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MESCALINE ANALOGS. I. 2,4,6-TRIALKOXY-β-PHENETHYLAMINES

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Mescaline, *3,4,5*-$(CH_3O)_3C_6H_2CH_2CH_2NH_2$, is one of the active principles of the cacti *Anhalonium lewinii* (1) and *Trichocenreus terschecki* (2). The most striking physiological effect of mescaline is the production of both euphoria and visual color hallucinations in human subjects (3–6). A number of isomers of mescaline as well as mescaline-like compounds have been prepared and tested physiologically for possible hallucinatory action (6–12). According to Reti (13), none of these compounds causes the euphoria or the distortion in color vision which is produced by mescaline. Iwamoto and Hartung (8) have stated that these unique psychological effects can be attributed to the presence of the three vicinal methoxyl groups on the pressor-active β-phenethylamine structure. Mescaline, however, does not appear to have the pressor activity which is usually associated with this class of amines (14).

Of the five possible ring-positional isomers of mescaline, only the 2,3,4- (15) and 2,4,5-trimethoxyphenethylamines (12) have been synthesized. As a part of a program for studying the effect of changes in structure on the hallucinating power of this physiologically interesting class of compounds, we have undertaken the synthesis of the remaining isomers, the 2,4,6-, 2,3,5-, and 2,3,6-trimethoxyphenethylamines. Other structural analogs of mescaline included in this program are the dialkoxy derivatives of hydroxyphenethylamines wherein these substituents occupy the 2,4,6-, 2,3,5-, and 2,3,6-positions. Similar variations of this sort have already been reported for the 3,4,5-positions in β-phenethylamine (9, 15, 16).

To date, none of the possible ring-substituted tetra- or penta-methoxyphenethylamines have been synthesized. A discussion of these isomers will be the subject of another communication.

A number of mescaline-like compounds containing a methoxyl group (11, 17, 18) or a methyl group (7, 15) in the side chain have been prepared. Elphick and Gunn (11) have concluded that while a β-methoxyl group tends to decrease the physiological activity of such compounds, the action is much like that of the parent compound. No conclusion appears to have been reached regarding the influence of the side chain methyl group.

The substitution of ethoxyl for methoxyl groups has been reported both for mescaline (6, 9, 19) and for its 2,3,4- analog (19). Noteboom (9) has also studied the physiological action of the mixed 3,4,5-ethoxy-methoxy-β-phenethylamines, and he concluded that replacement of the 3-methoxyl group in mescaline by an ethoxyl group caused a marked increase in toxicity. The latter arrangement of

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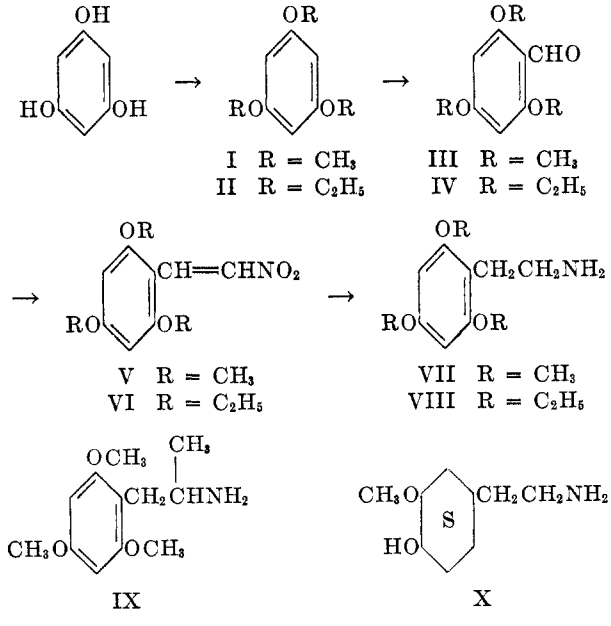
substituents has a more potent toxic action than has any of the corresponding phenolic compounds.

No extensive studies have been carried out on the hydroaromatic analogs of mescaline. The physiological activities of many aromatic compounds are frequently retained upon ring reduction, or even after opening the hydroaromatic ring. Barger and Dale (20) have shown that there are practically no qualitative differences among the pressor activities of β-phenethylamine, β-cyclohexylethylamine, and *n*-hexylamine. Accordingly, it seemed desirable to prepare various hexahydro analogs of mescaline and to study their physiological and psychological effects.

The synthesis of 2,4,6-trialkoxyphenethylamines is the subject of this communication. Phloroglucinol was the starting material for these isomers. A two-stage alkylation (21) gave the corresponding 1,3,5-trialkoxybenzenes (I and II), which were then converted to the 2,4,6-trialkoxybenzaldehydes (III and IV) by the Gatterman-Koch reaction using HCN and $ZnCl_2$ (22). Condensation of the aldehydes with nitromethane to form the corresponding 2,4,6-trialkoxy-β-nitrostyrenes (V and VI) was best effected by the method of Raiford and Fox (23) in glacial acetic acid in the presence of ammonium acetate. Reduction of the β-nitrostyrenes to the phenethylamines (VII and VIII) was accomplished with lithium aluminum hydride in accordance with the method described by Ramirez (15, 24) for the reduction of some related nitrostyrenes.

CHART I

Synthesis of 2,4,6-trialkoxy-β-phenethylamines



dl-1-(2,4,6-Trimethoxyphenyl)-2-aminopropane (IX) was prepared by condensation of III with nitroethane in the presence of *n*-butylamine (7) followed by reduction of the nitropropene with lithium aluminum hydride. In the condensation step, the amine was a more effective catalyst than ammonium acetate; the reverse was true in the condensation with nitromethane.

Attempted hydrogenation of VII to β-(2,4,6-trimethoxycyclohexyl)ethylamine over Raney nickel at 150 atmospheres of hydrogen and 175° for four hours was unsuccessful. Similarly, treatment with hydrogen over Adams' catalyst failed to give the desired product; unchanged VII was recovered. However, β-4-hydroxy-3-methoxycyclohexylethylamine (X) was obtained readily from β-4-hydroxy-3-methoxyphenethylamine by hydrogenation of an alcoholic solution of the hydrochloride over Adams' catalyst at 3 atmospheres of hydrogen pressure. Tyramine hydrochloride and β-phenethylamine hydrochloride were also readily reduced to the corresponding cyclohexyl compounds under these conditions.

The results from the physiological testing of these compounds will be published at a later date.

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EXPERIMENTAL

All melting points are uncorrected.

2,4,6-Trimethoxybenzaldehyde (III). Following the procedure of Mannich (21) a mixture of 100 g. of phloroglucinol dihydrate, 320 ml. of methanol, and 55 ml. of sulfuric acid was refluxed for 12 hours. To the cooled mixture was added 500 ml. of water, and methanol was removed by distillation under reduced pressure. The water-insoluble oil which separated was recovered by three extractions with ether. After removing the ether under reduced pressure, the residue was dissolved in 500 g. of 40% potassium hydroxide and was treated with 300 g. of dimethyl sulfate. The mixture was refluxed for ½ hour, diluted with water, and extracted with ether. The ether layer was dried and evaporated to give a solid residue, m.p. 52–53°, [Lit. m.p. 52° (21)], sufficiently pure for the next step; yield, 60.6 g. (59%).

The procedure described by Herzig, *et al.* (22) proved to be most satisfactory for conversion of phloroglucinol trimethyl ether to 2,4,6-trimethoxybenzaldehyde. To a solution of 20 g. of phloroglucinol trimethyl ether in 80 ml. of dry reagent benzene cooled to 0° was added 20 g. of powdered fused anhydrous zinc chloride and 16.5 ml. of anhydrous liquid hydrogen cyanide. Into the stirred mixture was passed a stream of dry hydrogen chloride. The crude imine hydrochloride which separated was collected and hydrolyzed by adding to 1500 ml. of water containing 10 ml. of hydrochloric acid at 85°. The crude product, weighing 18.6 g. (79.5%), crystallized as tan crystals melting at 119–120°. Sublimation at 0.3 mm. gave a nearly colorless product melting at 120–121°, [Lit. m.p. 118° (22)].

2,4,6-Trimethoxy-β-nitrostyrene (V). A mixture of 14.5 g. of crude 2,4,6-trimethoxybenzaldehyde, 6.2 ml. of redistilled nitromethane, 50 ml. of glacial acetic acid, and 4.9 g. of ammonium acetate was refluxed gently for 1.5 hours, as described for the preparation of 3,4-dimethoxy-β-nitrostyrene (23). On cooling, the product crystallized as yellow prisms melting at 177–177.5°; yield, 15.1 g. (85%). The melting point was unchanged after crystallization from ethanol.

Anal. Calc'd for $C_{11}H_{13}NO_5$: N, 5.86. Found: N, 5.65.

2,4,6-Trimethoxy-β-phenethylamine (VII). Reduction of the nitrostyrene (V) with lithium aluminum hydride by the procedure of Ramirez and Burger (24) gave the phenylethylamine (VII) in excellent yield. From 10 g. of 2,4,6-trimethoxy-β-nitrostyrene, added by the Soxhlet extraction technique, and 8 g. of lithium aluminum hydride in 400 ml. of absolute ether there was obtained 18 g. (97%) of *2,4,6-trimethoxy-β-phenethylamine picrate*; m.p. 204–205°, unchanged after recrystallization from ethanol.

Anal. Calc'd for $C_{17}H_{20}N_4O_{10}$: C, 46.4; H, 4.6.
Found: C, 46.4; H, 4.4.

The picrate was converted to the *hydrochloride* by dissolving 11.5 g. of the picrate in 1150 ml. of boiling water and then adding 140 ml. of hydrochloric acid. The warm solution was extracted with three 50-ml. portions of nitrobenzene to remove picric acid, and finally extracted with benzene and with ether. Concentration of the aqueous solution under reduced pressure gave a total of 5.2 g. (81%) of 2,4,6-trimethoxy-β-phenethylamine hydrochloride, m.p. 234–235° from methanol-ethyl acetate.

Anal. Calc'd for $C_{11}H_{18}ClNO_3$: N, 5.66; Cl, 14.4.
Found: N, 5.62; Cl, 14.3.

2,4,6-Triethoxybenzaldehyde (IV). Phloroglucinol triethyl ether was prepared in 66% yield from 100 g. of phloroglucinol, 360 g. of ethanol, and 55 ml. of sulfuric acid and 500 g. of 40% potassium hydroxide and 366 g. of diethyl sulfate by the procedure described for the 2,4,6-trimethyl ether. The product was purified by distillation; b.p. 125–130°/2.5 mm.; m.p. 40°, [Lit. m.p. 43° (25)].

2,4,6-Triethoxybenzaldehyde was prepared from 12.6 g. of phloroglucinol triethyl ether, 40 ml. of dry reagent benzene, 10 g. of fused anhydrous zinc chloride, 12 ml. of anhydrous HCN, and dry HCl as described for the trimethoxy derivative. Hydrolysis of the intermediate aldimine hydrochloride gave 10.6 g. (74%) of crude aldehyde, m.p. 95–97°. Purification by evaporative distillation at 0.1 mm. gave white crystals, m.p. 99–100°.

Anal. Calc'd for $C_{13}H_{18}O_4$: C, 65.6; H, 7.6.
Found: C, 65.7; H, 7.7.

2,4,6-Triethoxy-β-nitrostyrene (VI). By a procedure similar to preparation of V, a mixture of 5.3 g. of 2,4,6-triethoxybenzaldehyde, 1.6 ml. of redistilled nitromethane, 15 ml. of acetic acid, and 1.5 g. of ammonium acetate was refluxed for 1.5 hours. The yellow, crystalline product was recovered from the cooled mixture; yield, 4.9 g. (78%); m.p. 145–147°. After recrystallization from 80% acetic acid, a sample melted at 151–152°.

Anal. Calc'd for $C_{14}H_{19}NO_5$: N, 4.98. Found: N, 4.90.

2,4,6-Triethoxy-β-phenethylamine (VIII). Reduction of 15.6 g. of 2,4,6-triethoxy-β-nitrostyrene with 10.5 g. of lithium aluminum hydride in 650 ml. of dry ether gave 26.8 g. (99%) of *2,4,6-triethoxy-β-phenethylamine picrate*, m.p. 202–204°. A sample recrystallized from alcohol melted at 206–207°.

Anal. Calc'd for $C_{20}H_{26}N_4O_{10}$: C, 49.8; H, 5.4.
Found: C, 49.8; H, 5.3.

Decomposition of the picrate was troublesome because of the low solubility in water, but by using concentrated hydrochloric acid, the picrate was converted to the hydrochloride. To 150 ml. of hot concentrated hydrochloric acid was added 4.7 g. of 2,4,6-triethoxyphenethylamine picrate. The mixture was boiled until the picrate dissolved. After cooling to room temperature, the solution was extracted with three 25-ml. portions of nitrobenzene and then twice with ether. The aqueous solution was concentrated under reduced pressure to recover the crystalline 2,4,6-triethoxy-β-phenethylamine hydrochloride; yield, 2.14 g. (81%); m.p. 198–198.5° from methanol-ethyl acetate.

Anal. Calc'd for $C_{14}H_{24}ClNO_3$: N, 4.84; Cl, 12.3.
Found: N, 4.85; Cl, 12.2.

dl-1-(2,4,6-Trimethoxyphenyl)-2-aminopropane (IX). Condensation of 2,4,6-trimethoxybenzaldehyde with nitroethane was best effected by an amine-catalyzed reaction. A mixture of 9.8 g. of 2,4,6-trimethoxybenzaldehyde, 3.2 ml. of redistilled nitroethane, 40 ml.

of ethanol, and 0.36 ml. of *n*-butylamine was warmed on a steam-bath at about 75° for 8 hours. Upon cooling, the 1-(2,4,6-trimethoxyphenyl)-2-nitropropene crystallized; yield, 9.1 g. (88%); m.p. 147.5–148.5°, unchanged after recrystallization from ethanol.

Anal. Calc'd for $C_{12}H_{15}NO_5$: N, 5.53. Found: N, 5.57.

The nitropropene (14 g.) was reduced to the aminopropane compound (IX) by treatment with 10.5 g. of lithium aluminum hydride in 500 ml. of dry ether as previously described. The product was isolated as the *picrate*; yield, 22.7 g. (92%); m.p. 212–213° from ethanol.

Anal. Calc'd for $C_{18}H_{20}N_4O_{10}$: C, 47.8; H, 4.5.
Found: C, 47.6; H, 4.8.

The picrate was converted to the *hydrochloride* by boiling 22 g. of the picrate with 350 ml. of concentrated hydrochloric acid. After extraction of the solution with nitrobenzene and ether, the aqueous solution was evaporated under reduced pressure to obtain 10.6 g. (84%) of *dl*-1-(2,4,6-trimethoxyphenyl)-2-aminopropane hydrochloride; m.p. 214–215° from methanol-ethyl acetate.

Anal. Calc'd for $C_{12}H_{20}ClNO_3$: N, 5.39; Cl, 14.1.
Found: N, 5.43; Cl, 14.2.

Hydrogenation of substituted β-phenethylamines; 4-hydroxy-3-methoxy-β-cyclohexylethylamine. Reduction of substituted β-phenethylamines to the corresponding cyclohexylethylamines proceeded readily in the case of the 4-hydroxy-3-methoxy compound and unsubstituted phenethylamine. Shaking an ethanol solution of the amine hydrochloride with hydrogen under a pressure of 3 atmospheres in the presence of Adams' catalyst and a small amount of hydrochloric acid resulted in high conversion to the saturated compounds. A solution of 5.1 g. of 4-hydroxy-3-methoxy-β-phenethylamine hydrochloride in 150 ml. of ethanol containing 3 drops of hydrochloric acid was shaken with hydrogen for 20 hours at a pressure of 60 p.s.i.g. The hydrogen absorbed agreed with that calculated for three moles of hydrogen. The catalyst was removed, and the 4-hydroxy-3-methoxy-β-cyclohexylethylamine hydrochloride was recovered by evaporation of the filtrate under reduced pressure; yield, 4.7 g. (90%); m.p. 204–205° from methanol-ethyl acetate.

Anal. Calc'd for $C_9H_{20}ClNO_2$: C, 51.6; H, 9.5.
Found: C, 51.5; H, 9.3.

Hexahydrotyramine. Hydrogenation of 5.2 g. of tyramine hydrochloride in 150 ml. of alcohol in the presence of 0.5 g. of Adams' catalyst at 50 p.s.i.g. of hydrogen was complete within two hours and a 95% yield of hexahydrotyramine hydrochloride was obtained; m.p. 189–191° from methanol-ethyl acetate.

Anal. Calc'd for $C_8H_{18}ClNO$: C, 53.5; H, 10.0.
Found: C, 54.0; H, 10.2.

Waser and Fauser (26) reported m.p. 160° for hexahydrotyramine hydrochloride obtained from hexahydrotyrosine.

2,4,6-Trimethoxy-β-phenethylamine hydrochloride could not be hydrogenated to the cyclohexyl derivative in spite of repeated attempts. Adams' catalyst at ordinary temperature and at 150° and 1500 p.s.i.g., Raney nickel at 150° and 175° and 2500 p.s.i.g. for reaction times up to four hours all were ineffective methods for hydrogenation of this compound. In all cases, the starting material was recovered unchanged. Reduction of this class of compounds is being investigated further.

SUMMARY

1. The synthesis of 2,4,6-trimethoxy-β-phenethylamine, 2,4,6-triethoxy-β-phenethylamine, and *dl*-1-(2,4,6-trimethoxyphenyl)-2-aminopropane from phloroglucinol is described.

2. 2,4,6-Trimethoxy-β-phenethylamine hydrochloride failed to undergo ring reduction, whereas 4-hydroxy-3-methoxy-β-phenethylamine hydrochloride and

tyramine hydrochloride were readily hydrogenated to the corresponding β-cyclohexylethylamine salts.

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