 104 g. (99%). Recrystallization from benzene-petroleum ether (30-60°) gave 90.6 g. (92%); m.p. 124-126°; ir (Nujol mull): 790(m)  $\text{cm}^{-1}$  (S-O-C).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{14}\text{O}_3\text{S}$ : C, 64.12; H, 5.34. Found: C, 64.23; H, 5.47.

##### 2,4-Dinitro-3,5-dimethylphenol.

Mixed acid, prepared from 30 ml. of 96% sulfuric acid and 30 ml. of nitric acid,  $d = 1.5$ , was cooled to 10° and stirred mechanically. The above ester (10 g., 0.038 mole) was added in approximately 1 g. portions at such a rate that the reaction mixture stayed between 10 and 20°. The resulting orange solution was stirred at room temperature for 0.5 hour and then added to 400 ml. of ice and water. The solid product was collected and washed with water. Recrystallization from ethyl acetate-ethanol gave a total of 12 g. (79% as a trinitration product) of yellow crystals, m.p. 149-150°.

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_9\text{S}$ : C, 42.3; H, 2.77. Found: C, 42.4; H, 2.86.

The above ester (10 g.) was added to 150 ml. of 1 *N* sodium hydroxide, and the mixture was stirred and refluxed for 1 hour. The resulting turbid orange solution was filtered while hot, and the filtrate was cooled and acidified with hydrochloric acid. The yellow crystalline product was filtered off, washed with water and air dried; yield, 4.7 g. (87%), m.p. 111-112°. Recrystallization from hot chloroform-hexane gave yellow needles, m.p. 115-116° (lit. (5) 107-108°).

*Anal.* Calcd. for  $\text{C}_8\text{H}_8\text{N}_2\text{O}_5$ : N, 13.2. Found: N, 13.3.

##### Nitration of *O*-Pivaloyl-3,5-dimethylphenol.

Pivaloyl chloride (100 g., 0.83 mole) and 3,5-dimethylphenol (101.3 g., 0.83 mole) were refluxed until evolution of hydrogen chloride ceased. The cooled reaction mixture was diluted with three volumes of benzene-ether (1:1), washed twice with water, once with 1 *N* sodium hydroxide, and again with water. After drying (anhydrous magnesium sulfate) and filtration, the solvents were evaporated and the residue was distilled; b.p. 135-137°/23 mm., yield, 160.8 g. (94%) of colorless oil. This compound (20.6 g., 0.1 mole) was nitrated by dropwise addition to a stirred mixture of 40 ml. of 96% sulfuric acid and 40 ml. of 90% nitric acid at a temperature of 5 to 7°. After addition to ice water, the yellow solid product was collected, washed with water and air-dried. Recrystallization from boiling chloroform-petroleum ether (b.p. 30-60°) gave 16.0 g. (96%) of yellow crystals, m.p. 103-105°. Analysis showed this substance to be 2,4,6-trinitro-3,5-dimethylphenol rather than the desired product, which is nearly identical in melting point.

*Anal.* Calcd. for  $\text{C}_8\text{H}_7\text{N}_3\text{O}_7$ : N, 16.35. Found: N, 16.45.

##### 4-Methoxy-2,6-dimethylnitrobenzene (2).

4-Methoxy-2,5-dimethylpyrillium perchlorate (**1**) was prepared from 2,5-dimethylpyrone in 85% yield by the procedure of Baeyer (10). A solution of sodium *t*-butoxide in *t*-butyl alcohol was prepared by refluxing sodium chips (4.6 g., 0.2 g. atom) and anhydrous *t*-butyl alcohol (340 ml.) for 24 hours. The resulting solution was clarified by addition of more *t*-butyl alcohol. The perchlorate salt **1** (23.8 g., 0.1 mole) was placed in a 3-necked flask fitted with a stirrer, and 90 ml. of nitromethane was added through a dropping funnel; the mixture was stirred until a clear colorless solution was obtained. The previously prepared solution of sodium *t*-butoxide was added in one portion, and the resulting dark-red solution was stirred and refluxed for one hour. The still warm reaction mixture was poured into 1500 ml. of water containing 16 ml. of hydrochloric acid, and the precipitated oil was

washed with water, dried (anhydrous magnesium sulfate), filtered, and evaporated under reduced pressure. The dark oily residue was extracted with five portions of petroleum ether (b.p. 30-60°), and the combined extracts were cooled to induce crystallization; yield, 13.0-13.6 g. (72-75%) of pure **2**, m.p. 50.5-51.5° (lit. (9) 53°).

#### 2-Nitro-3-methyl-5-methoxy- $\beta$ -(*N,N*-dimethylamino)styrene (**3**).

To a solution of 18.1 g. (0.1 mole) of **2** in 100 ml. of *N,N*-dimethylformamide (dried and redistilled under reduced pressure before use) was added 16 g. (0.13 mole) of *N,N*-dimethylformamide dimethylacetal. The reaction mixture was placed in a 250-ml. round-bottom flask fitted with a nitrogen gas inlet and a 24 x 1.5 cm. distillation column packed with single-turn glass helices and attached to a total reflux variable takeoff still head. Reflux was maintained for eight hours during which time takeoff was adjusted so that the head temperature did not exceed 70°. A total of 8.4 ml. of distillate was collected; the calculated volume of methanol was 8.2 ml. The distillate was evaporated under reduced pressure, and the residue was distilled in a Kugelrohr apparatus at 0.01 mm. The colorless oily distillate was dissolved in hexane containing a small amount of benzene and allowed to crystallize, yield, 12.3 g. (54%) of colorless crystals, m.p. 100-101°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 61.00; H, 6.78; N, 11.86. Found: C, 61.15; H, 6.97; N, 11.88.

#### 5-Methoxy-7-methylindole (**4**).

The enamine **3** (12 g., 0.051 mole) was dissolved in 100 ml. of benzene in a 500-ml. Parr hydrogenation bottle, and 1 g. of 10% palladium-on-carbon catalyst was added. The bottle was attached to a Parr low-pressure hydrogenation apparatus, flushed with hydrogen and pressured to 4.22 KG./cm<sup>2</sup> with hydrogen. Hydrogen uptake was rapid, and the calculated quantity of hydrogen was absorbed in 35 minutes. After removing the spent catalyst, the filtrate was washed three times with 4% hydrochloric acid, then with water and dried (anhydrous magnesium sulfate). The solvent was evaporated, and the residue was purified by Kugelrohr distillation at 0.15 mm. (bath temperature, 100-110°), yield, 5.4 g. (66%) of colorless plates of pure **4**.

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>NO: C, 74.5; H, 6.82; N, 8.70. Found: C, 74.3; H, 7.10; N, 8.41.

#### 5-Methoxy-7-methyl-3-indole-*N,N*-dimethylglyoxalamide (**6**).

To a cooled (ice bath) and stirred solution of 12 g. (0.075 mole) of indole **4** in 150 ml. of anhydrous ether was added dropwise 12 ml. of oxalyl chloride in 20 ml. of dry ether at such a rate to prevent the temperature from rising above 20°. The orange intermediate glyoxalyl chloride **5** which precipitated was collected on a large funnel and rapidly washed with dry ether to remove excess oxalyl chloride. The dry **5** was resuspended in 150 ml. of dry ether and treated with 15 ml. of anhydrous dimethylamine in

20 ml. of dry ether while stirring and cooling (ice bath). When reaction was complete, the solid mixture of crude **6** and dimethylamine hydrochloride was filtered off, slurried in water and the insoluble crude **6** was collected on a filter and washed with water and air dried; yield, 8.6 g. (44%); m.p. 190-200°. This product was used in the final step without further purification. An analytical sample purified by Kugelrohr distillation at 0.01 mm. melted at 236-237°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 64.6; H, 6.16; N, 10.77. Found: C, 64.8; H, 6.29; N, 10.54.

#### 7-(*N,N*-Trimethyl)-5-methoxytryptamine (**7**).

To a stirred and cooled (ice bath) mixture of 5.1 g. (0.128 mole) of lithium aluminum hydride in 125 ml. of anhydrous ether was added dropwise a solution of 7.7 g. (0.0295 mole) of the amide **6** in 100 ml. of warm benzene. The reaction mixture was then stirred and refluxed for two hours, cooled (ice bath) and the complex formed was hydrolyzed by the slow and careful addition of cold water. After filtration to remove inorganic matter, the filtrate was dried (anhydrous magnesium sulfate), filtered and the solvents evaporated. The residue was purified by Kugelrohr distillation at 0.01 mm. The resulting colorless oil solidified upon standing at room temperature to give 3.04 g. (45%) of pure **7** as colorless plates melting at 83-84°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O: C, 72.4; H, 8.62; N, 12.07. Found: C, 72.19; H, 8.64; N, 11.82.

#### REFERENCES AND NOTES

- (1) S. Szara, *Experientia*, **12**, 441 (1956).
- (2) F. Benington, R. D. Morin and L. C. Clark, Jr., *J. Org. Chem.*, **23**, 19 (1958).
- (3) F. Benington, R. D. Morin and L. C. Clark, Jr., *ibid.*, **25**, 1542 (1960).
- (4) F. Benington, R. D. Morin and L. C. Clark, Jr., *Alabama J. Med. Sci.*, **2**, 397 (1965).
- (5) R. Adams and H. W. Stewart, *J. Am. Chem. Soc.*, **63**, 2859 (1941).
- (6) G. Schapperli, *Gazz. Chim. Ital.*, **11**, 77 (1881) reports exclusively *p*-nitration of phenylbenzenesulfonate under these conditions.
- (7) A. Eichengrün and A. Einhorn, *Ann. Chem.*, **262**, 137 (1891).
- (8) A. Klages, *Ber.*, **32**, 1518 (1899).
- (9) M. Ohta and H. Kato, *J. Chem. Soc. Japan*, **32**, 709 (1959).
- (10) A. Baeyer, *Ber.*, **43**, 2337 (1910).
- (11) W. Leimgruber and A. D. Batcho, "A New Indole Synthesis," Third International Congress of Heterocyclic Chemistry, Japan, Aug. 23-27, 1971.
- (12) M. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).