605. *Alkaloids of* Physostigma venenosum. *Part IV.*[1] *The Synthesis of* (±)-*Eseramine* *

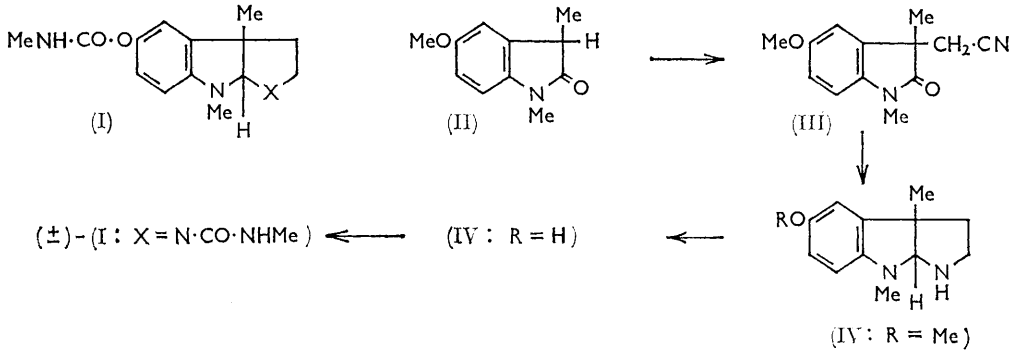
By B. Robinson

A synthesis of (±)-eseramine, verifying the structure proposed for (−)-eseramine on spectral evidence,[2] is described.

(−)-Eseramine is one of the minor alkaloids of *Physostigma venenosum* seeds (Calabar beans) and was first isolated in 1893 when a molecular formula $C_{16}H_{25}N_4O_3$ was determined for it.[3] A second isolation was effected in 1911 [4] but the quantity of the alkaloid obtained was too small at the time to allow further structural studies to be carried out. The third isolation of the alkaloid was reported in 1964 [2] when it was obtained from the residues remaining after the industrial extraction of physostigmine (the major alkaloid) from *Physostigma venenosum* seeds. The alkaloid was then found to be lævorotatory, the previously determined formula was corrected to $C_{16}H_{22}N_4O_3$, and, on evidence obtained from ultraviolet, infrared, proton magnetic resonance, and mass spectra, and by comparison with physostigmine (I; X = NMe) [5] and physovenine (I; X = O),[6] structure (I; X = N·CO·NHMe) was proposed [2] for (−)-eseramine.

This proposal has now been verified by the following synthesis, outlined in the chart, of racemic (I; X = N·CO·NHMe), which had the same infrared and ultraviolet spectra and thin-layer chromotographic behaviour as the natural base, (−)-eseramine.

Treatment of 4-hydroxy-*N*-methylaniline hemisulphate with acetic anhydride afforded 4-hydroxy-*N*-acetyl-*N*-methylaniline,[7] which after *O*-benzylation with benzyl chloride in



the presence of sodium ethoxide followed by hydrolytic removal of the *N*-acetyl group gave 4-benzyloxy-*N*-methylaniline. This was then subjected to the Stollé oxindole synthesis [8] (see also ref. 9) by reaction with α-bromopropionyl chloride to give the anilide which on fusion with anhydrous aluminium chloride (which also effected *O*-debenzylation) cyclised to (±)-5-hydroxy-1,3-dimethyloxindole. *O*-Methylation with dimethyl sulphate then gave (±)-5-methoxy-1,3-dimethyloxindole (II) [10] which on reaction with chloroacetonitrile

* Preliminary communication, *Chem. and Ind.*, 1965, 87.

[1] Part III, B. Robinson, *J. Pharm. Pharmacol.*, 1965, **17**, 89.
[2] B. Robinson and G. Spiteller, *Chem. and Ind.*, 1964, 459.
[3] A. Ehrenberg, *Verhandl. Ges. Deut. Nat. Aerzte*, 1893, **2**, 102 (*Chem. Zentr.*, 1894, **2**, 439).
[4] A. H. Salway, *J.*, 1911, **99**, 2148.
[5] For a recent review, see B. Robinson, *Chem. and Ind.*, 1963, 218.
[6] B. Robinson, *J.*, 1964, 1503.
[7] R. Meldola and W. F. Hollely, *J.*, 1914, **105**, 2073.
[8] R. Stollé, *J. prakt. Chem.*, 1930, **128**, 1.
[9] P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, 1935, **57**, 563.
[10] M. N. Kolosov and N. A. Preobrazhenskii, *Zhur. obshchei Khim.*, 1953, **23**, 1563.

in the presence of sodium ethoxide was converted into (±)-3-cyanomethyl-5-methoxy-1,3-dimethyloxindole (III) (cf. the analogous reaction with 5-ethoxy-1,3-dimethyloxindole [11]).

Reduction of (III) with sodium and dry ethanol gave (±)-1,2,3,3a,8,8a-hexahydro-5-methoxy-3a,8-dimethylpyrrolo[2,3-*b*]indole (IV; R = Me) [cf. the synthesis of (±)-N_b-nordeoxyeseroline [11,12]]. This conversion of (III) into (IV; R = Me) proceeded in poor yield which could not be improved by varying the reaction conditions. Demethylation of (IV; R = Me) with hydrobromic acid afforded the (±)-compound (IV; R = H) which was dissolved in a mixture of dry benzene and dry tetrahydrofuran and treated with a " speck " of sodium [about 0·1 mg. per 100 mg. of (IV; R = H)] followed by an excess of methyl isocyanate, to give (±)-eseramine, the racemate of (I; R = N·CO·NHMe) (cf. the conversion of eseroline into physostigmine,[13] and other similar reactions [10]).

Experimental

Melting points were determined with a Kofler hot-stage apparatus. Ultraviolet spectra were measured in ethanolic solution (unless otherwise stated) on a Beckman DB spectrophotometer, and infrared spectra on a Unicam S.P. 200 spectrophotometer. Solutions were dried with anhydrous magnesium sulphate, and solvents were removed on a steam-bath under reduced pressure (water-pump).

4-*Hydroxy*-N-*acetyl*-N-*methylaniline*.—" Metol " (4-hydroxy-*N*-methylaniline hemisulphate) (227 g.) was dissolved in water (3 l.) at 45°, and to the solution was added acetic anhydride (153 ml.) in one portion with stirring. A solution of crystalline sodium acetate (200 g.) in water (600 ml.) was immediately added, with stirring, and a white crystalline solid began to separate. After cooling the mixture in ice–water for ¼ hr. the solid was removed and washed with water. Recrystallisation from aqueous ethanol (50 : 50 v/v) afforded prisms (176 g., 82·5%), m. p. 246—247° (lit.,[7] 245°).

4-*Benzyloxy*-N-*methylaniline*.—4-Hydroxy-*N*-acetyl-*N*-methylaniline (123 g.) was dissolved in a solution of sodium (17·3 g.) in dry ethanol (750 ml.) which was then boiled gently under reflux and stirred while benzyl chloride (96 g.) was added dropwise during 10 min. Stirring and boiling under reflux were continued for a further 3 hr., after which 600 ml. of the solvent were distilled off and the residue was poured into cold water (2 l.). After stirring, the white precipitate of 4-*benzyloxy*-N-*acetyl*-N-*methylaniline* was filtered off, washed with water, dissolved in a warm solution of potassium hydroxide (210 g.) in 90% ethanol (2 l.), and boiled under reflux for 15 hr. 1·8 l. of the solvent were then distilled off and the residue was extracted with ether (3 × 300 ml.). After drying and removal of the solvent the combined ethereal extracts afforded a dark brown oil which was distilled (b. p. 204—209°/11—12 mm.) to give a pale yellow oil (86·0 g., 54%) having an infrared spectrum (liquid film) identical with that of the sample liberated from the picrate (see below). A small sample of this oil was converted into the *picrate*, plates (from ethanol), m. p. 193—194° (sublimation from 174°) (Found: C, 53·8; H, 4·2; N, 12·45. $C_{20}H_{18}N_4O_8$ requires C, 54·3; H, 4·1; N, 12·65%).

The *base*, liberated from the picrate, distilled as a colourless oil, b. p. 204—206°/12 mm. (Found: C, 78·9; H, 7·15; N, 6·55. $C_{14}H_{15}NO$ requires C, 78·85; H, 7·1; N, 6·55%).

(±)-5-*Hydroxy*-1,3-*dimethyloxindole*.—α-Bromopropionyl chloride (33 g.) was added in one portion, with stirring, to a solution of 4-benzyloxy-*N*-methylaniline (77 g.) in dry benzene (200 ml.). An exothermic reaction ensued. Stirring was continued for a further 5 min., after which the mixture was warmed, with stirring, at 60° (steam-bath) for a further ½ hr. Water (400 ml.) was added and, after shaking, the white solid was filtered off and the benzene layer separated from the filtrate. After drying, the benzene was removed, to give the *anilide* as a deep yellow oil. This was cooled (ice-bath) for 5 min., and anhydrous aluminium chloride (60 g.) was mixed thoroughly with it. The mixture was heated carefully over a Bunsen flame until a vigorous reaction ensued, this being moderated by cooling (ice-bath). Alternate heating and cooling was continued until the reaction was complete. The resulting black solid was heated to 260—270°, and to the resulting melt anhydrous aluminium chloride (60 g.) was added. The mixture was kept at 260—270° for 40 min. with occasional stirring, after which it was

[11] P. L. Julian, J. Pikl, and D. Boggess, *J. Amer. Chem. Soc.*, 1934, **56**, 1797.
[12] P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, 1935, **57**, 539.
[13] M. Polonovski and C. Nitzberg, *Bull. Soc. chim. France*, 1916, **19**, 27.

poured into a mortar and allowed to cool. The resulting black solid was powdered, ice–water (400 ml.) was carefully added, and the water-insoluble solid was continuously extracted with ethanol (1·5 l.) for 7 hr. Evaporation of the ethanolic extract to about 150 ml. and cooling to 0° afforded brown prisms; a second crop was obtained by evaporation of the mother-liquors. After one recrystallisation from ethanol (charcoal), pale yellow prisms (10·4 g., 16%), m. p. 195—197° (sublimation from 183°) (lit.,[9] 219°) [second crop (3·1 g., 5%), m. p. 194—197° (sublimation from 183°)] were obtained (Found: C, 67·2; H, 6·0; N, 8·05. Calc. for $C_{10}H_{11}NO_2$: C, 67·7; H, 6·25; N, 7·9%), $\nu_{max.}$ (Nujol) 1667m cm.$^{-1}$ (oxindole C=O).

(±)-5-*Methoxy*-1,3-*dimethyloxindole* (II).—(±)-5-Hydroxy-1,3-dimethyloxindole (4·6 g.) was dissolved in 5% aqueous potassium hydroxide (35 ml.), and to this solution was added dimethyl sulphate (4·6 g.) in one portion with stirring. After warming (steam-bath) and stirring for ½ hr. (during this period a further 20 ml. of the potassium hydroxide solution had to be added dropwise to keep the mixture alkaline to litmus), the mixture was cooled to 10° and the liberated oil extracted with ether (2 × 50 ml.). After decolourisation (charcoal), drying, and removal of the solvent, the combined ethereal extracts afforded a pale yellow oil which completely crystallised upon cooling and scratching. Recrystallisation from aqueous ethanol afforded pale-yellow needles (3·1 g., 62·5%), m. p. 84—86° (lit.,[10] 86°).

(±)-3-*Cyanomethyl*-5-*methoxy*-1,3-*dimethyloxindole* (III).—(±)-5-Methoxy-1,3-dimethyloxindole (II) (6·0 g.) and chloroacetonitrile (3·5 g.) were dissolved in dry ethanol (50 ml.). This solution was gently boiled under reflux and stirred while a solution of sodium (0·85 g.) in dry ethanol (30 ml.) was added dropwise during ½ hr. After the addition was complete, stirring and boiling under reflux were continued for a further 3 hr., after which the ethanol was removed. The residue was partitioned between ether (150 ml.) and water (50 ml.), the ethereal layer was washed with 10% aqueous sodium hydroxide solution (2 × 50 ml.), water (2 × 100 ml.), dried, and the ether removed to leave a light brown oil (6·9 g.) which crystallised on cooling to 0° and trituration with ether–light petroleum (b. p. 60—80°). Recrystallisation from ether–light petroleum (b. p. 60—80°) afforded white prisms (6·3 g., 87%), m. p. 75—76° (Found: C, 67·0, 67·0; H, 5·9, 5·75; N, 12·3. $C_{13}H_{14}N_2O_2$ requires C, 67·8; H, 6·15; N, 12·15%), $\nu_{max.}$ (Nujol) 1703s (oxindole C=O), 2260w cm.$^{-1}$ (C≡N).

(±)-1,2,3,3*a*,8,8*a*-*Hexahydro*-5-*methoxy*-3*a*,8-*dimethylpyrrolo*[2,3-b]*indole* (IV; R = Me).—To a refluxing solution of (±)-3-cyanomethyl-5-methoxy-1,3-dimethyloxindole (III) (3·0 g.) in dry ethanol (500 ml.) was added sodium (34 g.) in pieces (1—2 g.) during 1 hr. After all the sodium had dissolved, the ethanol was removed, water (100 ml.) was added to the residue, and the water-immiscible oil was extracted with ether (2 × 50 ml.). The combined ethereal extracts were extracted with 3N-hydrochloric acid (3 × 30 ml.), the combined acidic extracts were carefully basified with concentrated aqueous sodium hydroxide, and the liberated base was extracted with ether (3 × 50 ml.). After drying and removal of the solvent the combined ethereal extracts afforded a light brown oil (1·1 g.). To this oil, dissolved in ethanol (4 ml.), was added picric acid (1·3 g.) in warm ethanol (10 ml.). The red oil which initially precipitated crystallised after standing at 5° for 18 hr. After four recrystallisations from ethanol, the *picrate* of (IV; R = Me) was obtained as dark red prisms (324 mg., 5·5%), m. p. 163—164° (Found: C, 51·2; H, 4·5; N, 15·5. $C_{19}H_{21}N_5O_8$ requires C, 51·0; H, 4·75; N, 15·65%).

The *base*, liberated from the picrate, distilled at 160—170°(bath)/12 mm. as a colourless oil (Found: C, 71·2; H, 7·85. $C_{13}H_{18}N_2O$ requires C, 71·5; H, 8·3%), $\nu_{max.}$ 3325m ± 10 cm.$^{-1}$ (N–H stretching) [cf. the N–H stretching band (liquid film) for (±)-1,2,3,3a,8,8a-hexahydro-3a,8-dimethylpyrrolo[2,3-*b*]indole at 3313m cm.$^{-1}$ [14]}, $\lambda_{max.}$ (in ethanol) 324, 250 mμ (ε 3000 and 9900), (in dilute ethanolic hydrochloric acid) 318, 245 (ε 3150 and 10,500) (the hypsochromic shift with retention of indoline-type absorption experienced by the spectrum on acidification verifies the presence of the Ph–N–C–N system).[5,15]

(±)-*Eseramine* (I; X = N·CO·NHMe).—(±)-1,2,3,3a,8,8a-Hexahydro-5-methoxy-3a,8-dimethylpyrrolo[2,3-*b*]indole (IV; R = Me) (141 mg.) was dissolved in hydrobromic acid (*d* 1·46—1·49) (3·5 ml.), the resulting light brown solution being gently boiled under reflux for 15 hr. After cooling and addition of water (15 ml.), the solution was carefully basified with solid sodium hydrogen carbonate and immediately continuously extracted with peroxide-free ether (150 ml.) under nitrogen for 15 hr. Removal of the ether from the extract afforded (±)-1,2,3,3a,8,8a-*hexahydro*-5-*hydroxy*-3a,8-*dimethylpyrrolo*[2,3-b]*indole* (IV; R = H) as a light brown gum which

[14] B. Robinson, M.Sc. Thesis, Manchester, 1958.
[15] H. F. Hodson and G. F. Smith, *J.*, 1957, 1877.

was immediately dissolved in a mixture of dry benzene (2 ml.) and dry tetrahydrofuran (1 ml.). To the solution was added sodium (*ca.* 0·1 mg.), followed by methyl isocyanate (0·35 ml). The resulting solution was set aside in a stoppered flask under nitrogen, with occasional shaking, for 4 days, after which the crystalline deposit which had gradually formed was removed and washed with ether to give (±)-*eseramine* as fine white needles (29·4 g., 14·5%). One recrystallisation from ethanol afforded fine white needles, m. p. 197—201° (slight decomposition) (Found: C, 60·35; H, 7·0. $C_{16}H_{22}N_4O_3$ requires C, 60·35; H, 6·95%), which had the same ultraviolet and infrared (Nujol) spectra and R_F value [0·82 on a thin layer of alumina–calcium sulphate (20 : 1 w/w) using as solvent acetone–ethyl acetate (1 : 1) and a solution of iodine in chloroform as developer] as (−)-eseramine.

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