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Synthesis of 5,6,7-Trimethoxy-2,3-dihydroindole and 6,7-Dimethoxyindole

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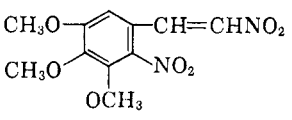
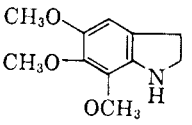
5,6,7-Trimethoxy-2,3-dihydroindole has been synthesized by catalytic hydrogenation of the corresponding indole. Several alternative routes to this dihydroindole were unsuccessful. The synthesis of 6,7-dimethoxyindole is also described.

In a previous communication,[3] we described the synthesis of 5,6,7-trimethoxyindole from 2-nitro-3,4,5-trimethoxy-β-nitrostyrene (I) which was obtained in 9% yield by nitration of 3,4,5-trimethoxy-β-nitrostyrene. At that time, we indicated our interest in obtaining 5,6,7-trimethoxy-2,3-dihydroindole (II), a possible primary *in vivo* oxidative cyclization product of mescaline (3,4,5-trimethoxy-β-phenethylamine). The present study was undertaken with the idea of examining several alternative routes for the synthesis of II in better overall yield than would be expected from a two-step reduction of I.



I

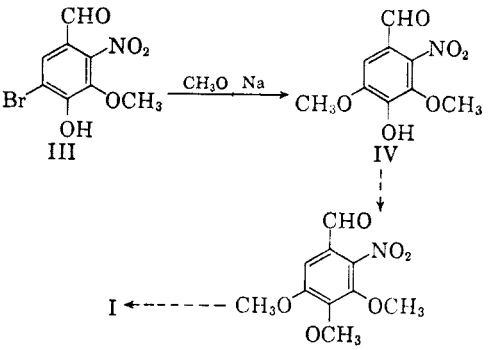


II

We had attempted unsuccessfully to synthesize the *N*-benzyl derivative of II[4] directly by the action of ethylene chlorobromide on *N*-benzyl-2,3,4-trimethoxyaniline; other routes were also sought for building up the 5,6,7-trimethoxyindole via the appropriate oxindole, dioxindole, and isatin derivatives[4] which were obtained from the aforementioned aniline. However, none of these approaches was deemed satisfactory for preparing II for the principal reason that cyclizations involving the open *ortho-* position to the amino group either occurred in poor yield or not at all. In an attempt to obtain *o*-bromo-*N*-benzylmescaline for other cyclization studies, debromination occurred when *o*-bromo-*N*-benzoylmescaline was treated with lithium aluminum hydride; the only product formed was *N*-benzylmescaline. *o*-Bromo-*N*-benzoylmescaline was obtained by bromination of *N*-benzoylmescaline with one mole equivalent of bromine in acetic acid.[5] Oxidation of this monobromo compound with alkaline permanganate gave a degradation product which was identified as 2-bromo-3,4,5-trimethoxybenzoic acid.[6]

Although the nuclear debromination of aromatic compounds by lithium aluminum hydride in ethers is somewhat unusual, it has been observed in several other instances. Erne and Ramirez[7] showed that 3,4-methylenedioxy-5-bromo-β-nitrostyrene is reduced to 3,4-methylendioxy-β-phenethylamine when refluxed with lithium aluminum hydride for 10 hr. Similarly, Gates and Tschudi[8] have noted that 1-bromocodeinone is simultaneously reduced and debrominated by this reagent. It is noteworthy that in all of these instances the halogen atom removed is originally present in an aromatic ring containing at least two alkoxy groups, one of which is either *ortho-* or *para-* to the halogen atom. In our recent work describing the syntheses of 4-halo-β-phenethylamines,[9] it was noted that the reduction of 4-halophenylacetonitriles could be carried out with lithium aluminum hydride without loss of the halogen atom.

In the following approach to the synthesis of II, in which improved yields of the intermediate I were hoped for, 2-nitro-5-bromovanillin[10] (III) was chosen as a starting material:



The possibility of replacing the bromine atom in III with methoxyl to form IV was suggested by the

(1) Battelle Memorial Institute.

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(3) R. D. Morin, F. Benington, and L. C. Clark, *J. Org. Chem.*, **22**, 331 (1957).

(4) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, **23**, 19 (1958).

(5) A. Heffter, *Ber.*, **31**, 1196 (1898) found that mescaline was converted to the corresponding 2,6-dibromo compound when treated with an excess of bromine.

(6) A. M. Hamburg, *Monatsh.*, **19**, 589 (1898).

(7) M. Erne and F. Ramirez, *Helv. Chim. Acta*, **53**, 912 (1950).

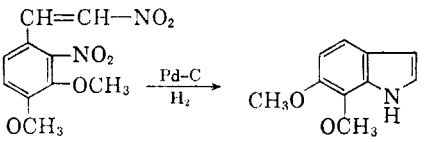
(8) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **74**, 1109 (1952).

(9) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, **23**, 1979 (1958).

(10) L. C. Raiford and W. C. Strosser, *J. Am. Chem. Soc.*, **50**, 2556 (1928).

fact that 5-bromovanillin has been converted to syringaldehyde[11] by the action of sodium methoxide and copper powder at elevated temperatures. It was thought that the presence of the nitro group in III would enhance the activity of the bromine atom. When a methanol solution of III was subjected to the action of sodium methoxide in the presence of copper powder under the conditions employed by Pepper and MacDonald,[11] only an intractable tar was formed from which none of the desired aldehyde (IV) could be isolated; carrying out the same reaction in refluxing methanol afforded only unchanged III.

The ready availability of 2-nitrovanillin, the precursor of III, did, however, offer a satisfactory route to the synthesis of the hitherto unknown 6,7-dimethoxyindole (VI). Methylation of 2-nitrovanillin gave 2-nitro-3,4-dimethoxybenzaldehyde,[12] which was condensed with nitromethane to form the β-nitrostyrene V. Reductive cyclization of V in accordance with the method of Huebner *et al.*[13] gave 6,7-dimethoxyindole (VI) in about 23% yield.



V VI

The indole VI exhibited a characteristic ultraviolet absorption spectrum and gave a positive Ehrlich color reaction. The possibility of preparing compounds having potential pharmacological activity from VI is currently being examined.

Because of these unsuccessful attempts to find new routes for the synthesis of 5,6,7-trimethoxy-2,3-dihydroindole (II), the possibility of selective reduction of the corresponding substituted indole was examined. Adkins and Coonradt[14] have reported that 2-methylindole undergoes hydrogenation (190°; 200–300 atm.) in the presence of a copper chromite catalyst to give largely 2-methyl-2,3-dihydroindole. These investigators also point out that hydrogenation at 230° over Raney nickel brings about perhydrogenation to 2-methyloctahydroindole. A later investigation reported by King *et al.*[15] states that indole in ethanol solution undergoes both perhydrogenation and alkylation with hydrogen and Raney nickel at temperatures above 150°, whereas, if the reaction is carried out at 90–100°, the primary reduction product is 2,3-dihydroindole. Previous work in this laboratory has shown that the aromatic ring in mescaline does not undergo hydrogenation in the presence of Raney nickel catalysts under the same conditions described by King. Accordingly, it was expected that the hydrogenation of 5,6,7-trimethoxyindole would stop at the point where one mole of hydrogen had been taken up by the pyrrole ring. The hydrogenation of this indole was done in ethanol solution with a commercial Raney nickel catalyst at 100° and at a hydrogen pressure of 1000 p.s.i.g. The behavior of the reaction product on distillation indicated that virtually no hydrogenation of the benzene ring had taken place, and the desired 5,6,7-trimethoxy-2,3-dihydroindole (II) was obtained in about 69% yield.

EXPERIMENTAL[16]

N-Benzoyl-2-bromo-3,4,5-trimethoxy-β-phenethylamine. To a solution of 20 g. of mescaline sulfate in 100 ml. of water was added 20 g. of NaOH and 14 g. of benzoyl chloride. Within a few minutes a solid began to deposit, and after warming on the steam bath for 10 min. and cooling, the crude *N*-benzoylmescaline was collected and recrystallized from alcohol-water; yield, 19.5 g. (86%); m.p. 123–124°; (reported,[17] 123°). To a solution of 19.5 g. of *N*-benzoylmescaline in 100 ml. of glacial acetic acid was added gradually a solution of 9.9 g. of Br_2 in 25 ml. of glacial acetic acid with swirling. Absorption of Br_2 was rapid, and immediately after addition of the Br_2 solution, the reaction mixture was poured into about 300 ml. of water. The colorless oil which separated was extracted with chloroform, and this extract was washed with $NaHCO_3$ solution and water. After drying over anhydrous $MgSO_4$, most of the chloroform was evaporated, and the residue was diluted with petroleum ether. A colorless crystalline solid was deposited which was collected and dried; yield, 23.1 g. (95%); m.p. 112–113°. After recrystallization from alcohol-water, an analytical specimen melted at 114–115°.

Anal. Calcd. for $C_{18}H_{20}BrNO_4$: Br, 20.3. Found: Br, 20.5.

Reduction of N-benzoyl-2-bromo-3,4,5-trimethoxy-β-phenethylamine with $LiAlH_4$. To a stirred solution of 7.7 g. of $LiAlH_4$ in 100 ml. of dry ether was added gradually a solution of 26.6 g. of *N*-benzoyl-2-bromo-3,4,5-trimethoxy-β-phenethylamine in 300 ml. of dry ether and 100 ml. of dry benzene. The mixture was then stirred and heated under reflux for 1.5 hr., cooled in an ice bath, and cautiously treated with ice water to hydrolyze the excess $LiAlH_4$ and the reaction complex. Precipitated inorganic salts were removed by filtration, and the filtrate was dried over anhydrous $MgSO_4$, filtered, and solvents were removed by distillation under reduced pressure. Distillation of the residue gave 16.8 g. (83%) of pale yellow oil, b.p. 210–220°/0.5 mm. This product contained no halogen, and analysis of the HCl salt, m.p. 158–159°, obtained by treatment of an ether solution with dry HCl gas and recrystallization from alcohol ether, showed this base to be *N*-benzylmescaline.

Anal. Calcd. for $C_{18}H_{24}ClNO_3$: C, 64.0; H, 7.1; Cl, 10.5; N, 4.15. Found: C, 63.6; H, 7.1; Cl, 11.2; N, 4.07.

To confirm the structure of 2-bromo-*N*-benzoylmescaline, a sample was oxidized to the known 2-bromo-3,4,5-trimethoxybenzoic acid[6] by refluxing 4 g. of the former with a solution of 8 g. of $KMnO_4$ and 1 ml. of 10% NaOH in 80 ml. of water for 5 hr. The mixture was filtered from MnO_2, extracted with chloroform and ether, and acidified with hydrochloric acid. On cooling, a nearly colorless solid slowly crystallized; m.p. 149–150°. For comparison, a small sample of authentic 2-bromo-3,4,5-trimethoxybenzoic acid

(11) J. M. Pepper and J. A. MacDonald, *Canadian J. Chem.*, **31**, 476 (1953).

(12) R. Pschorr and C. Sumuleanu, *Ber.*, **32**, 3409 (1899).

(13) C. F. Huebner, H. A. Troxell, D. C. Schroeder, *J. Am. Chem. Soc.*, **75**, 5887 (1953).

(14) H. Adkins and H. L. Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941).

(15) F. E. King, J. A. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945).

(16) All melting points are uncorrected.

(17) R. H. F. Manske and H. L. Holmes, *The Alkaloids*, Academic Press, Inc., New York, 1953, Vol. III, p. 325.

was prepared by bromination of 3,4,5-trimethoxybenzoic acid in acetic acid; m.p. 149–150° (reported,[6] 151°). The compound obtained by oxidation did not depress the melting point of the authentic 2-bromo-3,4,5-trimethoxybenzoic acid.

2-Nitro-5-bromovanillin (III). A mixture of 152 g. of vanillin and 150 ml. of acetic anhydride was refluxed for 3.5 hr., allowed to cool slightly, and poured with stirring into 1 l. of water. The oil which separated soon solidified and was collected and washed thoroughly with water; yield, 190 g. (98%); m.p. 73–74° (reported,[18] 77°). To 400 g. of fuming HNO_3 (d = 1.5) was added gradually 100 g. of acetylvanillin with stirring while maintaining the temperature at 2 to 6° with a cooling bath. After stirring an additional 10 min., the reaction mixture was poured into 1.5 l. of ice and water, and the yellow solid product collected and washed well with water. Without drying, the crude product was refluxed with a mixture of 50 ml. of CH_3OH, 50 ml. of water, and 60 ml. of 45% KOH for 15 min. Acidification with HCl gave a crude solid product which, after collection and drying, was stirred with 250 ml. of alcohol at room temperature; the solution was filtered from any insoluble material and concentrated under reduced pressure to permit crystallization of the 2-nitrovanillin; yield (2 crops), 62 g. (61%); m.p. 137–138°; (reported,[10] 136°). To a solution of 16.5 ml. of Br_2 in 200 ml. of glacial acetic acid was added 60 g. of 2-nitrovanillin and 1 g. of I_2. The mixture was warmed on a steam bath until all solid was dissolved and then allowed to stand overnight at room temperature. The mixture was poured into 1 l. of water, and the precipitated product collected, washed with water, and dried to obtain 79 g. (94%) of 2-nitro-5-bromovanillin (III) as a light tan powder, m.p. 152–153° (reported,[10] 150–151°), sufficiently pure for subsequent experiments.

Attempted conversion of III to 2-nitro-3,5-dimethoxy-4-hydroxybenzaldehyde (IV). Refluxing 27.6 g. of III with a solution of 5 g. of sodium in 100 ml. of absolute methanol for 5 hr. resulted in complete recovery of unchanged starting material on concentration and acidification. Heating 11 g. of III with a solution of 10 g. of sodium in 125 ml. of absolute methanol at 135° in a bomb for 2 hr. also resulted in recovery of unchanged starting material. Use of copper powder as a catalyst[11] under the latter conditions promoted extensive decomposition, but in all cases the products which could be isolated still contained bromine, and the desired replacement of Br by OCH_3 could not be achieved.

2-Nitro-3,4-dimethoxy-β-nitrostyrene (V). A solution of 52 g. of NaOH in 60 ml. of water was added gradually to a stirred mixture of 60 g. of 2-nitrovanillin, 80 ml. of alcohol, and 60 ml. of dimethyl sulfate while maintaining the reaction temperature at about 45–60°. An additional 20 ml. of dimethyl sulfate was added and the mixture was stirred for an hour longer, diluted with 800 ml. of water, and the oily product which separated was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$, and the ether evaporated to give 57 g. (80%) of crude 2-nitroveratric aldehyde as a dark brown oil which refused to crystallize (reported m.p. 64°[12]). A mixture of 33 g. of the crude 2-nitroveratric aldehyde, 15 ml. of nitromethane, 9 g. of ammonium acetate, and 50 ml. of acetic acid was refluxed for 2 hr. and cooled. The yellow solid which crystallized was collected, washed with water, and dried; yield, 12.6 g. (32%); m.p. 170–171°. An analytical specimen recrystallized from $CHCl_3$-petroleum ether melted at 171–171.5°.

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: N, 11.0. Found: N, 10.9.

6,7-Dimethoxyindole (VI). To a solution of 18.7 g. of V 185 ml. of ethyl acetate, 20 ml. of alcohol, and 25 ml. of acetic acid in a Parr hydrogenation bottle was added 2 g. of 10% Pd-C catalyst, and the mixture was shaken with hydrogen at about 3 atmospheres until hydrogen was no longer absorbed (about 4 hr.). The catalyst was removed by filtration, and the filtrate was added to a mixture of ether and saturated aqueous $NaHCO_3$ and stirred to neutralize acetic acid. The organic layer was separated, washed 3 times with water, and dried over anhydrous Na_2CO_3. After concentrating to a volume of about 20 ml., 250 ml. of petroleum ether was added, and the solvent phase was decanted from a dark oil which separated. Evaporation of the solvent on a steam bath and cooling gave 3 g. (23%) of VI as light yellow needles, m.p. 102–103°, unchanged after recrystallization from petroleum ether-benzene; ultraviolet absorption, λ_{max} (log ϵ): 208 (4.67); 270 (3.90).

Anal. Calcd. for $C_{10}H_{11}NO_2$: N, 7.91. Found: N, 7.93.

5,6,7-Trimethoxy-2,3-dihydroindole (II). A mixture of a solution of 6.5 g. of 5,6,7-trimethoxyindole[3] in 75 ml. of alcohol and 10 g. of Raney nickel was hydrogenated for 16 hr. at 100° and 75 atm. of hydrogen. The catalyst was removed by filtration, the solvent was stripped from the filtrate and the residue was distilled to give 4.4 g. (67%) of a pale yellow oil, b.p. 133–134°/0.7 mm. Treatment of an ether solution with dry HCl gave 5,6,7-trimethoxy-2,3-dihydroindole hydrochloride, m.p. 205–206° after recrystallization from alcohol-ether.

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: Cl, 14.5; N, 5.70. Found: Cl, 14.2; N, 5.88.

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(18) Tiemann and Nagai, *Ber.*, 11, 647 (1878).