CXVIII.— *β -Hydroxy- β -3:4-methylenedioxyphenylethylamine and its Derivatives.*

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SUBSTANCES of the type $R\cdot CH(OH)\cdot CH_2\cdot NH_2$ are of considerable interest owing to their relationships on the one hand to adrenaline, $C_6H_3(OH)_2\cdot CH(OH)\cdot CH_2\cdot NHMe$, and similar sympathomimetic products, and on the other to derivatives of *isoquinoline*.

The present investigation was begun with the hope of effecting a convenient synthesis of 6:7-methylenedioxy*isoquinoline* (V) from piperonaldehyde (I) by the steps shown :

The formyl derivative (IV) was obtained, but as the investigation

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had to be abandoned at this stage it has seemed desirable to place on record the results obtained.*

Various investigators have prepared adrenaline methylene ether from β -bromo- α -3:4-methylenedioxyphenylethyl alcohol (Barger and Jowett, T., 1905, **87**, 967; Barger, T., 1908, **93**, 2081; Pauly and Neukam, *Ber.*, 1908, **41**, 4151; Böttcher, *Ber.*, 1909, **42**, 253; Mannich, *Arch. Pharm.*, 1910, **248**, 127; D.R.-P. 209609, 209610, 212206), but the corresponding unmethylated compound (III) does not appear to have been prepared hitherto.†

The method adopted for the preparation of β -hydroxy- β -3:4-methylenedioxyphenylethylamine (III) was substantially that described by the Farbwerke Hoechst (D.R.-P. 193634; Eng. Pat. 27117, 1907) and consisted in the reduction of piperonaldehydecyanohydrin (II) in alcoholic solution by means of sodium amalgam. The method was extremely laborious and difficult to control, yields being obtained which varied from nothing up to about 17 per cent., although the latter yield was only obtained on very few occasions.

Other methods of reduction were also tried, for example, magnesium and acetic acid, magnesium amalgam, and aluminium amalgam, but no trace of the base was obtained.

Attempts to reduce the cyanohydrin electrolytically in a 50 per cent. alcoholic solution of potassium acetate with an ice-cooled potassium amalgam cathode and a water-cooled platinum anode were unsuccessful, as also were similar attempts with a sodium amalgam electrode and an aqueous-alcoholic solution of sodium acetate.

Preliminary experiments with the small amount of the formyl derivative available failed to give any detectable amount of 6:7-methylenedioxyisoquinoline by the interaction of the formyl compound and phosphoric oxide in toluene, but there can be little doubt that further work with a larger quantity of the substance would lead to the desired product, by Pictet and Gams's method for the synthesis of isoquinoline itself (*Ber.*, 1910, **43**, 2384).

EXPERIMENTAL.

β -Hydroxy- β -3:4-methylenedioxyphenylethylamine (Formula III).

The pasty mass obtained by adding sodium hydrogen sulphite (120 grams) dissolved in water (120 c.c.) to a solution of piperon-

* The investigation was carried out at various times during the period June 1914 to December 1915, when it was abandoned owing to the pressure of war work.

† For further details of related compounds, see G. Barger, "Simpler Natural Bases" (London 1914), pp. 81-105; and Meyer and Jacobson, "Organische Chemie," 2, III, (3) pp. 1014 *et seq.*, which gives full references to the literature.

aldehyde (50 grams) in warm alcohol (50 c.c.) was treated with potassium cyanide (50 grams) dissolved in water (200 c.c.) and the mixture stirred and gently shaken, care being taken to avoid emulsification, until the solid had almost disappeared. After the mixture had been kept for a few minutes the lower layer of the cyanohydrin thus obtained was run into a mixture of 600 c.c. of 95 per cent. alcohol and 400 c.c. of water cooled in a freezing mixture, and to the well-stirred solution were added 2500 grams of 4 per cent. sodium amalgam, in portions of 250 grams at intervals of about fifteen minutes, 250 c.c. of glacial acetic acid being run in at a suitable rate to keep the liquid faintly acid to phenolphthalein; the temperature was maintained at 6–8°. After about three hours the alcoholic layer was filtered from the large amount of sodium acetate formed, and from a small amount of tarry greenish-yellow by-product, which was not further examined, and the clear yellow filtrate was evaporated under 40 mm. pressure until all the alcohol had been removed. The aqueous layer, after being shaken thrice with ether* to remove the yellow oil that had separated, was made strongly alkaline with sodium hydroxide solution and extracted six times with an equal volume of ether, or better with a smaller quantity of chloroform, care being taken that the solvent did not become emulsified by too vigorous shaking. The extracts were dried with potassium carbonate, and the solvent was evaporated. The residue, consisting of a few c.c. of a thin yellow oil, easily soluble in alcohol or chloroform, insoluble in water, and sparingly soluble in ether, was covered with 30 c.c. of ether and concentrated hydrochloric acid added drop by drop with stirring until no further salt formation was observed. The oil solidified quickly to a white, crystalline paste of crude β -hydroxy- β -3 : 4-methylenedioxyphenylethylamine hydrochloride, which was filtered and pressed on porous tile; the yield was 12 grams or 17 per cent. of the theoretical.

Derivatives of the Base.

The *hydrochloride* was easily soluble in water and in alcohol, from which it separated in white, prismatic crystals, m. p. 176° (Found: C=49.5; H=5.8; Cl=16.6. $C_9H_{12}O_3NCl$ requires C=49.6; H=5.5; Cl=16.3 per cent.).

The *formate*, obtained in a similar manner by the addition of formic acid to the ether or chloroform solution of the base, formed

* The ethereal extracts, after removal of the solvent, left a large amount of oily product, which, on keeping, deposited large, yellow crystals of low melting point. The substance was extremely soluble in alcohol and consisted probably of piperonyl alcohol, but was not further examined.

white crystals, m. p. 138—139°, which were easily soluble in water and alcohol (Found * : C=53·4. $C_{10}H_{13}O_5N$ requires C=52·9 per cent.).

The *platinichloride*, obtained in the usual manner from the hydrochloride, formed brilliant orange scales, which were moderately soluble in water or alcohol, and blackened and decomposed above 170—200°.

The *urethane* derivative, $CH_2O_2C_6H_3CH(OH)CH_2NHCO_2Et$, was prepared by treating a solution of the hydrochloride with ethyl chloroformate and excess of sodium carbonate solution, when it was deposited in minute, colourless crystals, m. p. 105°, insoluble in water, and easily soluble in chloroform or alcohol.

The *benzoyl* derivative, $C_9H_9O_3NHCOPh$, was prepared by treating a solution of the hydrochloride with an ethereal solution of benzoyl chloride in presence of a little sodium carbonate solution. After recrystallisation from 50 per cent. alcohol, it formed glistening, white leaflets, m. p. 155—157°, easily soluble in alcohol, sparingly soluble in ether, and insoluble in water.

The *mono-p-nitrobenzoyl* derivative, $C_9H_9O_3NHCO \cdot C_6H_4NO_2$, was obtained by shaking 11·7 grams of the formate dissolved in 25 c.c. of water and a solution of 28·6 grams of sodium carbonate with 10 grams of *p*-nitrobenzoyl chloride dissolved in 25 c.c. of chloroform. The thick, crystalline, yellow precipitate was recrystallised from alcohol and the *p-nitrobenzoyl* derivative thereby obtained in small, yellow leaflets, m. p. 155—157°, soluble in alcohol, sparingly soluble in chloroform, and insoluble in water (Found : C=58·3; H=4·7. $C_{16}H_{14}O_6N_2$ requires C=58·2; H=4·22 per cent.).

The *di-p-nitrobenzoyl* derivative,

was obtained when solutions of 6 grams of the mono-acyl derivative, 6 grams of *p*-nitrobenzoyl chloride, and 3·5 c.c. of pyridine, each dissolved in 10 c.c. of chloroform, were mixed and boiled for one hour. The solvent was then evaporated and the residue triturated first with a few c.c. of alcohol until it set to a crystalline mass, then with a little sodium carbonate solution. After being filtered, washed with a few c.c. of alcohol, dried, and recrystallised from chloroform, the *di-p-nitrobenzoyl* derivative was obtained in small, orange-yellow crystals, m. p. 179—180°, which were sparingly soluble in most solvents.

The *veratroyl* derivative, $C_9H_9O_3NHCO \cdot C_6H_3(OMe)_2$, was prepared from 4·5 grams of the formate dissolved in 5 c.c. of water

* The analysis was kindly carried out by Dr. P. W. Robertson by his method (T., 1916, 109, 215).

and 4 grams of veratroyl chloride in 10 c.c. of dry ether, sodium carbonate being added until the alkalinity was permanent. The extract in chloroform of the yellow oil that separated was dried over potassium carbonate and the solvent evaporated, when a viscous, uncrystallisable gum was obtained, which, on evaporation in a vacuum, frothed up to a friable, resinous mass melting indefinitely at 60—80°. It was insoluble in water, ether, benzene, or light petroleum, but was very easily soluble in methyl or ethyl alcohol and in chloroform.

The *formyl* derivative, $C_9H_9O_3 \cdot NH \cdot CHO$, could be prepared satisfactorily neither by heating the base or its hydrochloride with formic acid, nor by heating the formate at 110°. It was obtained by boiling the base with purified formic ester and after recrystallisation from methyl alcohol formed hard, white crystals melting at 90—92°. It was insoluble in water, carbon disulphide, or ether, very sparingly soluble in hot benzene, easily soluble in hot methyl alcohol, but only slightly soluble in the cold solvent; it dissolved readily in ethyl alcohol, chloroform, or formic ester.

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