

Further syntheses of p-hydroxyphenylethylamine / by George Barger and George Stanley Walpole.

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Publication/Creation

London : Wellcome Physiological Research Laboratories, 1909.

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FURTHER SYNTHESSES OF
p-HYDROXYPHENYLETHYLAMINE

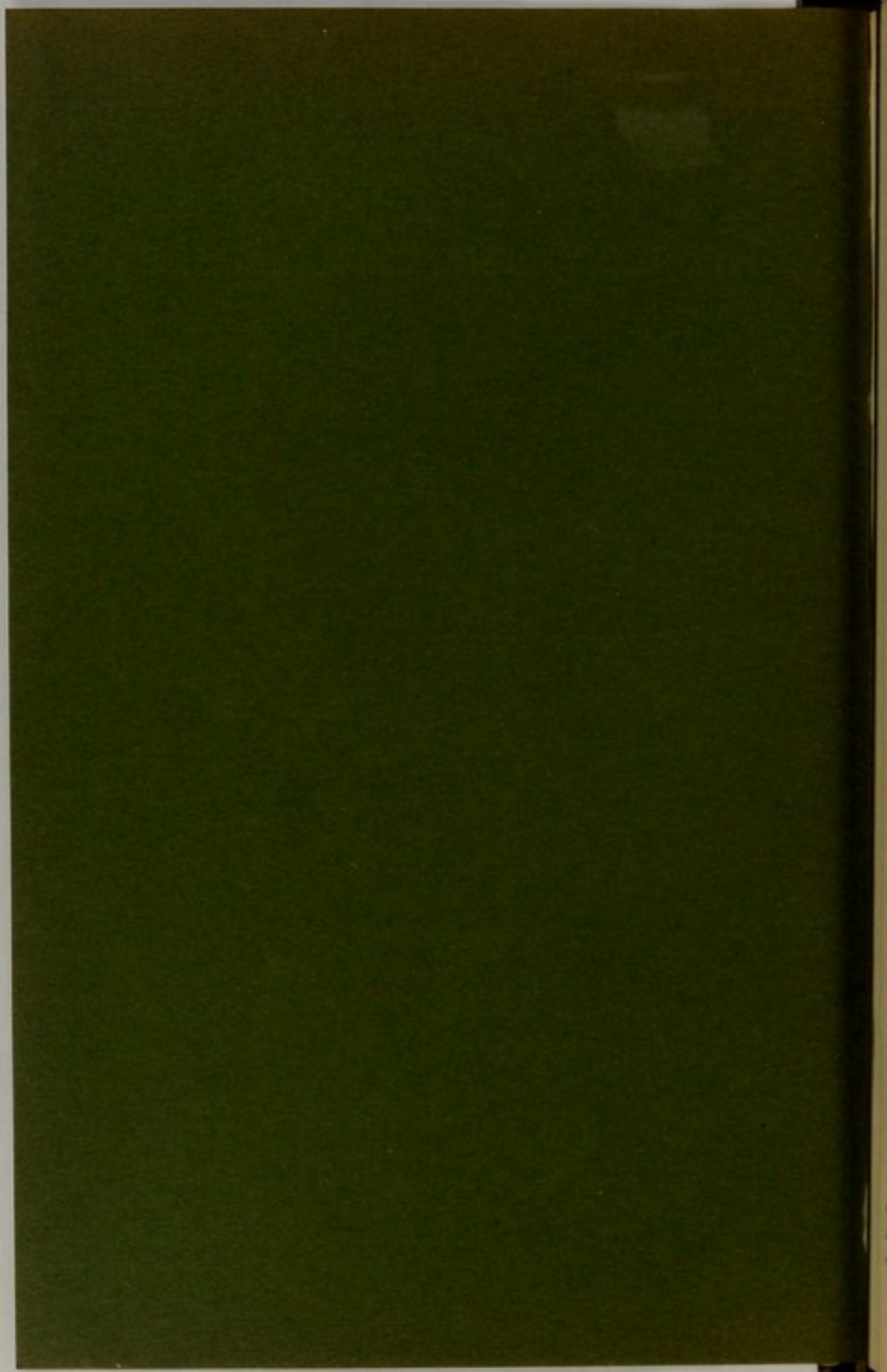


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(From the "Transactions of the Chemical Society," Vol. xcv, 1939)

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From
THE WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES no 22
BROCKWELL HALL
HERNE HILL
LONDON, S.E.





CLXXXVIII.—*Further Syntheses of p-Hydroxyphenyl-ethylamine.*

By GEORGE BARGER and GEORGE STANLEY WALPOLE.

ONE of us described recently (Trans., 1909, **95**, 1123) the isolation of a new physiologically active principle of ergot, its identification as *p*-hydroxyphenylethylamine, and its synthesis by the reduction of *p*-hydroxyphenylacetonitrile. On account of the therapeutical

interest of the substance, other syntheses were attempted, and two of these form the subject of the present paper.

In the first place, the introduction of a phenolic hydroxyl group into phenylethylamine was attempted. By nitrating benzoylphenylethylamine, a *p*-nitro-derivative was readily obtained, and this yielded by successive reduction and diazotisation the *N*-benzoyl derivative of the desired substance, which was readily converted into *p*-hydroxyphenylethylamine itself by heating with acids. Instead of benzoylation, we also used acetylation as a means of protecting the amino-group, but in this case the *p*-nitro-derivative is not so readily separated from its isomerides. Phenylethylamine can also be nitrated in the form of its benzylidene derivative when dissolved in concentrated sulphuric acid, but the mixture of nitro-compounds, which results on dilution with water, cannot be separated except by acetylation or benzoylation.

The second synthesis to be described starts from anisaldehyde, which was converted into *p*-methoxyphenylpropionic acid. This acid, first prepared by W. H. Perkin, sen. (Trans., 1877, **31**, 411), is more readily obtained by the method given by Perkin, jun., and Robinson for 3:4-dimethoxyphenylpropionic acid (Trans., 1907, **91**, 1071). The amide of this acid, $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}_2$, yielded by Hofmann's reaction *p*-methoxyphenylethylamine, $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$, from which the methyl group was finally removed by heating with hydrobromic acid.

EXPERIMENTAL.

I.—Synthesis of *p*-Hydroxyphenylethylamine from Phenylethylamine.

Benzoyl-p-nitrophenylethylamine, $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NHBz}$, was prepared by slowly adding benzoylphenylethylamine (8 grams) to fuming nitric acid (40 grams), the temperature being kept below 5°. After pouring on snow, the product solidified. On crystallisation from alcohol, 3.4 grams of the para-compound separated in long needles; the mother liquor contains isomeric nitro-compounds, which are much more soluble.

Benzoyl-p-nitrophenylethylamine was obtained pure by a second crystallisation from alcohol, and then melted at 162°. It is moderately soluble in boiling alcohol, but only sparingly so in cold alcohol:

0.2573 gave 22.2 c.c. N_2 (moist) at 11° and 748 mm. $\text{N} = 10.0$.
 $\text{C}_{15}\text{H}_{14}\text{O}_3\text{N}_2$ requires $\text{N} = 10.4$ per cent.

Benzoyl-p-aminophenylethylamine, $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NHBz}$.

Benzoyl-*p*-nitrophenylethylamine (13.5 grams) is suspended in 100 c.c. of alcohol, tinfoil (11 grams) is added, and then gradually 50 c.c. of concentrated hydrochloric acid. The temperature is at first kept below 50° ; finally the reaction is completed on the water-bath. When all the tin has dissolved, the solution is filtered, and the alcohol is removed by steam distillation. On cooling, the hydrochloride of the amino-compound separates. The free base was obtained by rendering the solution alkaline and extracting with ether. It forms crystals, melting at 134° :

0.3183 gave 31.4 c.c. N_2 (moist) at 17° and 759 mm. $\text{N} = 11.5$.
 $\text{C}_{15}\text{H}_{16}\text{ON}_2$ requires $\text{N} = 11.6$ per cent.

The *hydrochloride* melts and decomposes above 280° , and is very sparingly soluble in water:

0.2677 gave 0.1376 AgCl. $\text{Cl} = 12.7$.
 $\text{C}_{15}\text{H}_{16}\text{ON}_2 \cdot \text{HCl}$ requires $\text{Cl} = 12.7$ per cent.

Benzoyl-p-hydroxyphenylethylamine, $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NHBz}$.

To a boiling solution of the amino-compound in dilute sulphuric acid, a solution of sodium nitrite was slowly added in equivalent proportion. The hydroxy-compound formed is almost insoluble in water, and separated out; it was collected and crystallised from alcohol, when it formed hexagonal plates, melting at 162° :

0.1300 gave 6.5 c.c. N_2 (moist) at 15° and 750 mm. $\text{N} = 5.8$.
 $\text{C}_{15}\text{H}_{14}\text{O}_2\text{N}$ requires $\text{N} = 5.8$ per cent.

On heating with 20 per cent. hydrochloric acid to 140° , this substance is hydrolysed, yielding *p*-hydroxyphenylethylamine; on benzoylation by the Schotten-Baumann method, the dibenzoyl derivative, melting at 170° , is formed.

Acetyl-p-nitrophenylethylamine, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NHAc}$, is prepared by adding acetylphenylethylamine to nitric acid in the same way as was described for the benzoyl compound. After pouring on snow, the acetyl derivative, unlike the benzoyl derivative, remained liquid. The solution was therefore extracted with ether, and the ethereal solution was washed with sodium carbonate to free it from nitric acid, dried, and evaporated. Very little methyl alcohol was added to the syrupy residue; on keeping in a vacuum desiccator, crystals were slowly deposited, which were pressed on a porous tile, and recrystallised from methyl alcohol; they then melted at 142° :

0.1326 gave 0.2836 CO₂ and 0.0712 H₂O. C=58.2; H=5.9.

0.0869 „ 10.2 c.c. N₂ (moist) at 19° and 762 mm. N=13.5.

C₁₀H₁₂O₃N₂ requires C=57.8; H=5.8; N=13.5 per cent.

The nitro-compound thus obtained was reduced, the crude amino-compound diazotised, and the resulting solution was concentrated until it contained about 30 per cent. of sulphuric acid, and heated to 140°. *p*-Hydroxyphenylethylamine was then extracted by amyl alcohol and isolated as the dibenzoyl derivative (m. p. 169–170°), but none of the intermediate compounds were characterised.

p-Nitrophenylethylamine, NO₂·C₆H₄·CH₂·CH₂·NH₂.

This substance is readily obtained, mixed with its isomerides, when benzylidenephenylethylamine, CH₂Ph·CH₂·N:CHPh (melting at about 70°; prepared by warming the components), is nitrated in sulphuric acid solution by the addition of the calculated quantity of potassium nitrate. On diluting with water and removing, by steam distillation, the benzaldehyde formed, a yellow oil remains, which, on acetylation and benzoylation, yields the *p*-nitro-derivatives (melting respectively at 142° and 162°), which have been described above. The benzoyl derivative was hydrolysed by heating with ten times its weight of concentrated hydrochloric acid to 170° for four hours. *p*-Nitrophenylethylamine was thus obtained as a yellow syrup, which could not be crystallised, and was readily soluble in most organic solvents. It absorbed carbon dioxide from the air, forming a crystalline carbonate. The *hydrochloride* forms leaflets, melting at 214°, and was analysed:

0.2141 gave 0.1522 AgCl. Cl=17.6.

C₈H₁₀O₂N₂·HCl requires Cl=17.5 per cent.

II.—*Synthesis of p-Hydroxyphenylethylamine from Anisaldehyde.*

The *p*-methoxyphenylpropionic acid required was prepared according to the same method as that employed by Perkin and Robinson (Trans., 1907, 91, 1079) for the preparation of 3:4-dimethoxyphenylpropionic acid.

Anisaldehyde (100 grams) was condensed with ethyl acetate (245 grams) by means of finely-divided sodium (24.5 grams). After one hour, 102 grams of potassium hydroxide, dissolved in methyl alcohol, were added; after removal of the alcohol by distillation, the solution was treated with 3000 grams of 2½ per cent. sodium amalgam. The resulting methoxyphenylpropionic acid was crystallised from water; yield 46 grams, melting point 104°.

p-Methoxyphenylpropionamide, $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}_2$.

The acid obtained above (46 grams) was heated on a water-bath with one molecular proportion of phosphorus pentachloride in chloroform solution until no more hydrogen chloride was evolved. On fractionally distilling the mixture, 30 grams of *p*-methoxyphenylpropionyl chloride, boiling at $161\text{--}165^\circ/15$ mm., were collected. Gaseous ammonia was passed into the ethereal solution of the chloride, and gave a quantitative yield of the amide, which crystallised from alcohol in prisms, melting at 124° :

0.1009 gave 7.2 c.c. N_2 (moist) at 24° and 758 mm. $\text{N} = 8.0$.

$\text{C}_{10}\text{H}_{13}\text{O}_2\text{N}$ requires $\text{N} = 7.8$ per cent.

p-Methoxyphenylethylamine, $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$.

The amide (27 grams) was heated with 7.9 c.c. of bromine dissolved in 150 c.c. of water containing 36.5 grams of sodium hydroxide, the temperature not exceeding 55° . On extraction of the base with ether, drying, and fractionally distilling, 8 grams of *p*-methoxyphenylethylamine, boiling at $138\text{--}140^\circ/20$ mm., were obtained. The base forms a colourless liquid, very sparingly soluble in water. On passing hydrogen chloride into the ethereal solution of the base, a crystalline hydrochloride, melting at 206° , was obtained:

0.0946 gave 0.0717 AgCl. $\text{Cl} = 18.8$.

$\text{C}_9\text{H}_{13}\text{ON}\cdot\text{HCl}$ requires $\text{Cl} = 18.8$ per cent.

0.5 Gram of the above hydrochloride was heated for four hours to 160° with 5 c.c. of hydrobromic acid (D 1.4). On cooling, a salt crystallised out, but could not be readily freed from the mother liquor; the excess of hydrobromic acid was therefore removed under diminished pressure, and the remaining solid boiled in alcoholic solution with charcoal. On adding ether to the filtrate, a salt separated which gave Millon's reaction; after benzoylation, the dibenzoyl derivative of *p*-hydroxyphenylethylamine, melting at $169\text{--}170^\circ$, was isolated.

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