

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

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No. 22

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FURTHER SYNTHESSES OF
p-HYDROXYPHENYLETHYLAMINE

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BY

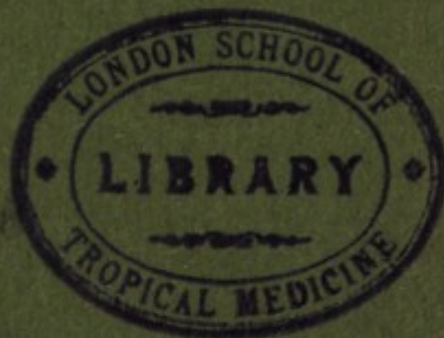
GEORGE BARGER, M.A., D.Sc.

AND

GEORGE STANLEY WALPOLE, B.Sc., A.I.C.

(From the "Transactions of the Chemical Society," Vol. xcv, 1909)

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From

THE WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES
BROCKWELL HALL
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CLXXXVIII.—*Further Syntheses of p-Hydroxyphenylethylamine.*

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

0.1326 gave 0.2836 CO_2 and 0.0712 H_2O . $\text{C}=58.2$; $\text{H}=5.9$.

0.0869 „ 10.2 c.c. N_2 (moist) at 19° and 762 mm. $\text{N}=13.5$.

$\text{C}_{10}\text{H}_{12}\text{O}_3\text{N}_2$ requires $\text{C}=57.8$; $\text{H}=5.8$; $\text{N}=13.5$ 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, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH}_2$.

This substance is readily obtained, mixed with its isomerides, when benzylidenepheneylethylamine, $\text{CH}_2\text{Ph} \cdot \text{CH}_2 \cdot \text{N} : \text{CHPh}$ (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 benzylation, 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 . $\text{Cl}=17.6$.

$\text{C}_8\text{H}_{10}\text{O}_2\text{N}_2 \cdot \text{HCl}$ requires $\text{Cl}=17.5$ 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 $2\frac{1}{2}$ 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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