Syntheses of p-hydroxyphenylethylalkylamines / by George Stanley Walpole.

31

SYNTHESES OF
p-HYDROXYPHENYLETHYLALKYLAMINES

BY

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

From
THE WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES
BROCKWELL HALL
HERNE HILL
LONDON, S.E.

no 24

LXX.—*Syntheses of* p-*Hydroxyphenylethylalkylamines.*

By George Stanley Walpole.

The methylamino- and ethylamino-homologues of *p*-hydroxyphenylethylamine have been prepared in order that their physiological properties might be examined and compared with those of allied compounds.

p-*Hydroxyphenylethylmethylamine*, $HO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NHMe$, is of particular interest, in that it stands in the same relationship to methyltyrosine as does *p*-hydroxyphenylethylamine to tyrosine. The crystalline form, melting point, and platinum content of the platinichloride of this substance have been found to agree with the data given by Blau (*Zeitsch. physiol. Chem.*, 1908, **58**, 153) for the corresponding compound prepared from the base obtained by the destructive distillation of surinamine. There is no longer room for doubt, therefore, that the latter substance is, as supposed, methyltyrosine.

No attempt was made to obtain it by the direct methylation of *p*-hydroxyphenylethylamine since Barger (Trans., 1909, **95**, 2195) and, later, Rosenmund (*Ber.*, 1910, **43**, 305) have drawn attention to the difficulty of isolating products intermediate between this substance and hordenine methiodide. The method first adopted was suggested by the process employed by Hepp (*Ber.*, 1877, **10**,

328) for the preparation of methylaniline. The starting point was *p*-methoxyphenylethylamine, prepared from anisaldehyde by the method described by Barger and the author.

The acetyl derivative of this was prepared, and methylation of the imino-group brought about in dry xylene solution by metallic sodium followed by methyl iodide. The product, on hydrolysis, gave acetyl-*p*-hydroxyphenylethylmethylamine and *p*-hydroxyphenylethylmethylamine.

While the investigation of the hydrolysis of acetyl-*p*-methoxyphenylethylmethylamine was in progress, a paper by Johnson and Guest (*Amer. Chem. J.*, 1909, **42**, 340) describing the monomethylation of phenylethylamine was published. The preparation of *benzenesulphonyl-*p*-methoxyphenylethylmethylamine* on lines suggested by their preparation of benzenesulphonylphenylethylmethylamine was carried out, and this substance gave, on partial hydrolysis, *benzenesulphonyl-*p*-hydroxyphenylethylmethylamine,* and on complete hydrolysis, *p*-hydroxyphenylethylmethylamine. The synthesis of the corresponding ethylamino-base was accomplished in a similar manner.

EXPERIMENTAL.

Synthesis of p-*Hydroxyphenylethylmethylamine from* p-*Methoxyphenylethylamine.*

The steps involved in obtaining *p*-methoxyphenylethylamine from anisaldehyde through *p*-methoxyphenylpropionic acid have been already described (Trans., 1909, **95**, 1720). In later preparations the conditions under which the last step (Hofmann's reaction) was carried out were altered slightly, with the result that the yield of amine from amide was considerably increased. To a cold solution of 31 grams of potassium hydroxide in 120 c.c. of water, 5·3 c.c. of bromine were added. The amide (18 grams) was finely powdered and rubbed to a cream with a little water, and then washed rapidly with 200 c.c. of water into the hypobromite solution. The mixture was maintained at 55° for one hour, then cooled, and extracted with ether. The ethereal extracts after filtration and evaporation on the water-bath left a residue which, when fractionated under 20 mm. pressure, yielded 7·5—8·5 grams of the amine, boiling at 138—142°, and a crystalline residue of higher boiling point. This consisted largely of a substance melting at 127°, which was probably the *iso*cyanate, since, on hydrolysis with strong aqueous potassium hydroxide, it yielded more amine. The residues were therefore collected and converted separately into the amine.

Acetyl-p-*methoxyphenylethylamine*, $MeO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NHAc$.

7·8 Grams of *p*-methoxyphenylethylamine, dissolved in 15 c.c. of acetic anhydride, were boiled with 5 grams of anhydrous sodium acetate for four hours in an oil-bath under an air condenser fitted with a drying tube. The mixture was poured into boiling water, allowed to cool, and extracted with ether. The extract was washed with sodium carbonate solution to remove acid, dried, and fractionated. The yield of acetyl derivative, boiling at 195—200°/15 mm., was 9·85 grams. It is a colourless, oily liquid, insoluble in water, but readily miscible in all proportions with alcohol, ether, xylene, benzene, etc.

Acetyl-p-*methoxyphenylethylmethylamine*,
$MeO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NMeAc$.

To 9·85 grams of the above acetyl derivative, dissolved in 25 c.c. of dry xylene, 0·97 gram of sodium was added, and the flask heated under an air condenser in an oil-bath until the xylene boiled. The solution of the sodium, except 0·02 gram, was complete in twenty minutes. When still warm, the small remaining bead of sodium was removed, and a large excess, 8 c.c., of methyl iodide added. Sodium iodide separated rapidly, there was considerable evolution of heat, and after a few minutes' further warming, the reaction was considered complete. From the product after dilution with ether, sodium iodide was removed by extraction with water. The xylene-ether layer was dried and fractionated, yielding 5·25 grams of a colourless, oily liquid similar in its solubility relationships to the acetyl derivative. It was crystalline, but this property could not be used as a means of further purification. The oil boiled at 205—208°/18 mm.:

0·1560 gave 0·3979 CO_2 and 0·1168 H_2O. C = 69·5; H = 8·3.
$C_{12}H_{17}O_2N$ requires C = 69·6; H = 8·2 per cent.

Acetyl-p-*hydroxyphenylethylmethylamine*,
$HO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NMeAc$.

The oil just described (5·25 c.c.) was boiled for twenty minutes with 15 c.c. of hydriodic acid (D 1·70), the excess of acid removed on a water-bath under diminished pressure, and the residue dissolved in water. From the ethereal extracts a crystalline substance, melting at 142°, was obtained. In a later experiment colourless hydriodic acid was used, and the hydrolysis conducted in a stream of carbon dioxide. This alteration in procedure, together with the substitution of amyl alcohol for ether as an extracting agent, had the effect of slightly facilitating the separation of this substance. The residue from the evaporation of the extracts was extracted in its turn with successive small quantities of boiling toluene, and after some time these deposited aggregates of white needles, which were washed with dry ether, and of which small samples were recrystallised from ethyl alcohol, methyl alcohol, and ethyl acetate. From these solvents the substance very slowly crystallises in small, isolated hexagonal plates, although from aqueous solution by slow evaporation in a vacuum desiccator, thin, colourless, spear-shaped needles are obtained. All the purified samples melted at 142°:

0·1547 gave 0·3856 CO_2 and 0·1092 H_2O. C=67·98; H=7·84.

$C_{11}H_{15}O_2N$ requires C=68·38; H=7·77 per cent.

($C_{10}H_{13}O_2N$ „ C=67·00; H=7·76 „)

A minute quantity of the purified material gives Millon's reaction. It dissolves slowly in a small quantity of water or sodium carbonate solution, but instantly in aqueous sodium hydroxide. Its aqueous solution gives a heavy precipitate with phosphotungstic acid. From an attempted hydrolysis, by heating with 10 per cent. alcoholic potash for two hours on the water-bath, some of the material was recovered unaltered. 0·08 Gram was heated at 170° for two hours with 2 c.c. of concentrated hydrochloric acid, and then evaporated to dryness in a vacuum desiccator. The small residue was crystallised from alcohol by cautious addition of dry ether yielding 0·05 gram of slender, slightly coloured scales. The melting point of this substance and its benzoyl derivative, its crystalline form, and its physiological action were examined. A comparison with equal quantities of the hydrochlorides of *p*-hydroxyphenylethylamine and *p*-hydroxyphenylethylmethylamine showed that these crystals consisted of the latter substance. In view of these facts, it is suggested that the compound melting at 142° has the constitution $HO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NMeAc$.

p-*Hydroxyphenylethylmethylamine*, $HO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NHMe$.

4·43 Grams of acetyl-*p*-methoxyphenylethylmethylamine were heated with 12 c.c. of concentrated hydrochloric acid at 165° for two hours. The excess of acid was removed by distillation under diminished pressure on the water-bath, and an aqueous solution of the residue was extracted completely with amyl alcohol. Over and above that amount required for neutralisation, 4 grams of sodium hydroxide were then added to the aqueous solution. Two extractions with the same solvent were made with the object of removing any base not phenolic, and finally the liquid was again neutralised, and in it were dissolved 6 grams of hydrated sodium carbonate. Four extractions with 20 c.c. of amyl alcohol sufficed to remove nearly all the phenolic base. The residue, on evaporation of these extracts, was crystallised from boiling xylene. The substance sought, still impure, separated in oily drops, which soon resolved themselves into fine needles, melting at 114—116°, of which 1·4 grams were collected.

Distillation under diminished pressure yielded 1·09 grams of material, boiling at 183—185°/9 mm., which solidified at once in the condenser. From a concentrated solution in hot alcohol it slowly separated, on cooling, in bundles of colourless, four-sided prisms, melting sharply at 130°:

0·1449 gave 0·3783 CO_2 and 0·1124 H_2O. C=71·2; H=8·61.

$C_9H_{13}ON$ requires C=71·5; H=8·6 per cent.

It is moderately soluble in water or sodium carbonate solution, and instantly dissolves in dilute acid or sodium hydroxide. It reddens phenolphthalein, gives Millon's reaction very intensely, reduces acid potassium permanganate in the cold, and may be precipitated by addition of excess of ammonia to an aqueous solution of a salt.

The *hydrochloride* is extremely soluble in water or alcohol. 0·2 Gram of the pure base was dissolved in a few drops of alcoholic hydrochloric acid. Slender, colourless scales, melting at 148·5°, separated on the addition of ether. They did not gain weight on exposure to the air for half an hour, and were recrystallised from alcohol and ether for analysis:

0·1391 gave 0·1059 AgCl. Cl=18·8.

$C_9H_{13}ON,HCl$ requires Cl=18·9 per cent.

The platinichloride, obtained by adding platinic chloride solution to a solution of the pure base in dilute hydrochloric acid, separates, after some time, in yellow needles. These melt and decompose at 205° (corr.), and correspond in this respect with the platinichloride of the base from surinamine described by Blau, the melting point of which is given as 205°:

0·0756 gave 0·0209 Pt. Pt=27·6.

$(C_9H_{13}ON)_2H_2PtCl_6$ requires Pt=27·3 per cent.

Methylation to Hordenine Methiodide.—This procedure was initiated in order to confirm the constitution of the substance and its relation to the allied base hordenine. 0·1 Gram of the pure base, dissolved in a few drops of methyl alcohol, were warmed for a few minutes with 3 c.c. of methyl iodide. On cooling, long needles of hordenine methiodide separated. They were recrystallised from water, when they melted at 229°, which is the melting point of hordenine methiodide. A mixture of equal weights of the two substances melted also at 229°.

A *dibenzoyl* derivative, prepared by the Schotten-Baumann method, was found to be very soluble in alcohol (0·3 gram in 0·5 c.c.), from which it crystallised on cautious dilution with water from time to time. Recrystallisation twice repeated from benzene and light petroleum yielded it in a pure condition in rosettes of colourless prisms, melting at 99°. From 0·40 gram of base, 0·28 gram of pure dibenzoyl derivative was obtained:

0·1510 gave 0·4260 CO_2 and 0·0808 H_2O. C=76·94; H=5·94.
0·1062 ,, 3·3 c.c. N_2 (moist) at 14° and 747 mm. N=3·6.
$C_{23}H_{21}O_3N$ requires C=76·88; H=5·84; N=3·9 per cent.

The *hydrogen oxalate*, prepared by pouring an alcoholic solution of the base into a saturated solution of oxalic acid in dry ether, was found to be very insoluble in absolute alcohol even at the boiling point. It melts and decomposes at 250° (uncorr.), and crystallises from alcohol in colourless needles.

The *picrate* melts at 149°.

A yellow *picrolonate*, extremely insoluble in water, was obtained by mixing aqueous solutions of picrolonic acid and the hydrochloride of the base. It melts and decomposes at 234—235°.

An alternative synthesis on similar lines to that described was performed. The benzenesulphonyl group, however, instead of the acetyl group, was attached to the nitrogen atom through all the stages up to the final hydrolysis.

*Benzenesulphonyl-*p*-methoxyphenylethylamine,*
$MeO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NH\cdot SO_2Ph$.

9·23 Grams of benzenesulphonyl chloride and 7·9 grams of *p*-methoxyphenylethylamine were mixed with 70 c.c. of benzene. The mixture became warm, and after a minute 4·40 grams of potassium hydroxide in 30 c.c. of water were added, and the whole was shaken vigorously. The benzene layer which separated was dried and concentrated on the water-bath. On cooling, a mass of crystals separated, which could readily be obtained in the pure condition by recrystallisation from alcohol or benzene and light petroleum. The yield of purified material, which melted at 79—80°, was 15·5 grams:

0·1277 gave 5·6 c.c. N_2 (moist) at 14° and 746 mm. N=5·0.
$C_{15}H_{17}O_3NS$ requires N=4·9 per cent.

*Methylation of Benzenesulphonyl-*p*-methoxyphenylethylamine and Hydrolysis of the Product.*

To a solution in alcohol of 10 grams of the benzenesulphonyl derivative, prepared as described above, 2 grams of sodium hydroxide dissolved in a little water were added, and then 7 grams of methyl iodide. To ensure the completion of the reaction, the mixture was heated on the water-bath for fifteen minutes. The alcohol was then expelled, and the residue shaken with ether and water. The ethereal layer, on evaporation, left a clear, yellow oil.

7·3 Grams of this oil were heated with 10 c.c. of concentrated hydrochloric acid at 130—150° for two hours in a sealed tube. The excess of hydrochloric acid was then removed by evaporation in a vacuum, and the residue, a viscous liquid, was dissolved in 30 c.c. of water, and the solution extracted completely by shaking six times with 10 c.c. of amyl alcohol. The residue obtained from these extracts crystallised on cooling (A).

The aqueous layer was now neutralised, and a solution containing 5 grams of sodium hydroxide added. Three extractions with 10 c.c. of amyl alcohol yielded very little material, indicating that only a small quantity of non-phenolic base was present. The solution was again neutralised, 8 grams of hydrated sodium carbonate dissolved in it, and it was then completely extracted with ten portions of 15 c.c. of amyl alcohol. The extracts, after washing with a little sodium carbonate solution and filtering, gave, on evaporation, a residue (B).

*Benzenesulphonyl-*p*-hydroxyphenylethylmethylamine,*
$HO{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}NMe{\cdot}SO_2Ph$.

The residue (A) was extracted with ether, leaving 4 grams of a highly crystalline material. Boiling with animal charcoal in alcoholic solution removed a purple colouring matter accompanying this substance, and the subsequent addition of ether caused it to separate in white leaflets, melting at 133·5°. It is readily soluble in water, and a minute quantity of the pure material gives Millon's reaction:

0·2161 gave 8·7 c.c. N_2 (moist) at 15° and 760 mm. N=4·71.
0·1704 „ 0·1375 $BaSO_4$. S=11·09.
$C_{15}H_{17}O_3NS$ requires N=4·81; S=10·99 per cent.

The residue (B) was extracted with boiling xylene, from which, on cooling, needles, melting at 123°, separated. These were washed with a little ether, and gave on distillation 0·4 gram of pure *p*-hydroxyphenylethylamine. From further extracts another 0·2 gram was obtained.

Under the above conditions, therefore, hydrolysis of benzenesulphonyl-*p*-methoxyphenylethylamine is not complete. Some phenolic secondary amine is obtained, and a considerable quantity of the intermediate product, benzenesulphonyl-*p*-hydroxyphenylethylmethylamine.

A second hydrolysis conducted in the same manner, except that the temperature was maintained at 170°, gave scarcely any of the intermediate product, the yield of pure base from 5 grams of benzenesulphonyl-*p*-methoxyphenylethylamine being nearly 1 gram.

Three grams of pure benzenesulphonyl-*p*-hydroxyphenylethylmethylamine also gave about a gram of *p*-hydroxyphenylethylmethylamine on hydrolysis with concentrated hydrochloric acid for two hours.

Synthesis of p-*Hydroxyphenylethylethylamine from* p-*Methoxyphenylethylamine.*

This synthesis was conducted through the benzenesulphonyl derivative of *p*-methoxyphenylethylamine in a manner analogous to that described for the methyl base, methyl iodide being replaced by ethyl iodide. No attempt was made to isolate the intermediate phenolic benzenesulphonyl compound, and the hydrolysis was therefore conducted at 170°. Commencing with 6·9 grams of benzenesulphonyl-*p*-methoxyphenylethylamine, it was found possible to isolate 0·9 gram of the hydrochloride of the ethylamino-base. A slight modification of technique was necessitated in the later stages of this preparation, as it was found impossible to obtain the free base in the crystalline condition from xylene. The residue from the amyl-alcoholic extracts containing the ethylamino-phenolic base was therefore dissolved in 10 c.c. of amyl alcohol, and thoroughly shaken with dilute hydrochloric acid. The acid extracts were boiled with a small quantity of animal charcoal, filtered, and evaporated to dryness in a vacuum at the ordinary temperature. Needles up to 2 cm. in length of the nearly pure *hydrochloride* were thus obtained. These melted at 184—185°, and were not so extremely soluble in alcohol as the hydrochloride of the methyl homologue. On dilution with ether, the alcoholic solution deposited the hydrochloride in colourless needles. These, when dry, were found to be tinted very faintly pink, and not hygroscopic. Recrystallisation did not alter the melting point, but removed the colour:

0·0872 gave 0·0612 AgCl. Cl = 17·3.

0·1161 „ 7·0 c.c. N_2 (moist) at 12° and 743 mm. N = 6·9.

$C_{10}H_{15}ON,HCl$ requires Cl = 17·1; N = 6·9 per cent.

The free base liberated from the hydrochloride by sodium carbonate and extracted by means of amyl alcohol was distilled. It crystallised in the receiver, but the amount of material was insufficient to draw any accurate conclusion as to its boiling point, which, however, appeared to be 185—187°/9 mm. It crystallised from alcohol in rosettes of colourless needles, melting at 157—158°.

A *picrolonate*, very insoluble even in boiling water, was formed by adding an aqueous solution of the purified hydrochloride to a cold saturated solution of picrolonic acid. It melts and decomposes at 216°, and this melting point remained unchanged even after repeatedly boiling the substance with water.

No platinichloride could be obtained. The residue left after careful evaporation of the mixed aqueous solution of platinic chloride and the hydrochloride of the base was instantly soluble in cold water and concentrated hydrochloric acid. This suggests a ready means of separating the ethyl base from its methyl homologue.

An alcoholic solution of the free base added to a saturated solution of oxalic acid in ether gave a cloudy precipitate of the *hydrogen oxalate*, which crystallised from alcohol in colourless, rhombic plates, melting and decomposing at 245°. This salt is much more soluble in alcohol than that of the corresponding methyl compound.

Dr. H. H. Dale has examined the physiological properties of the two bases described. The methylamino-base is almost, but not quite, as active as *p*-hydroxyphenylethylamine, whilst the ethylamino-base is considerably less active than either.

THE WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES,
HERNE HILL, LONDON, S.E.

R. CLAY AND SONS, LTD., BREAD ST. HILL, E.C., AND BUNGAY, SUFFOLK.