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MESCALINE ANALOGS. III. 2,4,6-TRIALKYL- AND 3,4-DIHYDROXY-5-METHOXY-β-PHENETHYLAMINES

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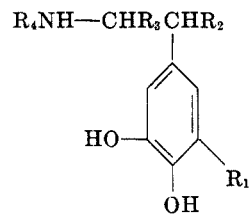
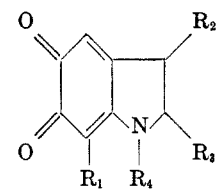
The marked inhibition of cytochrome oxidase activity in brain homogenates shown by 2,4,6-trimethoxy-β-phenethylamine and the corresponding triethoxy compound (1) prompted investigation of the effect of substitution of methyl and ethyl for methoxy and ethoxy respectively in the β-phenethylamine molecule. Trimethyl- and 2,4,6-triethyl-β-phenethylamine were obtained by chloromethylation of mesitylene and 1,3,5-triethylbenzene respectively to give the corresponding benzyl chlorides (2), which then gave the trialkylphenylacetonitriles upon treatment with sodium cyanide (3); the resulting nitriles were reduced by means of lithium aluminum hydride, and the corresponding β-phenethylamines formed were isolated as their hydrochlorides.

3,4-Dihydroxy-5-methoxy-β-phenethylamine (I) was of interst both as a partially demethylated mescaline and as a possible precursor of 7-methoxy-2,3-dehydro-5,6-indoloquinone (II), an analog of adrenochrome (IV); the latter substance has been reported to have marked hallucinatory activity at concentrations much lower than mescaline (4–6). Adrenochrome results from selective oxidation of (−) epinephrine (III) with silver oxide (7); it was hoped that II would be formed by a similar oxidation of I.





$R_1 = OCH_3$; $R_2 = R_3 = R_4 = H$	I	II
$R_1 = R_3 = H$; $R_2 = OH$; $R_4 = CH_3$	III	IV
$R_1 = R_2 = R_4 = H$; $R_3 = CO_2H$	V	VI
$R_1 = OH$; $R_2 = R_3 = R_4 = H$	VII	VIII

The synthesis of I was effected from vanillin *via* 5-bromovanillin (8), which was converted to 3,4-dihydroxy-5-methoxybenzaldehyde by treatment with dilute sodium hydroxide at 210° in the presence of copper bronze (9). Condensation of the latter aldehyde with nitromethane in the presence of methylamine afforded the corresponding β-nitrostyrene, which was reduced to I with lithium aluminum hydride.

Treatment of I in methanol solution with silver oxide, as described for the oxidation of III to IV (10), gave a deep orange-red solution from which no solid

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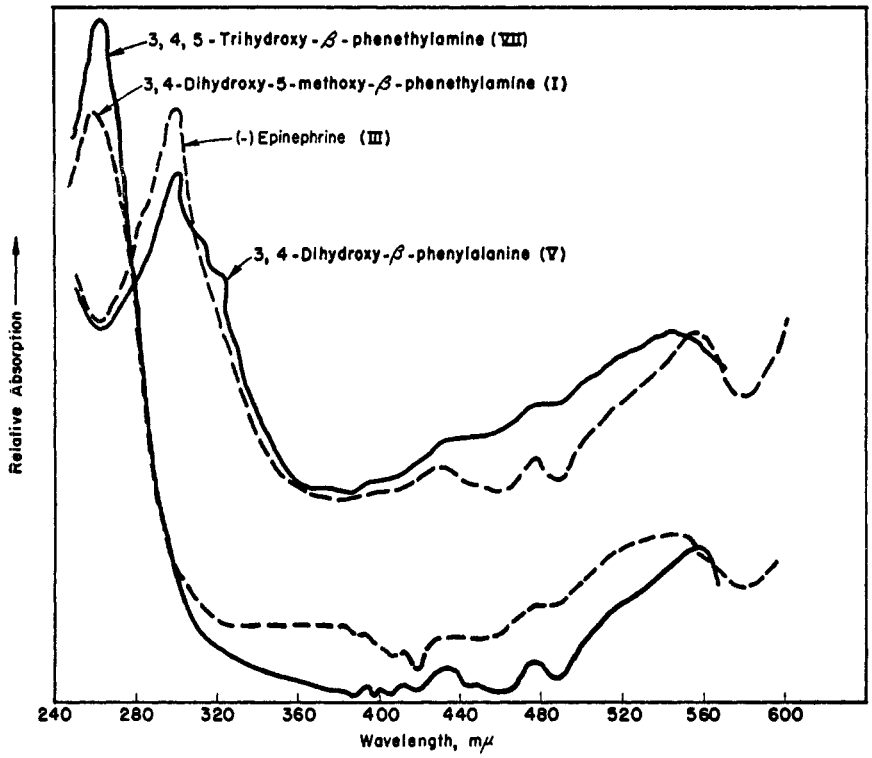

FIG. 1. ULTRAVIOLET AND VISIBLE ABSORPTION CURVE FOR OXIDATION PRODUCTS OF I, III, V, AND VII.

product could be isolated. Similar results were obtained when 3,4,5-trihydroxy-β-phenethylamine (VII) was subjected to oxidation under similar conditions. Solutions of III, VII, and 3,4-dihydroxy-β-phenylalanine (V), which had been prepared at concentrations in the range of 1 to 2×10^{-4} M in a standard buffer (*p*H = 5.6), were shaken vigorously with a weighed amount of silver oxide at room temperature and then filtered. Each solution then was examined spectrophotometrically in the near ultraviolet and visible regions.

The spectral curves for the resulting oxidation products are shown in Figure 1. The locations of the principal maxima observed for adrenochrome (IV), and dopachrome (VI) which results from the oxidation of V, are in satisfactory agreement with the wavelengths reported by Mason (10); (IV: λ_{max} = 305 and 480 mμ; and VI: λ_{max} = 305 and 475 mμ). However, the anticipated adrenochrome absorption at 480 mμ appears as a shoulder rather than as a sharp band. All of these oxidation products exhibit strong absorption between 525 and 535 mμ and appear to have in common a number of bands of weaker intensity which are located at nearly the same wavelengths. The oxidation products of I and VII exhibit nearly identical maxima which are hypsochromically shifted 38 to 40 mμ away from the corresponding maxima for IV and VI. The lower wavelength

maxima, which are typical features of the spectra of a number of 2,3-dihydroindole compounds (11), are probably intensified by an auxochromic influence of the cross-conjugated —CH=CH—C(O)— groups which are present in the aminochrome pigments. Hallachrome, which has been reported to be a 2,3-dihydroindole derivative, shows a maximum absorption at 225 mμ with an accompanying weaker band at 500 mμ (12).

The structural similarities of the parent β-phenethylamines as well as the spectral similarities of their oxidation products suggest that I and VII are converted respectively to the *o*-quinoid compounds II and VIII under the stated oxidation conditions.

Several investigators have noted that the most potent hallucinogens, *e.g.* lysergic acid diethylamide, adrenochrome, and bufotenine, possess an indole nucleus, whereas the less potent hallucinogens mescaline and desoxyephedrine are possibly converted to indole compounds by oxidation *in vivo* (6, 15, 16). To examine further this correlation, a number of hitherto unknown 5,6,7-trimethoxyindole compounds are being synthesized currently by alternative routes to determine whether they are more active hallucinogens than mescaline itself.

All biochemical and physiological results obtained from these compounds will be published separately.

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EXPERIMENTAL

All melting points are uncorrected.

2,4,6-Trimethyl-β-phenethylamine hydrochloride. 2,4,6-Trimethylphenylacetonitrile was prepared according to the procedure of Fuson and Rabjohn (13). A solution of 15.9 g. of the nitrile in 150 ml. of absolute ether was added to a stirred slurry of 7.6 g. of lithium aluminum hydride at such a rate as to maintain gentle reflux. The mixture then was refluxed for an additional five minutes. Excess lithium aluminum hydride was hydrolyzed by cautiously adding 10 ml. of water. The precipitated alumina was dissolved by the addition of 250 ml. of 10 per cent aqueous sodium hydroxide. After separating the ether layer, the aqueous phase was extracted with a fresh portion of ether. The combined ether solution of the product was dried over magnesium sulphate, filtered, and the filtrate was saturated with dry anhydrous hydrogen chloride. Filtration gave colorless prisms which, after washing several times with ether, weighed 12 g. (60%) and melted at 296–297° (dec).

Anal. Calc'd for $C_{11}H_{18}ClN$: Cl, 17.8; N, 7.0.

Found: Cl, 17.6; N, 6.9.

2,4,6-Triethylbenzyl chloride. A mixture of 40.5 g. of 1,3,5-triethylbenzene, 22 g. of chloromethyl ether, and 75 ml. of glacial acetic acid was heated on a steam-bath (90°) for 40 hours. The reaction mixture then was poured into 400 ml. of water, and the oily product which separated was extracted with petroleum ether (boiling range 30–60°). The extract was washed with aqueous sodium carbonate and with water, and then dried over calcium sulfate. The solvent was removed by distillation, and vacuum distillation of the residue gave 37.6 g. (72%) of the product, b.p. 160–170°/31 mm. A redistilled fraction, b.p. 167–169°/31 mm., was taken for analysis.

Anal. Calc'd for $C_{13}H_{19}Cl$: Cl, 16.9. Found: Cl, 16.8.

2,4,6-Triethylphenylacetonitrile. A solution of 37 g. of 2,4,6-triethylbenzyl chloride in

40 ml. of ethanol was added dropwise to a well stirred solution of 11.5 g. of sodium cyanide in 15 ml. of water. Following the addition, the mixture was refluxed with stirring for three hours. After cooling and diluting with several volumes of water, the dark-brown oil was removed by extraction with ether. The ether layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent in an air stream gave a dark residue, which upon distillation gave 27.4 g. (77%) of the nitrile, b.p. 187–190°/36 mm.

Anal. Calc'd for $C_{14}H_{19}N$: C, 83.5; H, 7.0.

Found: C, 83.6; H, 6.9.

2,4,6-Triethyl-β-phenethylamine. The corresponding nitrile (20 g.) was reduced with 7.6 g. of lithium aluminum hydride, in a total volume of 200 ml. of absolute ether, by following the procedure used for preparing the 2,4,6-trimethyl compound. There was obtained 9.1 g. (38%) of pure 2,4,6-triethyl-β-phenethylamine hydrochloride, m.p. 244–245°, as colorless plates.

Anal. Calc'd for $C_{14}H_{24}ClN$: Cl, 14.7; N, 5.8.

Found: Cl, 14.5; N, 5.9.

3,4-Dihydroxy-5-methoxy-β-nitrostyrene. 5-Bromovanillin was obtained in 96% yield by bromination of vanillin in acetic acid solution (8). Conversion to 3,5-dihydroxy-5-methoxybenzaldehyde in 45% yield was accomplished by the procedure of Robinson (9). Vacuum distillation was the best method found for purification of the crude product.

To a solution of 3.4 g. of 3,4-dihydroxy-5-methoxybenzaldehyde and 1.6 g. of nitromethane in 10 ml. of methanol was added 1.4 ml. of a 3% solution of methylamine in methanol. All operations were conducted in an atmosphere of nitrogen. The tightly stoppered reaction mixture was allowed to stand at room temperature for 27 hours and then was cooled to −10°. The red-orange crystalline product was collected, washed thoroughly with cold methanol, and dried in a vacuum oven at room temperature; yield, 3.7 g. (88%); m.p. 209–210° (dec.). A sample recrystallized from methanol melted at 214–215° (dec.).

Anal. Calc'd for $C_9H_9NO_5$: C, 51.2; H, 4.3.

Found: C, 51.2; H, 4.4.

3,4-Dihydroxy-5-methoxy-β-phenethylamine (I). Reduction of 21.8 g. of 3,4-dihydroxy-5-methoxy-β-nitrostyrene with 19 g. of lithium aluminum hydride in 800 ml. of dry ether by the procedure of Ramirez and Burger (14) gave 20 g. (48%) of 3,4-dihydroxy-β-phenethylamine picrate, m.p. 222–223° (dec.), unchanged after recrystallization from ethanol.

Anal. Calc'd for $C_{15}H_{16}N_4O_{10}$: C, 43.8; H, 3.9.

Found: C, 44.1; H, 3.9.

The picrate (19.5 g.) was converted to the hydrochloride by dissolving in 500 ml. of boiling 6 *N* hydrochloric acid. Picric acid was removed from the cooled solution by filtration and triple extraction with 50-ml. portions of nitrobenzene. After two extractions with ether, the aqueous solution was evaporated to dryness under reduced pressure to give 7.9 g. (76%) of 3,4-dihydroxy-5-methoxy-β-phenethylamine hydrochloride, m.p. 206–207°. Recrystallization from methanol-ethyl acetate-ether did not change the melting point.

Anal. Calc'd for $C_9H_{14}ClNO_3$: Cl, 16.2; N, 6.4.

Found: Cl, 16.0; N, 6.2.

Oxidation products of I, III, V, and VII. To a solution of 2.2 g. of 3,4-dihydroxy-5-methoxy-β-phenethylamine hydrochloride in 25 ml. of methanol containing 1 ml. of formic acid was added 7.3 g. of silver oxide. The reaction mixture warmed somewhat and was maintained at 40° for 3 minutes. The mixture was quickly filtered from the precipitated silver and excess silver oxide. The red filtrate was chilled to −75°, but no solid product was deposited. Concentration of the solution at low temperature under reduced pressure caused decomposition of the red compound, and no pure products were isolated.

The ultraviolet and visible region absorption data which are shown in Figure 1 were obtained by following the general method given by Mason (10). Solutions of DL-[3,4-dihydroxy-β-phenylalanine] (1.3×10^{-4} M), 3-methoxy-4,5-dihydroxy-β-phenethylamine (1.5×10^{-4} M), (−)epinephrine (1.5×10^{-4} M), and 3,4,5-trihydroxy-β-phenethylamine (1.5×10^{-4} M) were prepared by dissolving weighed quantities of each compound in a standard

buffer; the latter was prepared by mixing quantities of 0.1 *N* sodium hydroxide and 0.1 *M* potassium dihydrogen phosphate in order to give a final solution of each amine having *p*H 5.6 (glass electrode). Ten-ml. portions of each solution were shaken vigorously with 50 mg. of C. P. silver oxide at room temperature for 3 minutes and then were filtered. The resulting filtrates were examined using a Beckman type DU spectrophotometer.

SUMMARY

1. The synthesis of 2,4,6-trimethyl-, 2,4,6-triethyl-, and 3,4-dihydroxy-5-methoxy-β-phenethylamine is described.

2. Although solutions of 3,4-dihydroxy-5-methoxy- and 3,4,5-trihydroxy-β-phenethylamine became highly colored upon treatment with silver oxide, none of the oxidation products could be isolated.

3. The absorption spectra of soluble oxidation products were compared with solutions of adrenochrome and dopachrome. From similarities which appear in these spectra, it is tentatively concluded that both the di- and tri-hydroxy-β-phenethylamines undergo oxidation to form *o*-quinones which are derived from 5,6-dihydroxy-2,3-dihydroindole.

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