Synthesis of the Physostigmine Ring System from Cycloprop[*b*]indoles

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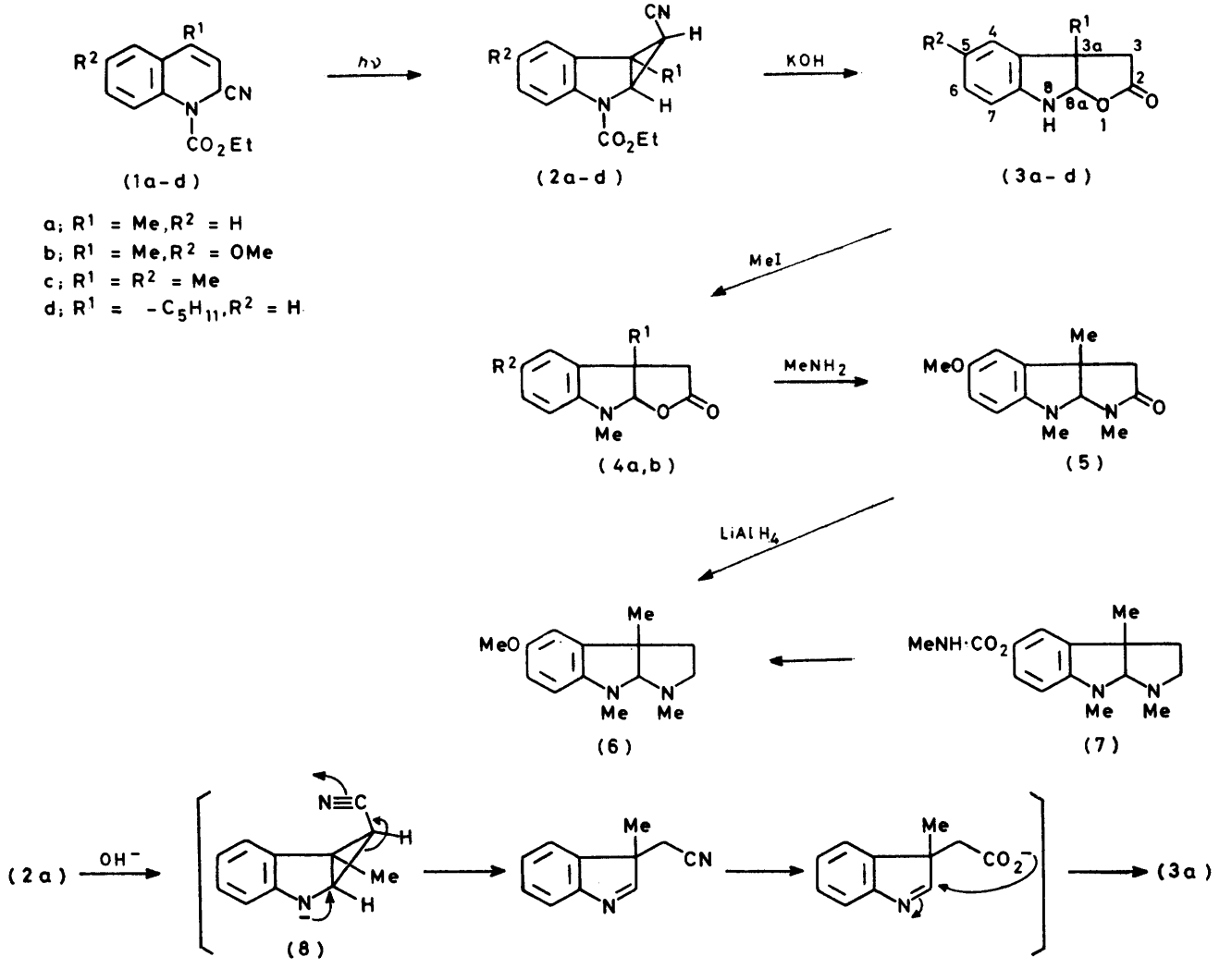
The transformation of cycloprop[*b*]indoles into derivatives of the physostigimine ring system is described.

We have previously reported[1] the photochemical synthesis of ethyl 1-cyano-1,1a,2,6b-tetrahydrocycloprop[*b*]indole-2-carboxylates (2) from ethyl 2-cyano-1,2-dihydroquinoline-1-carboxylates (Reissert compounds) (1) and some chemical transformations of the products (2) including their conversion into 2-cyanomethylindoles (9). in aqueous ethanol at 120—130 °C led to the furo[2,3-*b*]indole (3a) in 72% yield. This compound showed i.r. bands ($CHCl_3$) at 3 430 (NH) and 1 770 cm^{-1} (γ-lactone), and u.v. absorption characteristic of the indoline system.[2] The n.m.r. spectrum agreed with the structure assigned. Treatment of the product (3a) with methyl



SCHEME 1

We now describe the transformation of the cycloprop[*b*]indole (2) into derivatives of the physostigmine ring system.

Heating compound (2a) with 10% potassium hydroxide iodide in refluxing acetone gave the *N*-methyl derivative (4a) in 13% yield, from which a Rosenmund synthesis gave deoxyeserine in two steps.[3] In a similar manner, the cycloprop[*b*]indoles (2b—d) were converted into the

[1] M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi, and Y. Tamura, *J.C.S. Chem. Comm.*, 1974, 433; M. Ikeda, S. Matsugashita, F. Tabusa, and Y. Tamura, *J.C.S. Perkin I*, 1977, 1166.

[2] B. Gilbert, 'The Alkaloids,' ed. H. F. Manske, Academic Press, New York, 1965, vol. 8, p. 335.

[3] P. Rosenmund and A. Sotiriou, *Angew. Chem.*, 1964, **76**, 787.

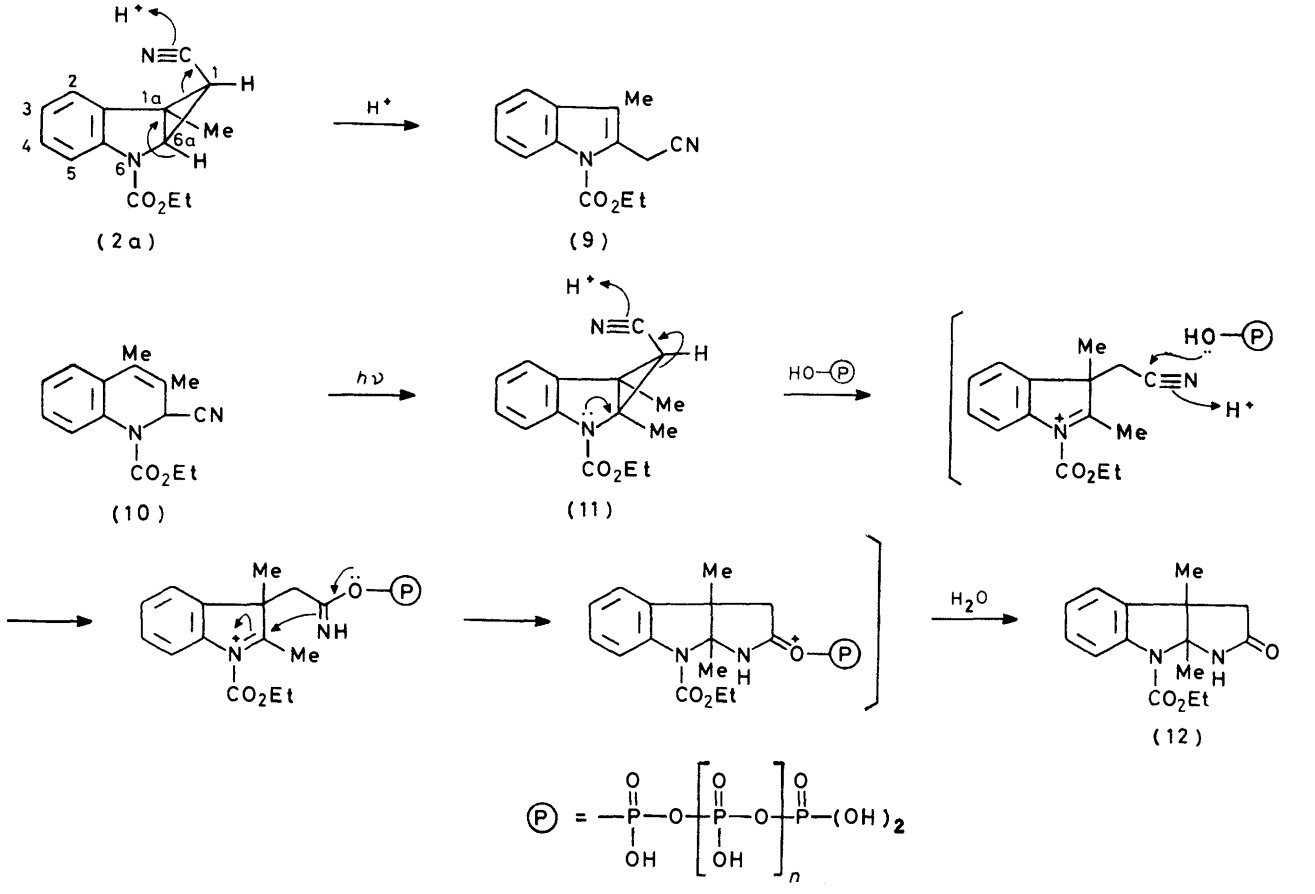
corresponding furo[2,3-*b*]indoles (3b—d) in 69, 34, and 20% yields, respectively. Methylation of (3b) with methyl iodide gave (4b) in 25% yield.

A mechanistic rationalisation of the formation of the furoindoles (3) involves the assumption that the cyclopropindole (2) is first hydrolysed to the anion [*e.g.* (8)], which undergoes ring opening (perhaps for reasons of internal strain) and hydrolysis of the cyano group to carboxylate followed by recyclisation (see Scheme 1).

The *N*-methylfuroindole (4b) was converted into (±)-esermethole (6) by Rosenmund's method: treatment with methylamine followed by reduction ($LiAlH_4$) of the resulting lactam (5). The product (6) was identical with an authentic sample obtained from physostigmine (7).[4]

As previously noted,[1] the reactions of the cyclopropindole (2a) with acids (*e.g.* refluxing hydrochloric acid, hydrogen chloride in ethanol at room temperature, or polyphosphoric acid at 60—70 °C) lead to ethyl 2-cyanomethylindole-1-carboxylate (9) and its derivatives. This process can be formulated as proceeding by ring opening between positions 1 and 1a with synchronous hydrogen atom transfer, followed by aromatisation. In sharp contrast, heating the cyclopropindole (11) (the *endo*-isomer was used) obtained from the Reissert compound (10)[1] in polyphosphoric acid gave the pyrrolo[2,3-*b*]indole (12) in 85% yield, identified from i.r. and n.m.r. data.

In the case of the cyclopropindole (11) the presence of the 6b-methyl group inhibits aromatisation, and an alternative ring opening between positions 1 and 6b becomes preferred; this may be initiated by protonation at the cyano group with simultaneous participation of the lone pair of the indoline nitrogen atom. This is followed by attack of polyphosphoric acid, cyclisation, and hydrolysis to (12) (Scheme 2).



SCHEME 2

EXPERIMENTAL

N.m.r. spectra were determined with a Hitachi R-22 spectrometer (90 MHz; tetramethylsilane as internal standard). I.r. spectra were recorded with a Hitachi EPI-G2 spectrophotometer. High-resolution mass spectra were obtained with a JEOL-JMS-01SG instrument at 75 eV. Preparative layer chromatography (p.l.c.) was carried out on Merck silica gel GF_{254} or alumina PF_{254}.

General Procedure for Synthesis of 3,3a,8,8a-*Tetrahydro*-3a-*methylfuro*[2,3-b]*indol*-2-*ones* (3a—d). A solution of the cyclopropindole (2) (100 mg) in ethanol (2 ml) and aqueous 10% potassium hydroxide (2 ml) was heated in a sealed tube at 120—130 °C for 3.5 h. The mixture was neutralised with 10% hydrochloric acid and extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and concentrated. 3,3a,8,8a-*Tetrahydro*-3a-*methylfuro*[2,3-b]*indol*-2-*one* (3a) (72%) formed white needles, m.p.

[4] F. E. King and R. Robinson, *J. Chem. Soc.*, 1932, 326.

101—102 °C (from ether–hexane) (Found: C, 70.1; H, 6.0; N, 7.25. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%); $\nu_{max.}$ ($CHCl_3$) 3 430 and 1 770 cm^{-1}; $\lambda_{max.}$ (EtOH) (end absorption) 240 and 294 nm (log ε 3.88 and 3.40); δ ($CDCl_3$) 6.5—7.2 (4 H, m, aromatic), 5.60 (1 H, s, 8a-H), 4.96br (1 H, s, NH), 2.79 and 2.96 (1 H each, ABq, *J* 18 Hz, 3-H), and 1.42 (3 H, s, 3a-CH_3); the *5-methoxy-derivative* (3b) (69%) formed white needles, m.p. 126—127 °C [from benzene–light petroleum (b.p. 60—80 °C)] (Found: C, 65.8; H, 6.0; N, 6.2. $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%); $\nu_{max.}$ ($CHCl_3$) 3 420 and 1 770 cm^{-1}; $\lambda_{max.}$ (EtOH) (end absorption) 238 and 307 nm (log ε 3.56 and 3.92); δ ($CDCl_3$) 6.5—7.3 (3 H, m, aromatic), 5.66 (1 H, s, 8a-H), 4.55br (1 H, s, NH), 3.72 (3 H, s, OCH_3), 2.79 and 2.90 (1 H each, ABq, *J* 18 Hz, 3-H), and 1.42 (3 H, s, 3a-CH_3); the *5-methyl derivative* (3c) (34%) formed white needles, m.p. 161 °C (from benzene) (Found: C, 71.2; H, 6.5; N, 6.8. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%); $\nu_{max.}$ ($CHCl_3$) 3 430 and 1 770 cm^{-1}; $\lambda_{max.}$ (EtOH) (end absorption) 243 and 299 nm (log ε 3.44 and 3.94); δ ($CDCl_3$) 6.5—7.0 (3 H, m, aromatic), 5.61 (1 H, s, 8a-H), 4.90br (1 H, s, NH), 2.78 and 2.96 (1 H each, ABq, *J* 18 Hz, 3-H), 2.26 (3 H, s, 5-CH_3), and 1.44 (3 H, s, 3a-CH_3); 3,3a,8,8a-*tetrahydro*-3a-*pentylfuro*[2,3-b]*indol*-2-*one* (3d) (20%) was an oil (Found: *m/e*, 245.140 9. $C_{15}H_{19}NO_2$ requires *M*, 245.141 5); $\nu_{max.}$ ($CHCl_3$) 3 430 and 1 770 cm^{-1}; $\lambda_{max.}$ (EtOH) (end absorption) 240 and 293 nm (log ε 3.50 and 3.91); δ ($CDCl_3$) 6.6—7.2 (4 H, m, aromatic), 5.68 (1 H, s, 8a-H), 4.96br (1 H, s, NH), 2.80 and 2.91 (1 H each, ABq, *J* 18 Hz, 3-H), and 0.6—2.0 (11 H, m, C_5H_{11}).

3,3a,8,8a-*Tetrahydro*-3a,8-*dimethylfuro*[2,3-b]*indol*-2-*one* (4a).—A solution of (3a) (73 mg) and methyl iodide (0.3 ml) in acetone (2 ml) was refluxed for 24 h. The solvent was removed and the residue subjected to p.l.c. on silica gel ($CHCl_3$ as solvent) to give the *furoindole* (10 mg) (4a),* m.p. 107 °C [from light petroleum (b.p. 60—80 °C)] (Found: C, 71.0; H, 6.5; N, 7.0. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N. 6.9%); $\nu_{max.}$ ($CHCl_3$) 1 770 cm^{-1}; δ ($CDCl_3$) 6.4—7.2 (4 H, m, aromatic), 5.49 (1 H, s, 8a-H), 3.00 (3 H, s, NCH_3), 2.75 and 2.93 (1 H each, ABq, *J* 18 Hz, 3-H), and 1.43 (3 H, s, 3a-CH_3).

3,3a,8,8a-*Tetrahydro*-5-*methoxy*-3a,8-*dimethylfuro*[2,3-b]-*indol*-2-*one* (4b).—A solution of the furoindole (3b) (100 mg) and methyl iodide (0.25 ml) in acetone (4 ml) was heated in a sealed tube at 60 °C for 4.5 h. The solvent was removed and the residue subjected to p.l.c. on silica gel [$CHCl_3$–AcOEt (1 : 1) as solvent] to give the *product* (4 b) (27 mg, 25%) as an oil (Found: *m/e*, 233.107 8. $C_{13}H_{15}NO_3$ requires *M*, 233.105 1); $\nu_{max.}$ ($CHCl_3$) 1 760 cm^{-1}; δ ($CDCl_3$) 6.4—6.8 (3 H, m, aromatic), 5.50br (1 H, s, 8a-H), 3.74 (3 H, s, OCH_3), 2.96 (3 H, s, NCH_3), 2.79 and 2.90 (1 H each, ABq, *J* 19 Hz, 3-H), and 1.47 (3 H, s, 3a-CH_3).

3,3a,8,8a-*Tetrahydro*-5-*methoxy*-1,3a,8-*trimethylpyrrolo*-[2,3-b]*indol*-2-*one* (5).—A mixture of the furoindole (4b) (20 mg) and 2 : 3 ethanol–methylamine (4 ml) was heated at 50 °C for 1 h. Evaporation left the *product* (5), obtained quantitatively as an oil (Found: *m/e*, 246.135 9. $C_{14}H_{18}N_2O_2$ requires *M*, 246.136 8); $\nu_{max.}$ ($CHCl_3$) 1 675 cm^{-1}; δ ($CDCl_3$) 6.3—6.7 (3 H, m, aromatic), 4.50 (1 H, s, 8a-H), 3.72 (3 H, s, OCH_3), 2.99 (3 H, s, NCH_3), 2.91 (3 H, s, NCH_3), 2.53 and 2.67 (1 H, each, ABq, *J* 17 Hz, 3-H), and 1.42 (3 H, s, CH_3).

Esermethole (6).—(*A*) To a solution of lithium aluminium hydride (20 mg) in dry tetrahydrofuran (4 ml) was added a solution of the pyrroloindole (5) (20 mg) in dry tetrahydrofuran (4 ml). The mixture was refluxed for 4 h with stirring. Work-up then gave (±)-esermethole (6) in quantitative yield as an oil; picrate, m.p. 156—157 °C (from ethanol) (lit.,[5] 150 °C; lit.,[6] 162—163 °C); δ ($CDCl_3$) 6.25—6.8 (3 H, m, aromatic), 4.04 (1 H, s, 8-H), 3.72 (3 H, s, OCH_3), 2.88 (3 H, s, 8-CH_3), 2.68 (2 H, t, *J* 6 Hz, 2-H), 2.50 (3 H, s, 1-CH_3), 1.94 (2 H, t, *J* 6 Hz, 3-H), and 1.44 (3 H, s, 3a-CH_3), identical (i.r. and n.m.r. spectra) with an authentic sample prepared from physostigmine (7) [see (B)]

(*B*) Although essentially the procedure of Robinson [4] was employed, the initial product was different from the reported one. Thus, to a solution of sodium ethoxide in ethanol [from sodium (45 mg) in absolute ethanol (3 ml)] was added a solution of physostigmine (7) (500 mg) in absolute ethanol (3 ml), followed by methyl toluene-*p*-sulphonate (375 mg) in absolute ethanol (2 ml). The mixture was refluxed for 24 h, then diluted with water, and made slightly acidic with 10% hydrochloric acid. The ethanol was removed, and the aqueous layer was washed with ether, made alkaline with aqueous 10% sodium hydroxide, and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was subjected to p.l.c. on alumina (AcOEt as solvent) to give an oily product (47 mg), which was assumed to be 1,3-dimethyl-5-methoxy-3-(β-methylaminoethyl)indolin-2-one [6] on the basis i.r. spectral data [$\nu_{max.}$ ($CHCl_3$) 3 460 and 1 700 cm^{-1}]. For cyclisation of the indolinone, the procedure of Sugasawa and Murayama [6] was employed. To a solution of the indolinone (50 mg) in absolute ethanol (5 ml) sodium (200 mg) was added in portions during 2 h. The mixture was diluted with water and the ethanol was removed. The aqueous layer was extracted with benzene and the extract was dried (Na_2SO_4) and concentrated to give (−)-esermethole (38 mg) as an oil; *picrate*, m.p. 169—170 °C (from ethanol) (Found: C, 52.1; H, 5.2; N, 15.15. $C_{20}H_{23}N_5O_8$ requires C, 52.1; H, 5.0; N, 15.2%).

Ethyl 3,3a,8,8a-*Tetrahydro*-3a,8a-*dimethyl*-2-*oxopyrrolo*-[2,3-b]*indole*-8-*carboxylate* (12).—The cyclopropindole (11) (100 mg) in polyphosphoric acid (100 mg) was heated at 60—70 °C for 10 h with occasional stirring. The mixture was poured into ice–water, and the precipitated white solid was collected and recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give the *product* (12) (91 mg, 85%) as white crystals, m.p. 140—141 °C (Found: C, 65.6; H, 6.7; N, 10.0. $C_{15}H_{18}N_2O_3$ requires C, 65.7; H, 6.6; N, 10.2%); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 700, and 1 680 cm^{-1}: $\lambda_{max.}$ (EtOH) 235, 273, and 282 nm (log ε 4.25, 3.46, and 3.42); δ ($CDCl_3$) 6.9—7.75 (5 H, m, aromatic and NH), 4.47 (2 H, q, *J* 7 Hz, $CO_2{\cdot}CH_2{\cdot}CH_3$), 2.50 and 2.60 (1 H each, ABq, *J* 18 Hz, 3-H), 1.70 (3 H, s, 8a-CH_3), 1.50 (3 H, s, 3a-CH_3), and 1.41 (3 H, t, *J* 7 Hz, $CO_2{\cdot}CH_2{\cdot}CH_3$).

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* No physical data given in the original paper.[3]

[5] M. N. Kolosov, L. I. Metreveli, N. A. Preobrazhenskii, *Zhur. obshchei Khim.*, 1953, **23**, 2027.

[6] S. Sugasawa and M. Murayama, *Chem. and Pharm. Bull.* (*Japan*), 1958, **6**, 194.