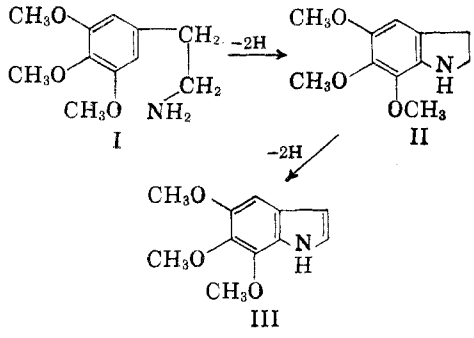
stemmed from the fact that the psychotogens *d*-lysergic acid diethylamide, bufotenine, yohimbine, and adrenochrome contain an indole ring. To explain the psychotomimetic activity of β-phenethylamines such as mescaline (I), amphetamine, and 3,4,5-trimethoxyamphetamine in terms of this hypothesis, it would be necessary that these substances be capable of undergoing oxidative cyclization, *in vivo*, to the corresponding indoles. Opposed to this generalization is the fact that a number of indoles which are closely related to *d*-lysergic acid diethylamide (*e.g.* 2-bromo-*d*-lysergic acid diethylamide) fail to show psychotomimetic activity.[9] If these concepts are meaningful, it would be reasonable to expect that either 5,6,7-trimethoxyindole (III) or 5,6,7-trimethoxy-2,3-dihydroindole (II) would show psychotomimetic activity under proper physiological conditions.



The synthesis of the hitherto unknown indole (III) presented unexpected difficulties. Only one of seven alternate routes explored was found to be practical. The critical step in several of these routes was the introduction of a nitro group into the 2-position of a suitably 1-substituted-3,4,5-trimethoxybenzene. Finally, this step was solved when conditions were found for the nitration of 3,4,5-trimethoxy-β-nitrostyrene in acetic anhydride solution with red fuming nitric acid to give 2-nitro-3,4,5-trimethoxy-β-nitrostyrene in 9% yield. Reductive cyclization of this compound to 5,6,7-trimethoxyindole (III) was accomplished with iron powder and acetic acid in a manner similar to that described by Ek and Witkop.[10] Although the biological evaluation of this compound will require various pharmacological tests, preliminary results, involving the intravenous injection of large doses in cats, which show a dramatic reaction to mescaline, indicate that III is without observable action in terms of changes in behavior or brain oxygen tension. Further biological studies of the action of both II and III at appropriately selected metabolic sites will be necessary in order to ascertain whether mescaline acts through these indole intermediaries.

The synthesis of II is currently underway, since this compound would presumably be the primary *in vivo* oxidative cyclization product of mescaline.

(9) E. Rothlin, paper presented at "Conference on the Pharmacology of Psychotomimetic and Psychotherapeutic Drugs," held in April 1956 at the New York Academy of Science.

(10) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5583 (1954).

EXPERIMENTAL[11]

2-Nitro-3,4,5-trimethoxy-β-nitrostyrene. A precooled solution (−8°) of 7.9 g. of 3,4,5-trimethoxy-β-nitrostyrene in 40 ml. of acetic anhydride was rapidly stirred during the dropwise addition of 5 ml. of red fuming nitric acid. The temperature of the nitration mixture was maintained at −7° to −8° during this phase of the reaction. Following the addition of the nitric acid, the nitration mixture was stirred for an additional 20 min. and then poured onto 200 ml. of an ice water mixture. Solid sodium carbonate was then added to the mixture to hasten the hydrolysis of the acetic anhydride. The crude precipitated nitro compound was collected on a filter, carefully washed with water and then recrystallized from aqueous ethanol. There was obtained 0.8 g. (9.4%) of 2-nitro-3,4,5-trimethoxy-β-nitrostyrene, m.p. 177–178°, as yellow needles.

Anal. Calcd. for $C_{11}H_{12}N_2O_7$: C, 46.5; H, 4.22; N, 9.85. Found: C, 46.7; H, 4.06; N, 9.56.

5,6,7-Trimethoxyindole (III). A solution of 2.5 g. of 2-nitro-3,4,5-trimethoxy-β-nitrostyrene in 18 ml. of ethanol was reduced with 8.8 g. of iron powder and 18 ml. of glacial acid in accordance with the procedure of Ek and Witkop.[10] After treating the reaction mixture with a solution of sodium bisulfite in 220 ml. of water, the crude indole was extracted with five portions of ether. Evaporation of the ether gave 1.4 g. of oily crude product which was taken up in a mixture of 15 ml. of dry benzene and 15 ml. of petroleum ether (30°–60°) and adsorbed on a column of 15 g. of chromatographic alumina. Treatment of the column with 36 ml. of the original benzene-petroleum mixture containing an additional 18 ml. of dry benzene was effective in selectively eluting the indole, since the tars and color bodies were more strongly adsorbed.

By evaporation of the eluate, there was obtained 0.9 g. of III, as a green oil which gradually solidified upon standing; the solid product melted at 70–72°. A colorless analytical specimen, m.p. 71–72°, was obtained by evaporative distillation at 0.4 mm.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8. Found: C, 63.7; H, 6.5; N, 6.7.

The ultraviolet spectrum in methanol–1-propanol showed λ_{max} (log ϵ) 268 (3.52); [287 (3.34)].

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(11) All melting points are uncorrected.

Mescaline Analogs. VII. 3,4,5-Trimethyl-β-phenethylamine

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A mescaline analog in which each of the methoxyl groups at the 3,4, and 5- positions is replaced by methyl has not been reported previously. The

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effect of replacement of alkoxyl by methyl or ethyl has been studied in the case of the 2,4,6-substituted phenethylamines,[3] but all compounds in this series produced markedly different effects on the respiratory enzymes present in brain homogenates than did compounds substituted in the 3,4- or 3,4,5-positions. Accordingly, 3,4,5-trimethyl-β-phenethylamine should provide a more reliable indication of the change in psychochemical activity brought about by replacement of methoxyl by methyl in the mescaline nucleus.

The key reaction in the synthesis of 3,4,5-trimethyl-β-phenethylamine was the isomerization of 2,4,6-trimethylacetophenone, readily obtained by Friedel-Crafts acetylation of mesitylene, to 3,4,5-trimethylacetophenone by heating with anhydrous aluminum chloride.[4] Transformation of the acetyl group to the β-aminoethyl side-chain was readily accomplished *via* the Kindler modification of the Willgerodt reaction. Conversion of the 3,4,5-trimethylphenylacetic acid so obtained to the corresponding amide, and reduction with lithium aluminum hydride, afforded the desired 3,4,5-trimethyl-β-phenethylamine. This route to β-phenethylamines is convenient when the corresponding acetophenones are available and is worthy of further exploitation.

Results of the physiological evaluation of 3,4,5-trimethyl-β-phenethylamine will be published elsewhere.

EXPERIMENTAL[5]

3,4,5-Trimethylphenylacetothiomorpholide. 2,4,6-Trimethylacetophenone, b.p. 109–111°/9 mm., was obtained in 88% yield by the action of acetic anhydride on mesitylene in the presence of anhydrous aluminum chloride in carbon disulfide solution.[6] Isomerization to 3,4,5-trimethylacetophenone was accomplished as described[4] by heating a mixture of 71 g. of 2,4,6-trimethylacetophenone with 116 g. of anhydrous aluminum chloride at 170° for 1.5 hr.; yield, 56.6 g. (80%) of a pale yellow oil, b.p. 135–140°/12 mm. A mixture of 48.6 g. of 3,4,5-trimethylacetophenone, 39 g. of redistilled morpholine, and 14.4 g. of sulfur was refluxed for 12 hr. The warm reaction mixture was poured into 175 ml. of hot ethanol and allowed to cool to permit the product to crystallize; yield, 62.6 g. (79%) of 3,4,5-trimethylphenylacetothiomorpholide, m.p. 120–122°, sufficiently pure for the next step. A sample recrystallized from ethanol melted at 123–124°.

Anal. Calcd. for $C_{15}H_{21}NOS$: N, 5.3; S, 12.2. Found: N, 5.2; S, 12.0.

3,4,5-Trimethylphenylacetic acid. A mixture of 51 g. of 3,4,5-trimethylphenylacetothiomorpholide, 110 ml. of acetic acid, 16 ml. of sulfuric acid, and 25 ml. of water was heated under reflux for 5 hr. and decanted from the small amount of tar formed into 850 ml. of water with stirring. The precipitated crude product was collected, washed with water, and heated with 225 ml. of 5% aqueous sodium hydroxide. Filtration from a small amount of insoluble matter and acidification with dilute hydrochloric acid gave 30 g. (88%) of 3,4,5-trimethylphenylacetic acid sufficiently pure for the next step. A sample recrystallized from benzene-petroleum ether melted at 125–126°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.8; Neutr. Equiv. 178. Found: C, 74.0; H, 7.9; Neutr. Equiv. 180.

3,4,5-Trimethylphenylacetamide. After the initial vigorous reaction had subsided, a mixture of 21.3 g. of 3,4,5-trimethylphenylacetic acid and 25 g. of phosphorus pentachloride was warmed on the steam bath for 10 min. The mixture was distilled under reduced pressure to remove phosphorus oxychloride, and the residue was added gradually to 100 ml. of ice-cooled concentrated aqueous ammonia. The precipitated amide was collected, washed with water, and air dried; recrystallization from benzene plus a small amount of ethanol afforded 18 g. (85%) of the pure amide, m.p. 183–184°.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.6; H, 8.5; N, 7.9. Found: C, 74.4; H, 8.6; N, 7.9.

3,4,5-Trimethyl-β-phenethylamine. To a stirred suspension of 8.6 g. of lithium aluminum hydride in 500 ml. of absolute ether, was added a solution of 10 g. of 3,4,5-trimethylphenylacetamide in 600 ml. of boiling reagent benzene, using additional hot benzene to redissolve material which crystallized during the addition. The reaction mixture was stirred and refluxed for 22 hr. and then hydrolyzed by cautious addition of water and 10% sulfuric acid. A white solid insoluble in both the ether and aqueous layers was formed and collected by filtration. This material proved to be the insoluble sulfate of 3,4,5-trimethyl-β-phenethylamine contaminated with aluminum salts. Upon heating with concentrated hydrochloric acid, the crude product dissolved, and the hydrochloride of 3,4,5-trimethyl-β-phenethylamine crystallized in the form of colorless lustrous plates on cooling. The yield was 10.1 g. (89%), m.p. 249–250° after recrystallization from methanol-ethyl acetate.

Anal. Calcd. for $C_{11}H_{15}ClN$: Cl, 17.8; N, 7.0. Found: Cl, 17.7; N, 6.9.

The *benzoyl derivative* melted at 153–154°.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.9; H, 7.9. Found: C, 80.6; H, 7.7.

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A Convenient Synthesis of *m*-Anisidine

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In studies on the preparation of ring derivatives of phenothiazines[1] beginning with the corresponding anilines, *m*-anisidine was required. This compound is not commercially available, in spite of its relative importance as a starting material, particularly in the synthesis and degradative studies of some indole alkaloids, notably harmine[2] and reserpine.[3] The conventional method of preparing *m*-

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