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MESCALINE ANALOGS. II. TETRA- AND PENTA-METHOXY-β-PHENETHYLAMINES

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In a further investigation into the preparation of β-phenethylamine derivatives related to mescaline, 3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2NH_2$, we have synthesized all of the possible ring-substituted tetra- and penta-methoxy-β-phenethylamines. Our previous communication (1) was concerned with the synthesis of a number of 2,4,6-trialkoxy analogs of mescaline. All of these compounds were prepared in order to study their possible effect on the respiratory enzyme activity of brain homogenates; several of these new β-phenethylamine derivatives have already been investigated physiologically, and their activities have been compared with both mescaline and lysergic acid diethylamide (2).

All of the tetramethoxy-β-phenethylamines and pentamethoxy-β-phenethylamine were synthesized from the corresponding polymethoxybenzenes through the routes and the intermediates which are shown in Chart I. Both 1,2,3,5-tetramethoxybenzene (I) and pentamethoxybenzene (IX) were prepared by the elegant methods which have been described by Baker (3). Modifications in Baker's procedure (4) were developed for the preparation of 1,2,3,4-tetramethoxybenzene (V) from gallacetophenone through 2-hydroxy-3,4-dimethoxyacetophenone and 1,2-dihydroxy-3,4-dimethoxybenzene as intermediates. 1,2,4,5-Tetramethoxybenzene (XIII) was prepared from *p*-benzoquinone *via* 2,5-dimethoxy-1,4-benzoquinone and 2,5-dimethoxyhydroquinone.

Both the 2,3,4,6- and 2,3,4,5-tetramethoxy-β-phenethylamines (IV and VIII) were prepared according to Route A. The synthesis of 2,3,4,6-tetramethoxybenzaldehyde (II) was carried out by subjecting the corresponding tetramethoxybenzene (I) to a Gatterman reaction (5). Although 1,2,3,4-tetramethoxybenzene (V) failed to undergo this reaction, it was readily formylated by N-phenyl-N-methylformamide in the presence of $POCl_3$ to the desired aldehyde (VI).

Aldehydes II and VI were converted respectively to nitrostyrenes III and VII by condensation with nitromethane in the presence of ammonium acetate-acetic acid. This condensation method has been employed by Raiford and Fox (6) for the preparation of a number of ring-substituted β-nitrostyrenes. The reduction of both III and VII to tetramethoxy-β-phenethylamines IV and VIII was accomplished with lithium aluminum hydride (7).

Route B proved to be advantagous for the synthesis of the pentamethoxy- and 2,3,5,6-tetramethoxy-β-phenethylamines (XII and XVI). The attempted conversion of pentamethoxybenzene (IX) to the corresponding benzaldehyde by the Gatterman reaction with hydrogen cyanide and hydrogen chloride in the presence

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CHART I

Route A

Compounds I–IV, R = 2,3,4,6-$(CH_3O)_4C_6H$—
Compounds V–VIII, R = 2,3,4,5-$(CH_3O)_4C_6H$—

RH → RCHO → RCH=CH—NO_2 → $RCH_2CH_2NH_2$

I	II	III	IV
V	VI	VII	VIII

Route B

Compounds IX–XII, R = $(CH_3O)_5C_6$—
Compounds XIII–XVI, R = 2,3,5,6-$(CH_3O)_4C_6H$—

RH → RCH_2Cl → RCH_2CN → $RCH_2CH_2NH_2$

IX	X	XI	XII
XIII	XIV	IV	XVI

of anhydrous zinc chloride failed, and the starting material was recovered unchanged. Also, the addition of a small quantity of anhydrous aluminum chloride to the zinc chloride catalyst did not bring about the desired reaction. However, chloromethylation of pentamethoxybenzene proceeded readily in good yield in the absence of any catalyst. Smith and Opie (8) reported similar results for the chloromethylation of several other penta-substituted benzenes. The chloromethylation of 1,2,4,5-tetramethoxybenzene (XIII) with aqueous formaldehyde and concentrated hydrochloric acid resulted chiefly in the formation of tarry products. However, a satisfactory procedure was developed for the preparation of XIV through the reaction of 1,2,4,5-tetramethoxybenzene with chloromethyl ether in glacial acetic acid as a solvent (9). The benzyl chlorides X and XIV then were converted to the nitriles XI and XV by treatment with potassium cyanide (10). Both of the nitriles underwent reduction with lithium aluminum hydride to give phenethylamines XII and XVI.

The chloromethylation of 1,2,3,4-tetramethoxybenzene failed to give a monochloromethylation product. Reaction of V with aqueous formaldehyde and concentrated hydrochloric acid resulted in bischloromethylation. Action of chloromethyl ether on V resulted in a halogen-free product, m.p. 163–164°, which was not further investigated.

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EXPERIMENTAL

All melting points are uncorrected.

2,3,4,6-Tetramethoxybenzaldehyde (II). 1,2,3,5-Tetramethoxybenzene was obtained in 50% over-all yield from pyrogallol trimethyl ether *via* 2,6-dimethoxybenzoquinone and 2,6-dimethoxyhydroquinone following the procedure of Baker (3). Purification of the tetramethoxybenzene was best achieved by vacuum distillation, collecting the fraction boiling at 109–110°/0.9 mm.

The Gattermann reaction to introduce the aldehyde group was carried out essentially

as described by Herzig, *et al.* (11). To a solution of 33 g. of 1,2,3,5-tetramethoxybenzene in 85 ml. of dry reagent benzene cooled in an ice-bath, was added 27.8 g. of freshly fused and powdered anhydrous zinc chloride and 29 ml. of anhydrous liquid hydrogen cyanide. Into the cold stirred mixture was passed a stream of dry hydrogen chloride for 40 minutes. After standing overnight at room temperature, the benzene solution was decanted from the crude yellow solid imine hydrochloride which separated. It was hydrolyzed by boiling with 100 ml. of water containing 10 ml. of hydrochloric acid; the crude aldehyde crystallized on cooling and scratching; yield 16.3 g. A second crop of 6.8 g. was obtained on concentration of the mother liquor to give a total yield of 23.1 g. (61%); m.p. 88.5–89°. Mauthner (5), who obtained II in 35% yield from 1,2,3,5-tetramethoxybenzene, $Zn(CN)_2$ and HCl in ether, reported a melting point of 88–89°.

2,3,4,6-Tetramethoxy-β-nitrostyrene (III). A mixture of 9 g. of crude 2,3,4,6-tetramethoxybenzaldehyde, 4 ml. of redistilled nitromethane, 15 ml. of glacial acetic acid, and 2.8 g. of ammonium acetate was refluxed gently for 0.5 hour (6). On cooling to room temperature, the crude product solidified and was collected and washed with water and with 50% aqueous methanol. After recrystallization from methanol, the product melted at 155–155.5°; yield, 10 g. (93%).

Anal. Calc'd for $C_{12}H_{15}NO_6$: C, 53.6; H, 5.6.

Found: C, 53.6; H, 6.0.

2,3,4,6-Tetramethoxy-β-phenethylamine (IV). Reduction of nitrostyrene III was carried out as described by Ramirez and Burger (7). From 14.3 g. of 2,3,4,6-tetramethoxy-β-nitrostyrene, added by Soxhlet extraction technique, and 10 g. of lithium aluminum hydride in 600 ml. of absolute ether there was obtained 21.7 g. (87%) of *2,3,4,6-tetramethoxy-β-phenethylamine picrate*; m.p. 189–190°, after recrystallization from ethanol.

Anal. Calc'd for $C_{18}H_{22}N_4O_{11}$: C, 46.0; H, 4.7.

Found: C, 46.2; H, 4.8.

To a boiling solution of 250 ml. of 6 *N* hydrochloric acid was added 20.9 g. of the picrate, and heating was continued until solution was complete. Picric acid was removed from the cooled mixture by filtration and extraction with three 50-ml. portions of nitrobenzene. After an ether extraction, the aqueous solution was treated with Norit, filtered, and evaporated nearly to dryness under reduced pressure to recover 10.5 g. (86%) of 2,3,4,6-tetramethoxy-β-phenethylamine hydrochloride; m.p. 168–169°, after crystallization from methanol-ethyl acetate-ether.

Anal. Calc'd for $C_{12}H_{20}ClNO_4$: N, 5.04; Cl, 12.8.

Found: N, 5.00; Cl, 12.6.

1,2,3,4-Tetramethoxybenzene (V). The method reported by Baker (4) for partial methylation of gallacetophenone to 3,4-dimethoxy-2-hydroxyacetophenone was unsuccessful in our hands. After considerable experimentation, the following procedure was developed. To a well-stirred solution of 84 g. of gallacetophenone (12) in 500 ml. of dry acetone was added 250 g. of finely divided anhydrous potassium carbonate and 62.5 ml. (exactly 2 equivalents) of redistilled methyl iodide. The mixture was refluxed for six hours with stirring, and then filtered hot from the inorganic salts, which were washed thoroughly with fresh acetone. The acetone solution was concentrated by distillation under reduced pressure until solids began to separate. Dilution with water and seeding caused the product to crystallize. The buff-colored crystals were collected, washed with water and with cold methanol, and air-dried; yield, 46.2 g. (47%); m.p. 78–79°; reported (4), 77°. This material was used without further purification. Oxidation to 1,2-dihydroxy-3,4-dimethoxybenzene by the Dakin reaction as described by Baker (3) proceeded in 64% yield; the viscous liquid product boiled at 122–124°/0.7 mm. 1,2,3,4-Tetramethoxybenzene was obtained in 96% yield by treatment of 1,2-dihydroxy-3,4-dimethoxybenzene with methyl sulfate and aqueous sodium hydroxide (4); m.p. 89.5–90°; reported, 89°.

2,3,4,5-Tetramethoxybenzaldehyde (VI). Attempted conversion of V to the corresponding benzaldehyde by a zinc chloride-catalyzed Gattermann reaction with anhydrous HCN in

benzene failed; the starting material was recovered unchanged. The Adams modification of the Gattermann reaction (13) using $Zn(CN)_2$ in ether also failed.

The aldehyde VI was finally obtained by treatment of V with N-methyl-N-phenylformamide and $POCl_3$ (14). To a mixture of 1 g. of N-methyl-N-phenylformamide and 1.6 g. of phosphorus oxychloride was added 1.3 g. of 1,2,3,4-tetramethoxybenzene. The mixture stood at room temperature for about 18 hours, during which time all solid dissolved and a viscous yellow oil was formed. After hydrolysis with ice-water, the crude product was extracted with ether; drying and concentration of the dried ether solution gave 1.4 g. (94%) of crude 2,3,4,5-tetramethoxybenzaldehyde as a nearly colorless oil which did not crystallize. This material was used directly in the next step. For analysis, a portion of the crude aldehyde was converted to the *2,4-dinitrophenylhydrazone*, which was obtained as dark red-brown crystals melting at 194–195° after recrystallization from ethyl acetate.

Anal. Calc'd for $C_{17}H_{18}N_4O_8$: C, 50.2; H, 4.4.

Found: C, 50.4; H, 4.5.

2,3,4,5-Tetramethoxy-β-nitrostyrene (VII). A mixture of 1.2 g. of crude 2,3,4,5-tetramethoxybenzaldehyde, 0.32 ml. of redistilled nitromethane, 0.23 g. of ammonium acetate, and 2.1 ml. of glacial acetic acid was refluxed for 15 minutes. After cooling, the mixture was carefully diluted with water and a little methanol to cause yellow crystals of crude product to deposit; yield, 0.9 g. (63%); m.p. 63–64°, unchanged after recrystallization from dilute methanol.

Anal. Calc'd for $C_{12}H_{15}NO_6$: C, 53.6; H, 5.5.

Found: C, 53.5; H, 5.5.

2,3,4,5-Tetramethoxy-β-phenethylamine (VIII). To a solution of 1.4 g. of lithium aluminum hydride in 50 ml. of absolute ether was added slowly a solution of 2 g. of 2,3,4,5-tetramethoxy-β-nitrostyrene in 50 ml. of absolute ether. The reaction was rapid and the white complex was deposited immediately. The mixture was hydrolyzed by cautious addition of 10% sulfuric acid until two almost clear layers formed. The aqueous layer was separated, neutralized to *p*H 6 with solid lithium carbonate, and filtered from precipitated alumina. Treatment with picric acid caused the deposition of an oily picrate, which could not be induced to crystallize. This crude product was converted directly to the hydrochloride of VIII by heating with 15 ml. of 6 *N* hydrochloric acid. Picric acid was removed by nitrobenzene and ether extraction, and the aqueous solution was concentrated to dryness under reduced pressure. The solid residue was twice crystallized from methanol-ethyl ether, using Norit; yield, 0.7 g. (34%); m.p. 155–156°.

Anal. Calc'd for $C_{12}H_{20}ClNO_4$: C, 52.0; H, 7.2.

Found: C, 52.1; H, 7.0.

Pentamethoxybenzyl chloride (X). Pentamethoxybenzene (IX) was obtained from 1,2,3,5-tetramethoxybenzene in 46% over-all yield *via* 2-hydroxy-3,4,6-trimethoxyacetophenone and 1,2-dihydroxy-3,4,6-trimethoxybenzene as described by Baker (3).

A rapid stream of dry hydrogen chloride was passed into a well-stirred mixture of 20 g. of pentamethoxybenzene, 62 ml. of 35% aqueous formaldehyde solution, and 75 ml. of concentrated hydrochloric acid. The temperature of the mixture rose to 55–58°, remained there for about 0.75 hour, and then started to fall. The temperature was maintained at 51 to 53° with gentle heating for an additional 1.25 hours while continuing passage of dry hydrogen chloride into the mixture. The reaction mixture was poured into 150 ml. of ice-water, and the nearly pure product slowly solidified when seeded; yield, 23.5 g. (97%); m.p. 46–48°. A small sample was purified for analysis by distillation; b.p. 145–147°/2.2 mm.

Anal. Calc'd for $C_{12}H_{17}ClO_5$: C, 52.1; H, 6.2; Cl, 12.8.

Found: C, 52.2; H, 6.2; Cl, 12.4.

Pentamethoxyphenylacetonitrile (XI). To a stirred solution of 8 g. of potassium cyanide in 15 ml. of water was added a solution of 23.5 g. of pentamethoxybenzyl chloride in 35 ml. of alcohol during about 15 minutes. The reaction mixture was stirred and heated under reflux for 4 hours. The solid inorganic salts were removed by filtration and washed with

alcohol and ether. The filtrate was concentrated, and the residue was distilled under reduced pressure; b.p. 112–114°/0.2 mm.; yield, 19.5 g. (86%) of a colorless oil.

Anal. Calc'd for $C_{13}H_{17}NO_5$: C, 58.4; H, 6.4.

Found: C, 58.0; H, 6.6.

Pentamethoxyphenethylamine (XII). To a stirred solution of 1 g. of lithium aluminum hydride in 45 ml. of absolute ether was added a solution of 2.7 g. of pentamethoxyphenylacetonitrile in 25 ml. of absolute ether at such a rate as to maintain gentle reflux. After refluxing for an additional hour, the solution was cooled and treated carefully with 2 *N* sulfuric acid until two clear layers were obtained. The aqueous solution was treated with solid lithium carbonate to *p*H 6, and the solution was filtered from precipitated alumina. The hot filtrate was treated with a hot alcoholic solution of 3 g. of picric acid, and the mixture was allowed to cool. The crude picrate which crystallized (4.1 g.; 82%) was converted directly to the hydrochloride by boiling with 15 ml. of 6 *N* hydrochloric acid, extracting the free picric acid with nitrobenzene and ether, and concentrating the aqueous solution under reduced pressure. The crude pentamethoxyphenethylamine hydrochloride was obtained as a light tan solid melting at 193–195°; yield, 1 g. (40%). After recrystallization from methanol-ethyl acetate-ether, it melted at 197–198°.

Anal. Calc'd for $C_{13}H_{22}ClNO_5$: N, 4.56. Found: N, 4.52.

2,5-Dimethoxy-1,4-benzoquinone. The reaction of methanol with *p*-benzoquinone in the presence of fused anhydrous $ZnCl_2$ as described by Knoevenagel (15) gave somewhat erratic results. Investigation of reaction conditions showed that the time of refluxing is critical and must be controlled carefully. The following procedure gave reproducible results in repeated runs. To a solution of 24 g. of freshly fused and powdered $ZnCl_2$ in 120 ml. of absolute methanol was added 21.6 g. of purified or freshly prepared *p*-benzoquinone. The mixture was heated under reflux on a steam-bath; during about the first ten minutes the condensate was yellow, indicating the presence of unchanged quinone. After about 15 minutes, a red-brown solid was deposited. The mixture was refluxed for a total of 30 minutes and then cooled to 0° for at least two hours. The crude 2,5-dimethoxy-1,4-benzoquinone was collected, washed with cold methanol, and air-dried; the yield of brown crystalline solid product was 10.8 g. (64%). This material was used in the next step without purification.

2,5-Dimethoxyhydroquinone. To a mixture of 10.8 g. of crude 2,5-dimethoxy-1,4-benzoquinone and 20 g. of sodium hydrosulfite was added 100 ml. of boiling water as described by Baker (3) for a similar compound. A nearly colorless solid was formed which was collected and washed with water after cooling the mixture to 5°; yield, 8.5 g. (78%). The crude 2,5-dimethoxyhydroquinone melted at 169–171° [reported (16) 166°] and was used directly in the next step.

1,2,4,5-Tetramethoxybenzene (XIII). To a stirred mixture of 10 g. of 2,5-dimethoxyhydroquinone, 24 ml. of alcohol, 35 ml. of methyl sulfate, and 1 g. of sodium hydrosulfite, was added a solution of 14.4 g. of sodium hydroxide in 32 ml. of water during one-half hour while maintaining the temperature of 15 to 20° with an ice-bath. The mixture was warmed to 70–80° for 20 minutes, diluted with 100 ml. of water, and cooled to 5°. The 1,2,4,5-tetramethoxybenzene was obtained as a nearly colorless granular solid melting at 102–103°; yield, 10 g. (86%). A melting point of 102.5° is recorded for this compound (17).

2,3,5,6-Tetramethoxybenzyl chloride (XIV). A mixture of 14.7 g. of 1,2,4,5-tetramethoxybenzene, 40 ml. of glacial acetic acid, and 5.6 ml. of chloromethyl ether was heated on a steam-bath under a reflux condenser protected with a drying tube for 3 hours. The mixture was added to 600 ml. of water to precipitate the crude product as a brown solid, which was collected, washed with water, and air-dried; yield, 12.9 g. Pure XIV was obtained by sublimation to 0.05 mm. followed by recrystallization from methanol; yield, 4.8 g. (26%) of colorless needles; m.p. 91–92°.

Anal. Calc'd for $C_{11}H_{15}ClO_4$: Cl, 14.4. Found: Cl, 14.7.

2,3,5,6-Tetramethoxyphenylacetonitrile (XV). A mixture of 5.4 g. of XIV, 10 ml. of ethanol, 2 g. of potassium cyanide and 6 ml. of water was refluxed for 5.5 hours. Upon cooling and dilution with about 10 ml. of water, the crude product crystallized directly

from the reaction mixture. Recrystallization from methanol water gave 4.3 g. (83%) of 2,3,5,6-tetramethoxyphenylacetonitrile melting at 93–94°.

Anal. Calc'd for $C_{12}H_{15}NO_4$: C, 60.8; H, 6.3.

Found: C, 60.9; H, 6.3.

2,3,5,6-Tetramethoxy-β-phenethylamine (XVI). A solution of 4.8 g. of 2,3,5,6-tetramethoxyphenylacetonitrile in 200 ml. of absolute ether was added slowly to a stirred solution of 2.5 g. of lithium aluminum hydride in 75 ml. of absolute ether. A white solid complex was deposited; after stirring for an additional 0.5 hour, the mixture was hydrolyzed by the cautious addition of water followed by sufficient (10%) aqueous sodium hydroxide to dissolve most of the precipitated alumina. The ether layer was separated, and the aqueous solution extracted once with an additional 100-ml. portion of ether. The combined ether solution was dried over anhydrous magnesium sulfate, filtered, and treated with dry hydrogen chloride gas to precipitate the product in the form of its hydrochloride. The oil which separated, solidified slowly, and the ether was removed by decantation. The semi-solid residue was dissolved in warm methanol, treated with Norit, filtered, diluted with ethyl acetate and ether to incipient crystallization, and cooled to 0° for several hours. The yield of solid 2,3,5,6-tetramethoxy-β-phenethylamine hydrochloride melting at 136–137° was 1.3 g. (24%).

Anal. Calc'd for $C_{12}H_{20}ClNO_4$: N, 5.05; Cl, 12.8.

Found: N, 4.98; Cl, 13.0.

Attempted chloromethylation of V. To a mixture of 2.7 g. of V and 1.4 g. of 35% aqueous formaldehyde was added 8 ml. of concentrated hydrochloric acid. After vigorously shaking the mixture for 18 hours at room temperature, a colorless, oily product separated from the aqueous phase. The oil layer was taken up in ether, and the extract was washed with a dilute sodium carbonate solution followed by water and then dried over magnesium sulfate. Following filtration, the ethereal solution was evaporated in an air stream. The residue was a colorless oil which gave a positive Beilstein halogen test and a precipitate of silver chloride on treatment with alcoholic silver nitrate.

An alcoholic solution of the chloromethylation product was converted to the corresponding S-alkyl isothiourea picrate by boiling with a solution of 1.0 g. of thiourea in 5 ml. of ethanol and then adding a saturated alcoholic solution of 0.4 g. picric acid. Upon cooling the resulting mixture, there was deposited a yellow crystalline solid. After recrystallization from a large volume of methanol, there was obtained *2,3,4,5-tetramethoxy-o-xylylene-S-isothiourea picrate* as small yellow prisms; m.p. 220–221° (dec).

Anal. Calc'd for $C_{26}H_{28}N_{10}O_{18}S_2$: C, 37.4; H, 3.4; S, 7.7.

Found: C, 37.1; H, 3.6; S, 7.6.

In a second chloromethylation reaction, which was carried out under anhydrous conditions, 2.0 g. of V and 0.8 ml. of chloromethyl ether were dissolved in 5 ml. of glacial acetic acid and the mixture was refluxed for 16 hours; the open end of the reflux condenser was provided with a drying tube during the reaction period. The reaction mixture was then poured into 75 ml. of water to hydrolyze any unreacted chloromethyl ether. The dark-brown oil which separated was taken up in ether, and the extract, in turn, was boiled with Norit. After evaporating the ether, the solid residue was recrystallized from a small volume of methanol. The dense colorless prisms which separated from the solvent amounted to 0.6 g.; m.p. 163–164°. The purified material gave neither a positive Beilstein test nor a silver halide precipitate with silver nitrate. Although no further examination was made of the compound, it was thought to be either bis-(2,3,4,5-tetramethoxyphenyl)methane or possibly octamethoxy-9,10-dihydroanthracene.

SUMMARY

The synthesis of all the possible ring-substituted tetramethoxy-β-phenethylamines and of pentamethoxyphenethylamine is described.

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