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HYDROXYPHENYLISOPROPYLAMINES CONTAINING NUCLEAR METHYL GROUPS

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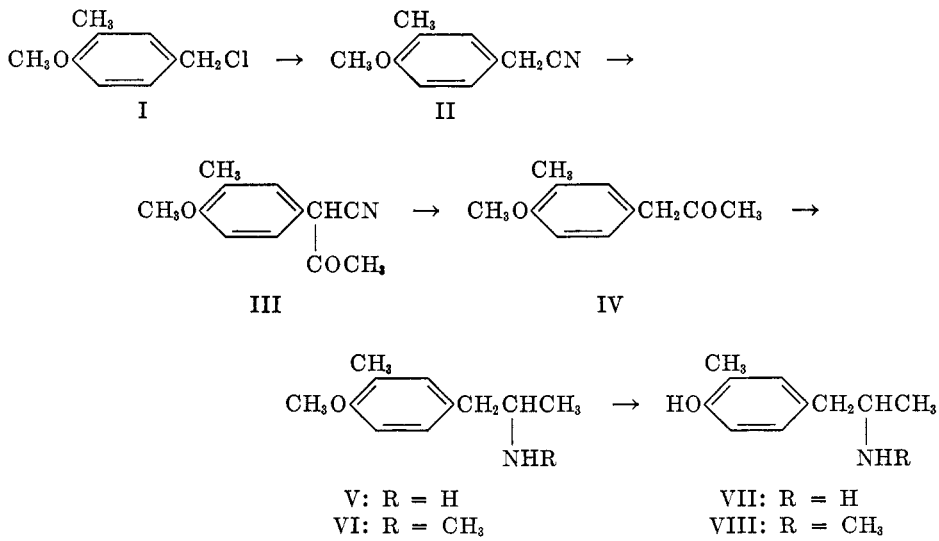
β-Phenylalkylamines exhibit a number of pharmacological properties which are summarized as sympathomimetic effects. Since this combination is of therapeutic importance, this class of compounds has been widely investigated in order to obtain drugs of maximum usefulness (2). The influence of numerous variations of the structure on pharmacological activity has been explored. However, in spite of the large number of compounds prepared, the literature does not seem to show the influence of nuclear alkyl substitution on the properties of hydroxyarylalkylamines. To determine this effect two methyl-substituted hydroxyphenylisopropylamines were prepared.

The synthesis was carried out by conventional methods illustrated by the following scheme:



To prove the constitution of the compounds, 3-methyl-4-methoxybenzyl chloride (I) was converted over the acetoxy derivative into 4-methoxyisophthalic acid (1). The position of the side-chain in II was further confirmed by the preparation of 3-methyl-4-methoxyphenylacetic acid (3) and of its amide.

The amines V, VI, VII, and VIII were tested pharmacologically by the late Dr. Lehmann of our Pharmacology Department. Table I summarizes his findings. The figures show that the new compounds have no advantages over the known compounds. Even the most active compound II is less potent and more toxic than β-(*p*-hydroxyphenyl)isopropylamine (Paredrine).

EXPERIMENTAL

The melting points are uncorrected.

1. *3-Methyl-4-methoxybenzyl chloride* (I). A mixture of 55 g. of *o*-cresol methyl ether, 44 g. of formalin (30%), 200 ml. of petroleum ether, and 500 ml. of conc'd hydrochloric acid is stirred vigorously for 2 hours at 15°. The top layer is separated and the petroleum ether evaporated. Fractionation of the oily residue *in vacuo* yields about 35 g. of 3-methyl-4-methoxybenzyl chloride of b.p. 110–150°/15 mm. Above 150°/15 mm. a viscous oil distills which is collected up to approximately 210°/15 mm.

The crude 3-methyl-4-methoxybenzyl chloride is redistilled, yielding about 30 g. of pure 3-methyl-4-methoxybenzyl chloride of $b.p._{20}$ 132–135°.

The high-boiling fraction does not crystallize on cooling. Fractionation gives pure 3,3′-dimethyl-4,4′-dimethoxydiphenylmethane of $b.p._{12}$ 208–209°.

Anal. Calc'd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86.

Found: C, 79.81; H, 8.03.

The preparation of this compound is described, because the procedure differs from those given by Quelet and co-workers (4, 5).

TABLE I

PHARMACOLOGICAL ACTIVITY OF AMINES

COMPOUND	RELATIVE POTENCY OF PRESSOR ACTIVITY[a] (EPINEPHRINE = 1)	RELATIVE DURATION OF PRESSOR ACTIVITY (EPINEPHRINE = 1)	LD 50, G. *per* KG. I.P.
V	1/250–1/500	4	0.15
VI	1/1000	6	.15
VII	1/70–1/150	6–16	.25
VIII	1/200–1/500	6	.25

[a] Determined in atropinized cats in urethan anesthesia.

2. *4-Methoxyisophthalic acid.* Five grams of 3-methyl-4-methoxybenzyl chloride and a solution of 5 g. of anhydrous potassium acetate in 100 ml. of glacial acetic acid are refluxed for 2 hours. The solvent is distilled off, and the residue is extracted with ether. The ether extract is distilled, leaving crude 3-methyl-4-methoxybenzyl alcohol acetate which, without further purification, is stirred with 600 ml. of 10% sodium hydroxide at 80–90° to remove the acetyl group. A solution of 30 g. of potassium permanganate in 500 ml. of water at 80° is slowly added with stirring. After heating to 80–90° for about 9 hours, the manganese dioxide is removed. The clear, colorless filtrate is concentrated to about 400 ml. and is acidified by the addition of conc'd hydrochloric acid. The crystalline precipitate is filtered, washed with water, and recrystallized first from 50% acetic acid, then from glacial acetic acid, yielding pure 4-methoxyisophthalic acid of m.p. 277–279° [Chattaway and Calvet (1) report m.p. 275–277°]. For the analysis the acid was dried at 120° *in vacuo*.

Anal. Calc'd for $C_9H_8O_5$: C, 55.10; H, 4.11.

Found: C, 55.04; H, 4.42.

3. *3-Methyl-4-methoxybenzyl cyanide* (II). To a solution of 65 g. of sodium cyanide and 5 g. of sodium iodide in 70 ml. of water, 75 g. of 3-methyl-4-methoxybenzyl chloride and 30 ml. of acetone are added. The mixture is stirred vigorously at 70–80° for 4 hours. The solution, containing crystals of sodium chloride, is diluted with water. The undissolved oil is extracted with ether. After washing with water and dilute hydrochloric acid, the ether extract is dried over sodium sulfate and distilled. The dark brown residue is fractionated *in vacuo*. After a small forerun, the main portion boils from 140–160°/12 mm. On redistillation 42 g. of the nitrile (II) of $b.p._{10}$ 150–154° is obtained. It turns brown on standing.

If the reaction is carried out in alcohol (instead of acetone-water), no nitrile is formed.

The oily reaction product yields a nitrogen-free compound on repeated and careful fractionation which analyzes almost correctly for 3-methyl-4-methoxybenzyl ethyl ether.

Anal. Calc'd for $C_{11}H_{16}O_2$: C, 72.72; H, 8.75.

Found: C, 73.33; H, 8.9.

To further establish the structure of the nitrile, 5 g. was refluxed for 20 hours with 10 g. of potassium hydroxide in 50 ml. of methanol. After cooling, about 400 ml. of water was added, and the solution was extracted with ether. The aqueous layer was acidified and extracted with ether. Evaporation of the ether gave crude 3-methyl-4-methoxyphenylacetic acid. After repeated crystallization, it melted at 87°. Kindler (3) gives m.p. 93°.

Anal. Calc'd for $C_{10}H_{12}O_3$: C, 66.63; H, 6.72.

Found: C, 66.34; H, 7.01.

4. *α-(3-Methyl-4-methoxyphenyl)-β-oxobutyronitrile* (III). A mixture of 42 g. of 3-methyl-4-methoxybenzyl cyanide and 42 g. of dry ethyl acetate was slowly added over a period of 1½ hours to a refluxing solution of 10 g. of sodium in 150 ml. of absolute alcohol. After about 20 minutes, a crystalline precipitate began to appear. When the total ester cyanide mixture had been added, heating was continued for 3 more hours. After standing overnight, the mixture was cooled to −10° for 4 hours and was filtered. The crystals were the crude sodium derivative of III and weighed about 60 g. The salt was dissolved in about 300 ml. of ice-cold water, and the filtered solution was acidified with dilute hydrochloric acid. About 40 g. of crude nitrile III was obtained. Recrystallization from methanol yielded 35 g. of pure α-(3-methyl-4-methoxyphenyl)-β-oxobutyronitrile, m.p. 135°.

Anal. Calc'd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89.

Found: C, 71.35; H, 6.22; N, 7.09.

5. *3-Methyl-4-methoxyphenylacetone* (IV). To 200 ml. of 80% sulfuric acid stirred at 60–65°, 35 g. of α-(3-methyl-4-methoxyphenyl)-β-oxobutyronitrile was added dropwise. The mixture was kept at 60° for about 10 hours. After cooling, 1500 ml. of water was added, and the solution was heated for 6 hours on the steam-bath. A dark oil separated which was extracted with ether after cooling. The clear solution was washed, dried over sodium sulfate, and distilled. The oily residue was fractionated *in vacuo*, yielding 14 g. of 3-methyl-4-methoxyphenylacetone of $b.p._{10}$ 148–150° as a colorless liquid of agreeable odor.

For identification a sample of the ketone was converted in the conventional manner into the semicarbazone which melted at 164–166° after recrystallization from alcohol.

Anal. Calc'd for $C_{12}H_{17}N_3O_2$: C, 61.25; H, 7.28.

Found: C, 61.57; H, 7.24.

6. *3-Methyl-4-methoxyphenylisopropylamine* (V). A mixture of 7 g. of 3-methyl-4-methoxyphenylacetone, 130 ml. of 20% ammonia in methanol, and 2 g. of Raney nickel catalyst was hydrogenated at 80–90° at 500 p.s.i. for 3 hours. The solution was filtered, the solvent distilled off, and the residue was distilled *in vacuo*, yielding 5 g. of 3-methyl-4-methoxyphenylisopropylamine as a colorless oil, $b.p._{12}$ 140–142°. The hydrochloride, prepared in ether, melted at 202–203° after recrystallization from alcohol-ether. The hydrobromide, made with alcoholic hydrobromic acid in ether, melted at 180°.

Anal. Calc'd for $C_{11}H_{17}NO \cdot HBr$: C, 50.77; H, 6.97; N, 5.38.

Found: C, 50.95; H, 6.77; N, 5.50.

The *picrate* melts at 163–164°.

7. *3-Methyl-4-hydroxyphenylisopropylamine* (VII). The methoxyamine (V, 3 g.) was dissolved in 80 ml. of 48% hydrobromic acid. The solution was heated to 90–100° under nitrogen for 4 hours and then evaporated *in vacuo* at 50°. The residue was dissolved in 100 ml. of water. The colored solution was refluxed for 2 hours with 3 g. of charcoal, filtered, and again distilled to dryness *in vacuo*. The residue was dried in a desiccator over potassium hydroxide. It was dissolved in absolute alcohol, refluxed with 1 g. of charcoal, and filtered. Addition of ether to the colorless filtrate precipitated the hydrobromide. 3-Methyl-4-hydroxyphenylisopropylamine hydrobromide melted at 204–206°.

Anal. Calc'd for $C_{10}H_{15}NO \cdot HBr$: C, 48.79; H, 6.55; N, 5.69.

Found: C, 48.80; H, 6.14; N, 5.70.

8. *3-Methyl-4-methoxyphenylisopropylmethylamine* (VI). Hydrogenation of 14 g. of the ketone (IV) in 80 ml. of 20% methylamine in methanol with 2 g. of Raney nickel at 90–100° and 1000 p.s.i. for 5 hours yielded the amine which distilled at 140–142°/12 mm. as a colorless oil (13 g.). The solution of the base in alcoholic hydrobromic acid was distilled to dryness *in vacuo*, leaving the crystallized hydrobromide. Recrystallization from alcohol-ether yielded pure 3-methyl-4-methoxyphenylisopropylmethylamine hydrobromide, m.p. 127°.

Anal. Calc'd for $C_{12}H_{19}NO \cdot HBr$: C, 52.56; H, 7.35; N, 5.11.
Found: C, 52.44; H, 7.34; N, 5.08.

9. *3-Methyl-4-hydroxyphenyl isopropylmethylamine* (VIII). 3-Methyl-4-methoxyphenylisopropylmethylamine (10 g.) is refluxed in 120 ml. of freshly distilled 48% hydrobromic acid under nitrogen for 5 hours. The mixture is then distilled to dryness *in vacuo*. The residue is refluxed with 200 ml. of water and 3 g. of charcoal for 2 hours. The filtered solution is again evaporated *in vacuo*. The residue crystallizes. After drying in a desiccator over potassium hydroxide, it is recrystallized from alcohol-ether, yielding 6 g. of pure 3-methyl-4-hydroxyphenylisopropylmethylamine hydrobromide, m.p. 155°.

Anal. Calc'd for $C_{11}H_{17}NO \cdot HBr$: C, 50.77; H, 6.97; N, 5.38.
Found: C, 50.50; H, 7.03; N, 5.21.

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SUMMARY

The preparation of four nuclear methyl-substituted derivatives of 4-hydroxyphenylisopropylamine is described.

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