TABLE I

γ-ARYLIDENE-α,β-DIMETHYLGLUTACONIC ANHYDRIDES

Aryl Group	Color	M.P.,[a] °C.	Yield, %	Analysis Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
p-Dimethylaminophenyl	Purple	237–239E	30	70.83	70.15	6.32	6.07
p-Diethylaminophenyl	Purple	163B	24	72.21	71.93	7.07	6.81
3,4-Dimethoxyphenyl	Yellow	159–160E	39	66.66	66.64	5.59	5.54
3,4-Diethoxyphenyl	Yellow	139–141B	37	68.34	67.98	6.37	6.23
1-Naphthyl	Orange	192–194E	33	77.68	77.77	5.07	4.80

[a] E, ethyl acetate; B, benzene.

densation takes place at the β-methyl group to give a structure V. In order for this reaction to occur the methyl group must be considered to be activated by the principle of vinylogy as one would expect the methyl group of ethyl crotonate or ethyl β,β-dimethylacrylate to be activated. Although there are analogies for such activation—for example, the base-catalyzed condensation of ethyl oxalate with ethyl crotonate to give diethyl oxaloacetate[5]—the analogy does not hold for the aldehyde condensations. It has been shown[6] that the base-catalyzed condensation between benzaldehyde and either crotonic acid or β,β-dimethylacrylic acid takes place at the α-carbon atom with rearrangement of the double bond. Thus, crotonic acid gives α-benzylidenevinylacetic acid. If such a reaction occurred with β-methylglutaconic anhydride, the accepted structure IV would result. At present there seems to be no more direct basis than this comparison for eliminating structure V. Positive identification of a band characteristic of the methyl group at 3.5 μ in the infrared is not practical because of the lack of resolution in this region using pellet techniques and the insolubility of the anhydride and its derivatives in solvents such as carbon disulfide and carbon tetrachloride which are transparent in this region. It is further interesting that apparently none of the known transformation and interconversions[7] of products obtained from this aldehyde-anhydride condensation can be used to clearly eliminate the possibility of structure V.

Coupling of α,β-dimethylglutaconic anhydride with a variety of aryldiazonium salts, using techniques previously described,[1-3] has given the γ-arylhydrazono derivatives (VII) listed in Table II.

EXPERIMENTAL

α,β-Dimethylglutaconic anhydride was prepared from the corresponding acid,[8] m.p. 103°, by cyclization with acetyl chloride on heating. In our hands the anhydride, b.p. 138–140°/3 mm, solidified, m.p. 38–42°, but could not be recrystallized. The derivatives listed in Tables I and II were prepared by procedures described in previous reports.[1-3]

TABLE II

γ-KETO-α,β-DIMETHYLGLUTACONIC ANHYDRIDE ARYLHYDRAZONES

Aryl Group	Color	M.p.,[a] °C.	Yield, %	Analysis Nitrogen % Calcd.	Nitrogen % Found
Phenyl	Orange	167–170H	49	11.47	11.50
p-Nitrophenyl	Yellow	214–218H	62	14.53	14.60
p-Tolyl	Yellow	177–178E	50	10.85	11.07
o-Anisyl	Orange	185–188F	29	10.21	10.31

[a] H, glacial acetic acid; E, ethyl acetate-petroleum ether; F, ethyl acetate or benzene.

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(5) Richard H. Wiley and A. S. Hart, *J. Am. Chem. Soc.*, **76**, 1942 (1954).

(6) R. Kuhn and S. Ishikawa, *Ber.*, **64**, 2347 (1931); S. Ishikawa and R. Kojima, *Science Repts Tokyo Bunrika Daigaku*, **1**, 297 (1934); *Chem. Abstr.*, **28**, 2697 (1934).

(7) See for example V. Petrow and O. Stephenson, *J. Chem. Soc.*, 1310 (1950).

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Synthesis of 5,6,7-Trimethoxyindole, a Possible Intermediary Metabolite of Mescaline[1]

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The hypothesis that the currently designated psychotomimetic substances owe their unique physiological activity to an indole nucleus has been proposed by several investigators.[4-8] This has

(1) This research was supported by Battelle Memorial Institute funds and in part by Public Health Service Grant No. M-600(R).

(2) Battelle Memorial Institute.

(3) Fels Research Institute.

(4) H. Fabing, *Neurology*, **5**, 603 (1955).

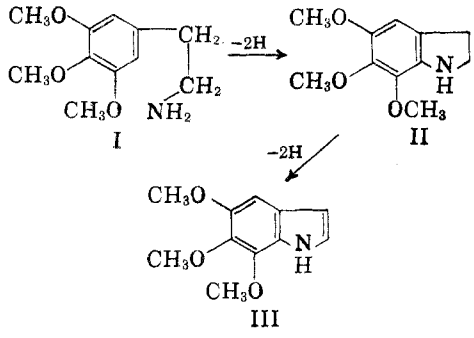
(5) A. Hoffer, H. Osmond, and J. Smythies, *J. Mental Sci.*, **100**, 29 (1954).

(6) A. S. Marazzi and E. R. Hart, *Science*, **121**, 365 (1955).

(7) D. W. Wooley and E. Shaw, *Science*, **119**, 587 (1954).

(8) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, **20**, 1292 (1955).

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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