Hydroxytryptamines. Part II. A New Synthesis of Physostigmine.*

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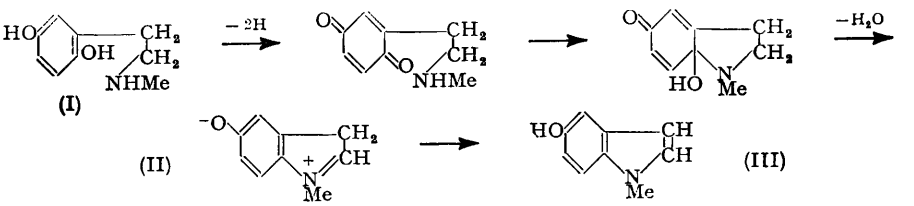
(±)-Eseroline has been synthesised by ferricyanide oxidation of 2-(2 : 5-dihydroxyphenyl)-2 : *N* : *N'*-trimethylbutane-1 : 4-diamine and converted into (±)-eserethole. Similar oxidation of 2-(2 : 5-dihydroxyphenyl)-*N*-methylethylamine gives 5-hydroxy-1-methylindole.

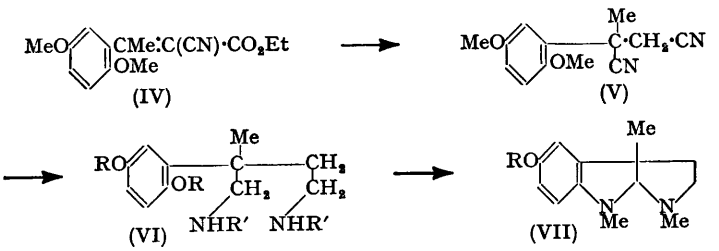
IN Part I * it was shown that ferricyanide oxidation of 2-(2 : 5-dihydroxyphenyl)butane-1 : 4-diamine gave 5-hydroxytryptamine (serotonin) in good yield. Eseroline (VII; R = H), the hydrolysis product of physostigmine (eserine), may be regarded as a trimethyl-5-hydroxytryptamine in which a second ring-closure has occurred, and we therefore investigated the oxidation of the appropriate trimethylbutanediamine. To determine the effect of *N*-methylation on the formation of 5-hydroxyindoles from 2 : 5-dihydroxyphenylethylamines a model experiment was first conducted. 2-(2 : 5-Dimethoxyphenyl)ethylamine with benzaldehyde gave a Schiff base which after being



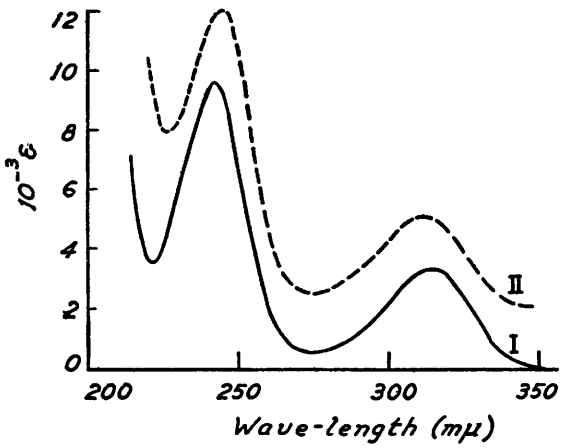
heated with methyl iodide and subsequent hydrolysis gave the monomethyl derivative. This with boiling hydrobromic acid gave 2-(2 : 5-dihydroxyphenyl)-*N*-methylethylamine (I). On oxidation with potassium ferricyanide 5-hydroxy-1-methylindole (III) was obtained. The mechanism of this reaction must differ from that of the conversion of the unmethylated amine into 5-hydroxyindole (Cromartie and Harley-Mason, *J.*, 1952, 2525), and it is suggested that the intermediates involved are as shown in the scheme.

* Part I, *J.*, 1954, 1165.

Synthesis of the diamine (VI; R = H, R′ = Me) was next undertaken. 2 : 5-Dimethoxyacetophenone was condensed with ethyl cyanoacetate, by the procedure devised by Cope, Hofman, Wyckoff, and Hardenburgh (*J. Amer. Chem. Soc.*, 1941, **63**, 5452), to



give ethyl 1-cyano-2-(2 : 5-dimethoxyphenyl)crotonate (IV), converted by treatment with potassium cyanide into α-(2 : 5-dimethoxyphenyl)-α-methylsuccinonitrile (V). On hydrogenation of (V) over platinum oxide in the presence of hydrochloric acid 2-(2 : 5-dimethoxyphenyl)-2-methylbutane-1 : 4-diamine (VI; R = Me, R′ = H) was obtained, and



Ultra-violet absorption spectra in buffer, pH 6·8.
I. *Eseroline.* II. *Eserethole.*
(*The* $10^{-3}\varepsilon$ *values in* II *have been increased by 2 units.*)

this with 2 mol. of benzaldehyde gave a dibenzylidene derivative which when heated with methyl iodide in a sealed tube gave the *NN′*-dimethyl derivative (VI; R = R′ = Me). This was de-*O*-methylated by boiling hydrobromic acid. Excellent yields were obtained in all the above stages. On treatment with potassium ferricyanide the dihydroxy-amine (VI; R = H, R′ = Me) gave in 30% yield a product whose properties were identical with those of (±)-eseroline (VII; R = H) (Kobayashi, *Annalen*, 1938, **536**, 143; Julian and Pikl, *J. Amer. Chem. Soc.*, 1935, **57**, 563). Identity was rigorously confirmed by ethylation with ethyl toluene-*p*-sulphonate to give (±)-eserethole (VII; R = Et), characterised as the known picrate and methopicrate. Furthermore, the ultra-violet and infra-red absorption spectra (in solution) of our product were identical with those of (−)-eseroline, prepared from the natural alkaloid. Since (±)-eserethole has earlier been resolved and converted into (−)-physostigmine (Kobayashi, *loc. cit.*), our process constitutes a conveniently brief formal synthesis of the natural product. The mechanism of the double ring-closure involved is of some interest; presumably an indolenine intermediate of the type (II) is formed, and the second nitrogen atom then adds on to the highly reactive double bond.

Experimental

2 - (2 : 5 - *Dimethoxyphenyl*) - N - *methylethylamine*. — 2 - (2 : 5 - Dimethoxyphenyl)ethylamine (Cromartie and Harley-Mason, *loc. cit.*) (6·7 g.) in benzene (25 c.c.) was treated with freshly distilled benzaldehyde (3·7 g.) in benzene (15 c.c.); heat was evolved and water separated. The benzene and water were removed under vacuum on the water-bath, the crude benzylidene

derivative was treated with methyl iodide (5·3 g.), and the mixture heated at 100° in a sealed tube for 2 hr. The solid product was extracted with 90% ethanol (50 c.c.), the solvent removed, and the residue taken up in warm dilute hydrochloric acid (25 c.c.). Benzaldehyde was removed by repeated ether extraction, and the aqueous layer was then basified and the amine extracted with ether. Solvent was removed from the dried (K_2CO_3) extracts and the residual 2-(2 : 5-dimethoxyphenyl)-*N*-methylethylamine distilled at 0·2 mm. (bath temp. 140°). The *hydrochloride* formed prisms, m. p. 96—97°, from ethanol–ether (Found: C, 56·7; H, 7·9; N, 6·2. $C_{11}H_{17}O_2N$,HCl requires C, 57·0; H, 7·8; N, 6·1%).

5-*Hydroxy*-1-*methylindole*.—The foregoing amine (2·5 g.) was refluxed with redistilled hydrobromic acid (15 c.c.; *d* 1·49) for 45 min. Evaporation of the resulting solution under reduced pressure of hydrogen gave the dihydroxy-amine hydrobromide as a brown glass.

A solution of the hydrobromide (0·77 g.) in water (50 c.c.) was stirred vigorously with ethyl acetate (100 c.c.) during the slow addition (45 min.) of potassium ferricyanide (2·05 g.) and sodium hydrogen carbonate (0·8 g.) in water (50 c.c.). The colour of the solution changed to deep brown and some dark flocculent precipitate separated, causing the mixture to form an emulsion. A little sodium dithionite was added and, after filtration through "Hyflo," the layers were separated and the aqueous layer again extracted with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$) and the solvent removed under hydrogen leaving a brown gum. Sublimation at 115°/10^{-4} mm. followed by recrystallisation from light petroleum (b. p. 80—100°) gave 5-*hydroxy*-1-*methylindole* as needles, m. p. 131—132° (Found: C, 71·8, 73·5; H, 6·1, 6·7; N, 9·7. C_9H_9ON requires C, 73·4; H, 6·1; N, 9·5%). Better figures for carbon and hydrogen could not be obtained; the ultra-violet absorption spectrum, measured in 95% ethanol ($\lambda_{max.}$ 3040, 2760 Å; $\varepsilon_{max.}$ 4000, 6680 : $\lambda_{min.}$ 2920, 2480 Å; $\varepsilon_{min.}$ 3540, 2270) was very similar to that of 5-hydroxyindole ($\lambda_{max.}$ 2970, 2700 Å; $\varepsilon_{max.}$ 3100, 5700 : $\lambda_{min.}$ 2920, 2450; $\varepsilon_{min.}$ 2920, 1550).

α-(2 : 5-*Dimethoxyphenyl*)-α-*methylsuccinonitrile* (V).—2 : 5-Dimethoxyacetophenone (18 g.), ethyl cyanoacetate (11·3 g.), ammonium acetate (1·5 g.), and acetic acid (4·8 g.) in benzene (50 c.c.) were refluxed for 5 hr. in a flask attached to a Dean and Stark separator (cf. Cope *et al.*, *loc. cit.*). The cooled mixture was washed with water (2 × 50 c.c.), and the benzene removed. The residual *ethyl* 1-*cyano*-2-(2 : 5-*dimethoxyphenyl*)*crotonate* (IV) (22 g., 80%) distilled at 160—165°/0·3 mm. as a very viscous yellow oil (Found: C, 65·3; H, 6·1. $C_{15}H_{17}O_4N$ requires C, 65·5; H, 6·2%).

The foregoing ester (10 g.) and "AnalaR" potassium cyanide (4·3 g.) in 90% ethanol (120 c.c.) were refluxed for 2 hr. The resulting orange solution was cooled, the separated potassium carbonate filtered off, and the filtrate evaporated to dryness under vacuum. The oily residue crystallised slowly and was recrystallised from aqueous ethanol (charcoal), giving α-(2 : 5-*dimethoxyphenyl*)-α-*methylsuccinonitrile* (6·6 g., 80%) as prisms, m. p. 70° (Found: C, 68·3; H, 5·7; N, 12·2. $C_{13}H_{14}O_2N_2$ requires C, 67·7; H, 6·1; N, 12·2%). The nitrile was characterised by boiling a small amount with concentrated hydrochloric acid for 15 hr.; α-(2 : 5-*dimethoxyphenyl*)-α-*methylsuccinic acid* formed prisms, m. p. 163—164°, from aqueous ethanol (Found: C, 58·3; H, 5·9. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

2-(2 : 5-*Dimethoxyphenyl*)-2-*methylbutane*-1 : 4-*diamine* (VI; R = Me, R′ = H).—The succinonitrile (5·0 g.), dissolved in ethanol (190 c.c.) and concentrated hydrochloric acid (10 c.c.), was hydrogenated at 4—5 atm. over Adams's platinum oxide (0·5 g.). Hydrogen uptake (4 mol.) was complete in 10—15 hr., and, after filtration from the catalyst, the solution was evaporated to dryness under vacuum. The viscous residue was triturated with a little propanol and ether, and slowly crystallised at 0°. Recrystallised from propanol–ether, 2-(2 : 5-*dimethoxyphenyl*)-2-*methylbutane*-1 : 4-*diamine dihydrochloride* (6 g., 90%) formed prisms, m. p. 173—174° (Found: N, 9·2. $C_{13}H_{22}O_2N_2$,2HCl requires N, 9·0%). The *dipicrate* formed yellow needles, m. p. 201—202°, from aqueous ethanol (Found: C, 42·9; H, 4·3; N, 15·9. $C_{13}H_{22}O_2N_2$,$2C_6H_3O_7N_3$ requires C, 43·1; H, 4·0; N, 16·1%).

2-(2 : 5-*Dihydroxyphenyl*)-2 : N : N′-*trimethylbutane*-1 : 4-*diamine* (VI; R = H, R′ = Me).—A solution of the above dihydrochloride (7 g.) in water (20 c.c.) was basified, saturated with potassium carbonate, and extracted with ether. The extract was dried (K_2CO_3), the ether removed, and the residual diamine (4·7 g.) dissolved in benzene (25 c.c.). A solution of freshly distilled benzaldehyde (4·2 g.) in benzene (25 c.c.) was then added. The benzene and water were removed under vaccum, and the residual viscous brown oil slowly solidified. A small portion was recrystallised by allowing a solution in ether–light petroleum to evaporate slowly, giving the *dibenzylidene* derivative as stout needles, m. p. 69° (Found: C, 77·7; H, 6·8; N, 6·6. $C_{27}H_{30}O_2N_2$ requires C, 78·2; H, 7·3; N, 6·7%).

The major portion was treated with methyl iodide (5·6 g.) at 100° for 2 hr. in a sealed tube. The solid product was extracted with 90% ethanol (50 c.c.), the solvent removed on the water-bath, and the residue taken up in dilute hydrochloric acid (30 c.c.). Benzaldehyde was removed by repeated ether extraction, and the aqueous layer then basified, saturated with potassium carbonate, and extracted with ether (3 × 50 c.c.). The extract was dried (K_2CO_3), the solvent removed, and the residual diamine (4·1 g., 70%) distilled at 155—160°/2 mm. The *dipicrate* formed yellow platelets, m. p. 105—106°, from aqueous ethanol (Found: C, 43·8; H, 4·3; N, 15·2. $C_{15}H_{26}O_2N_2,2C_6H_3O_7N_3,H_2O$ requires C, 43·6; H, 4·6; N, 15·1%).

The foregoing diamine (4 g.) and redistilled hydrobromic acid (25 c.c.; *d* 1·49) were refluxed for 45 min., and the solution was diluted with water, boiled with charcoal, and evaporated to dryness under reduced pressure of hydrogen. The solid residue was triturated with a little propanol and ether, giving the *dihydrobromide* (5·4 g., 90%) as small prisms; it had m. p. 235—237° (from propanol–ether) (Found: C, 38·8; H, 5·6; N, 7·1. $C_{13}H_{22}O_2N_2,2HBr$ requires C, 39·0; H, 6·0; N, 7·0%).

(±)-*Eseroline* (VII; R = H).—The dihydrobromide (1·2 g.) in water (75 c.c.) was stirred under nitrogen during the slow addition (30 min.) of a solution of potassium ferricyanide (1·95 g.) and sodium hydrogen carbonate (1·02 g.) in water (75 c.c.). The deep reddish-violet solution thus obtained was immediately transferred to a continuous extractor and extracted with peroxide-free ether under nitrogen for 30 hr., during which time the colour slowly faded. The ethereal extract was evaporated to dryness, leaving crude (±)-eseroline (0·49 g.; 75%) as a brown gum, which was dissolved in benzene; addition of light petroleum precipitated some dark brown amorphous impurities. The filtrate was evaporated to dryness, and the residue sublimed at 120°/10^{-4} mm., giving (±)-eseroline (0·2 g.) as prisms, m. p. 136—137° (Found: C, 71·7; H, 8·1; N, 13·2. Calc. for $C_{13}H_{18}ON_2$: C, 71·5; H, 8·3; N, 12·8%). Julian and Pikl (*loc. cit.*) give m. p. 138°; Kobayashi (*loc. cit.*) gives m. p. 137—138°. The ultra-violet absorption spectrum (see Figure) in aqueous buffer at pH 6·8 was identical with that of (−)-eseroline, prepared according to Ellis and Jones (*J. Pharm. Exp. Therap.*, 1943, **79**, 364). The infra-red absorption spectra of the natural and synthetic products in carbon tetrachloride and carbon disulphide solution were also identical.

(±)-*Eserethole*.—Crude (±)-eseroline (0·48 g.) in absolute ethanol (40 c.c.) and a solution of sodium ethoxide [from sodium (0·1 g.) in ethanol (10 c.c.)] were refluxed under nitrogen with ethyl toluene-*p*-sulphonate (0·47 g.) for 4 hr. The ethanol was removed and the residue treated with dilute sodium hydroxide solution (25 c.c.), saturated with potassium carbonate, and extracted with ether (3 × 50 c.c.). The dried (K_2CO_3) extracts were evaporated and the brown residue distilled at 1 mm. (bath temp. 120°) giving (±)-eserethole as a pale yellow oil. The ultra-violet absorption spectrum was identical with that of (−)-eserethole (see Figure). The picrate formed orange needles, m. p. 154° (Found: C, 52·8; H, 5·3; N, 15·1. Calc. for $C_{15}H_{22}ON_2,C_6H_3O_7N_3$: C, 53·0; H, 5·3; N, 14·7%). Julian and Pikl (*loc. cit.*) give m. p. 155°. The methopicrate was prepared following the latter authors and formed red prisms, m. p. 190—191° (decomp.) (Found: C, 53·6; H, 5·3; N, 14·6. Calc. for $C_{16}H_{24}ON_2,C_6H_3O_7N_3$: C, 53·3; H, 5·6; N, 14·3%). Hoshino, Kobayashi, and Kotake (*Annalen*, 1935, **516**, 81) give m. p. 191—192°, Julian and Pikl (*loc. cit.*) give m. p. 194°.

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