Studies on the Syntheses of Heterocyclic Compounds. Part DCXX.† Total Synthesis of (±)-Orientalidine and a Positional Isomer

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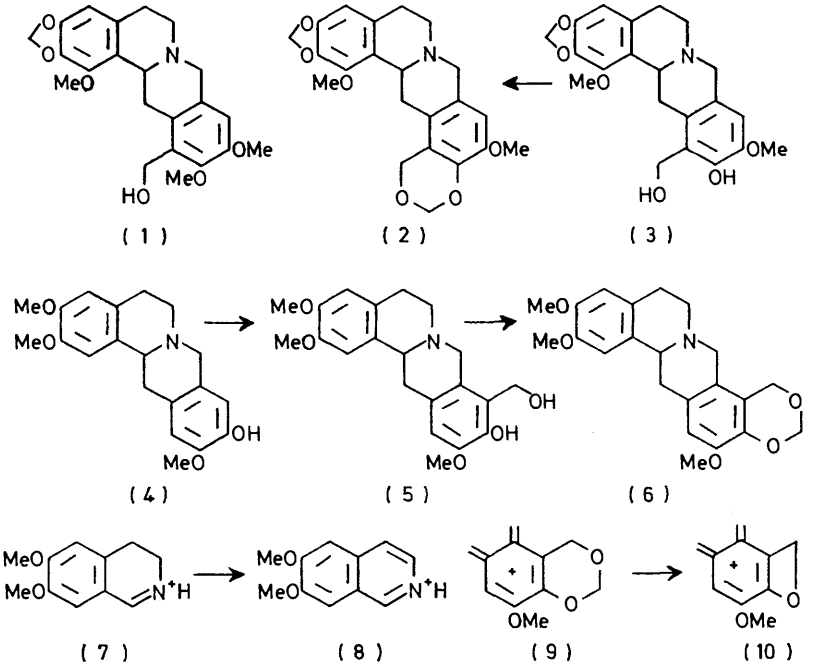
The total synthesis of (±)-orientalidine (2) was accomplished by treatment of (±)-demethylmecambridine (3) with methylene chloride and sodium hydride in dimethylformamide. 11-Hydroxy-12-hydroxymethyl-3,10-dimethoxy-1,2-methylenedioxyberbine (16) was synthesised from 1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-7,8-methylenedioxyisoquinoline (11) by way of 11-benzyloxy-3,10-dimethoxy-1,2-methylenedioxyberberine (12) and the corresponding phenolic base (15). Treatment of the hydroxymethylated berbines (5) and (16) under the same conditions as for the synthesis of orientalidine gave the corresponding berbines (6) and (18) containing a fused *m*-dioxin system.

MECAMBRIDINE and orientalidine, isolated from a number of *Papaver* species,[1] have been assigned the novel structures (1) and (2), respectively, with a hydroxymethyl group and a fused *m*-dioxin system on ring D on the basis of chemical degradations and spectral analyses.[2,3] We have recently reported the total synthesis of mecambridine, which confirmed the structure



(1), and now describe the confirmation of the structure (2) of orientalidine by total synthesis. (±)-Demethylmecambridine (3), synthesised during the synthetic work on (±)-mecambridine,[4] was utilised as starting material.

A preliminary study of the formation of the *m*-dioxin system was carried out with the easily available berbine (4). Hydroxymethylation of a phenolic berbine (4)[5] with formalin and N-sodium hydroxide at room temperature with stirring for 3 days gave the 9-hydroxymethyl derivative (5). When compound (5) was heated with a mixture of methylene iodide and sodium hydride in dimethylformamide or a mixture of dimethoxymethane and toluene-*p*-sulphonic acid in dimethylformamide, the desired compound (6) was formed in poor yield; it was detected by n.m.r. analysis. However if the reaction was carried out with an excess of dry methylene chloride and sodium hydride in dry dimethylformamide at 80 °C for 15 min under nitrogen, compound (6) was obtained in 85% yield. The i.r. spectrum showed no hydroxy-absorption and the n.m.r. spectrum [δ ($CDCl_3$) 3.88 (9 H, s, 3 × OMe), 6.74 and 6.63 (1 H,

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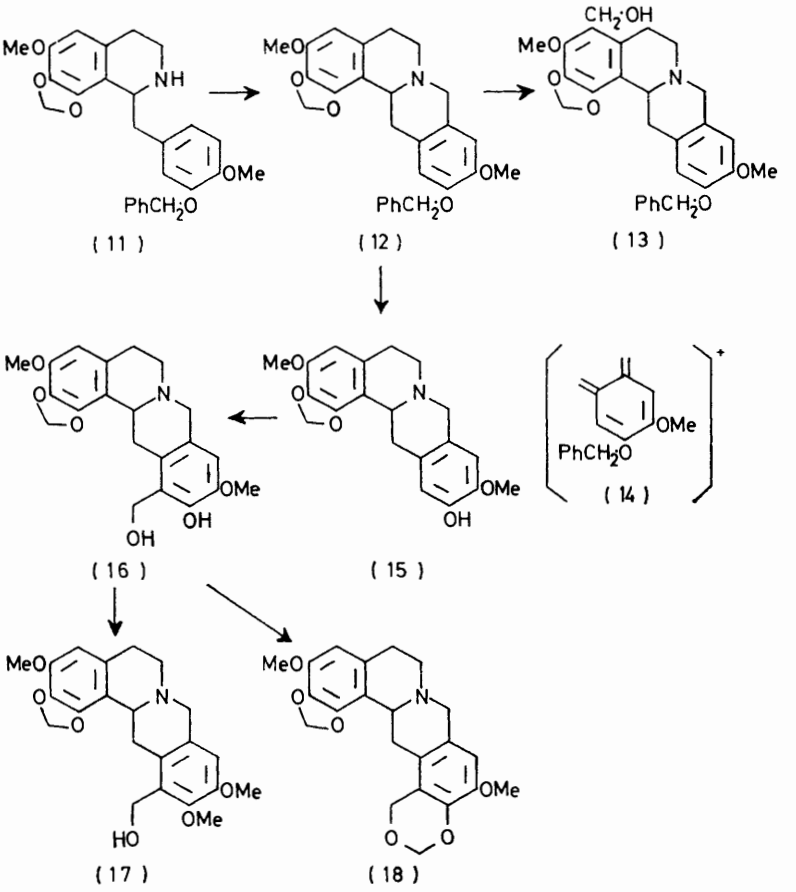
and 2 H, each s, 3 × ArH)] revealed the presence of four protons of the system $ArO{\cdot}CH_2{\cdot}O{\cdot}CH_2Ar$ as two singlets at δ 5.26 and 4.79. The mass spectrum showed a molecular ion at *m/e* 383 and fragments at *m/e* 192 [(7) and (9)], 190 (8), and 162 (10).[6]

(±)-Demethylmecambridine (3) was then treated with dry methylene chloride and sodium hydride in dry dimethylformamide as above to afford (±)-orientalidine (2), m.p. 190—192°, whose i.r. (in chloroform) and n.m.r. (in deuteriochloroform) spectra and t.l.c. behaviour in several solvent systems were identical with those of the natural product.

From a biogenetic point of view,[2] we were further interested in the syntheses of the position isomers (17) and (18) of mecambridine and orientalidine. A Mannich reaction of 1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-7,8-methylenedioxyisoquinoline (11) hydrochloride[4] with 37% formalin and 99% acetic acid at 100 °C for 2 h gave the 11-benzyloxy-10-methoxyberbine (12) [δ ($CDCl_3$) 6.26 (1 H, s, 4-H), 6.55 (1 H, s, ArH), and 6.63 (1 H, s, ArH)]. Hydroxymethylation of this base (12) with 37% formalin and 98% formic acid at 100 °C gave the 4-hydroxymethyl derivative (13). The position of the hydroxymethyl group was easily determined from the n.m.r. spectrum, which lacked the 4-proton signal. The mass spectrum showed the molecular ion peak at *m/e* 475 and a characteristic fragment ion at *m/e* 240 (14).

It was expected from a simple HMO calculation that the electron density at C-4 would be larger than those at C-9 and C-12. On the other hand, an electrophilic reaction of a phenolic compound under basic conditions might be expected to occur at the position *ortho* to the phenolic group as in the case of an enolate anion.[7] Therefore, the 11-benzyloxyberbine (12) was debenzylated to afford (15) in good yield with hydrochloric acid in the presence of a small zinc powder in boiling ethanol, but in a low yield in the absence of zinc powder. Hydroxymethylation of the 11-hydroxyberbine (15) with 37% formalin and methanolic sodium hydroxide at room temperature for 24 h afforded the expected 12-hydroxymethylberbine (16), whose n.m.r. spectrum ($CDCl_3$) showed the C-4 and -9 proton signals at δ 6.27 and 6.48, respectively, and the CH_2OH signal at δ 4.72. Methylation of (16) with diazomethane in methanol gave the isomer (17) of (±)-mecambridine, m.p. 160—161°.



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Formation of a *m*-dioxin system on structure (16) was carried out under the same conditions as above to afford the isomer (18) of orientalidine, m.p. 189—190°.

EXPERIMENTAL

M.p.s were measured with a Yanagimoto micro-apparatus. I.r. spectra were taken with a Hitachi 215 recording spectrophotometer, mass spectra with a Hitachi RMU-7 spectrophotometer, and n.m.r. spectra with Hitachi R-20, JEOL JNM-PMX 60, and JEOL PS-100 spectrophotometers.

5,6,13,13a-*Tetrahydro*-10-*hydroxy*-9-*hydroxymethyl*-2,3,11-*trimethoxy*-8H-*dibenzo*[a,g]*quinolizine* (5).—A solution of the phenolic berbine (4) hydrochloride [5] (1.3 g), methanolic N-sodium hydroxide (20 ml), and 37% formalin (40 ml) was stirred at room temperature for 3 days. The mixture was then neutralised with crystalline ammonium chloride and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give a crystalline mass, which was recrystallised from methanol–chloroform to give compound (5) (1 g) as *needles*, m.p. 186—188° (Found: C, 67.8; H, 6.7; N, 3.4. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.75%), $\nu_{max.}$ ($CDCl_3$) 3 540 cm^{-1} (OH), δ [$CDCl_3$–$(CD_3)_2SO$] 3.82 (9 H, s, 3 × OMe), 4.67 (2 H, s, CH_2·OH), and 6.61 (2 H) and 6.71 (1 H) (each s, ArH); *m/e* 371 (M^+) and 192.

1,7,7a,12,13,15-*Hexahydro*-5,9,10-*trimethoxy*-3H-*benzo*[a]-[1,3]*benzodioxino*[5,6-g]*quinolizidine* (6).—A mixture of the 9-hydroxymethylberbine (5) (40 mg) and sodium hydride (40 mg) in dry methylene chloride (4 ml) and dry dimethylformamide (8 ml) was stirred at 80 °C under nitrogen for 15 min. After cooling, crystalline ammonium chloride was added and the solvent was evaporated off under reduced pressure. The residue was extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give a solid, which was recrystallised from methanol to afford compound (6) (35 mg) as *needles*, m.p. 171—172° (Found: C, 69.05; H, 6.45; N, 3.7. $C_{22}H_{25}NO_5$ requires C, 68.9; H, 6.55; N, 3.65%); δ ($CDCl_3$) 3.88 (9 H, s, 3 × OMe), 4.79 (2 H) and 5.26 (2 H) (each s, $ArCH_2$·O·CH_2·OAr), and 6.63 (2 H) and 6.74 (1 H) (each s, ArH); *m/e* 383 (M^+), 192, 190, and 162.

(±)-*Orientalidine* (2).—The demethylmecambridine (3) (25 mg) was treated with sodium hydride (30 mg) and dry methylene chloride (3 ml) in dry dimethylformamide (6 ml) as above. The crude product was purified by preparative t.l.c. on silica gel (Wakogel B-5) in benzene–ethyl acetate–methanol (5 : 4 : 1 v/v), followed by recrystallisation from ethyl acetate to give (±)-*orientalidine* (2) (15 mg) as needles, m.p. 190—192° (Found: C, 66.4; H, 5.7; N, 3.5. $C_{23}H_{23}NO_6$ requires C, 66.5; H, 5.85; N, 3.5%), whose i.r. ($CHCl_3$), n.m.r. [δ ($CDCl_3$) 3.87 and 4.01 (each 3 H, s, 2 × OMe), 4.60 and 4.92 (each 1 H, d, *J* 15 Hz, $ArCH_2$·O), 5.26 (2 H, s, $ArO{\cdot}CH_2{\cdot}O{\cdot}CH_2$), 5.90 (2 H, s, $O{\cdot}CH_2{\cdot}O$), and 6.36 and 6.52 (each 1 H, s, 2 × ArH)], and mass spectra [*m/e* 397 (M^+), 204, 192, and 162] were identical with those of the natural product kindly donated by Professor F. Šantavý.

11-*Benzyloxy*-5,6,13,13a-*tetrahydro*-3,10-*dimethoxy*-1,2-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (12).—A mixture of the hydrochloride of (11) [4] (400 mg), 37% formalin (4 ml), and 99% acetic acid (4 ml) was heated on a water-bath for 2 h, cooled, basified with aqueous 10% sodium hydroxide, and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give a crystalline mass, recrystallisation of which from ethanol afforded compound (12) (310 mg) as *needles*, m.p. 156—158° (Found: C, 70.15; H, 6.3; N, 3.05. $C_{27}H_{27}NO_5,H_2O$ requires C, 69.95; H, 6.3; N, 3.0%), δ ($CDCl_3$) 3.81 and 3.84 (each 3 H, s, 2 × OMe), 5.05 (2 H, s, $O{\cdot}CH_2Ph$), 5.91 and 5.93 (each 1 H, d, *J* 6 Hz, $O{\cdot}CH_2{\cdot}O$), 6.26, 6.55, and 6.63 (each 1 H, s, 4-, 9-, and 12-H), and 7.32br (5 H, s, $O{\cdot}CH_2{\cdot}C_6H_5$).

11-*Benzyloxy*-5,6,13,13a-*tetrahydro*-4-*hydroxymethyl*-3,10-*dimethoxy*-1,2-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (13).—A mixture of compound (12) (25 mg), 37% formalin (2 ml), and 98% formic acid (2 ml) was heated on a water-bath for 4 h, cooled, basified with aqueous sodium hydrogen carbonate, and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to leave a solid, recrystallisation of which from ethanol gave compound (13) (15 mg) as *needles*, m.p. 179—181° (Found: C, 70.6; H, 6.15; N, 3.35. $C_{28}H_{29}NO_6$ requires C, 70.7; H, 6.15; N, 2.95%), δ ($CDCl_3$) 3.81 and 3.98 (each 3 H, s, 2 × OMe), 4.59 (2 H, s, CH_2·OH), 5.06 (2 H, s, $O{\cdot}CH_2Ph$), 5.86 and 5.90 (each 1 H, d, *J* 7 Hz, $O{\cdot}CH_2{\cdot}O$), 6.55 and 6.63 (each 1 H, s, 9- and 12-H), and 7.32br (5 H, s, $O{\cdot}CH_2{\cdot}C_6H_5$); *m/e* 475 ($M^+$), 384, and 240.

5,6,13,13a-*Tetrahydro*-11-*hydroxy*-3,10-*dimethoxy*-1,2-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (15).—A mixture of compound (13) (400 mg), concentrated hydrochloric acid (40 mg), and zinc powder (40 ml) was refluxed on a water-bath for 3 h. The solvent was evaporated off under reduced pressure and the residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to afford a crystalline mass, which was recrystallised from chloroform–methanol to give compound (15) (270 mg) as *prisms*, m.p. 241—243° (Found: C, 67.1; H, 5.9; N, 4.4. $C_{20}H_{21}NO_5$ requires C, 67.6; H, 5.95; N, 3.95%), $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1} (OH), δ ($CDCl_3$) 3.81 and 3.83 (each 3 H, s, 2 × OMe), 5.90 and 5.92 (each 1 H, d, *J* 6 Hz, $O{\cdot}CH_2{\cdot}O$), and 6.26, 6.48, and 6.64 (each 1 H, s, 4-, 9-, and 12-H).

5,6,13,13a-*Tetrahydro*-11-*hydroxy*-12-*hydroxymethyl*-3,10-*dimethoxy*-1,2-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (16).—A solution of compound (15) (80 mg), methanolic N-sodium hydroxide (10 ml), and 37% formalin (15 ml) was stirred at room temperature for 24 h, then neutralised with crystalline ammonium chloride. After removal of methanol under reduced pressure, the resulting aqueous solution was diluted with water and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to leave a solid, which was subjected to preparative t.l.c. on silica gel (Wakogel B-5) with benzene–ethyl acetate–methanol (5 : 4 : 1 v/v). The product of R_F 0.27 was extracted with chloroform–methanol (9 : 1) to give a yellow solid, which was recrystallised from chloroform to afford compound (16) (70 mg) as *needles*, m.p. 118—120° (Found: C, 63.85; H, 5.9. $C_{21}H_{23}NO_6,0.5H_2O$ requires C, 63.95; H, 6.15%), $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1} (OH), δ ($CDCl_3$) 3.83 and 3.86 (each 3 H, s, 2 × OMe), 4.72 (2 H, s, CH_2·OH), 5.91 and 5.93 (each 1 H, d, *J* 7 Hz, $O{\cdot}CH_2{\cdot}O$), and 6.27 and 6.48 (each 1 H, s, 4- and 9-H); *m/e* 385 (M^+) and 206.

5,6,13,13a-*Tetrahydro*-12-*hydroxymethyl*-3,10,11-*trimethoxy*-1,2-*methylenedioxy*-8H-*dibenzo*[a,g]*quinolizine* (17).—To a solution of the 13-hydroxymethylberbine (16)

(35 mg) in methanol (10 ml) was added ethereal diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide]. The mixture was set aside overnight at room temperature. Removal of the solvent afforded a solid which was recrystallised from methanol–ether to give compound (17) (30 mg) as *needles*, m.p. 160—161° (Found: C, 65.95; H, 6.15; N, 3.8. $C_{22}H_{25}NO_6$ requires C, 66.15; H, 6.3; N, 3.5%), δ ($CDCl_3$) 3.84 and 3.87 (each s, 3 × OMe), 4.68 (2 H, s, CH_2·OH), 5.93 and 5.96 (each 1 H, d, *J* 9 Hz, O·CH_2·O), and 6.29 and 6.58 (each 1 H, s, ArH); *m/e* 399 (M^+), 206, 204, and 194.

9,10,14b,15-*Tetrahydro*-5,12-*dimethoxy*-13,14-*methylenedioxy*-1H,3H,7H-*benzo*[a][1,3]*benzodioxino*[6,5-g]*quinolizidine* (18).—The 12-hydroxymethylberbine (16) (30 mg) was treated with sodium hydride (30 mg) and dry methylene chloride (3 ml) in dry dimethylformamide (6 ml) in the same manner as in the synthesis of (±)-orientalidine to give compound (18) (17 mg) as fine *needles*, m.p. 189—190° (from ethyl acetate) (Found: C, 66.2; H, 5.8; N, 3.65. $C_{22}H_{23}NO_6$ requires C, 66.5; H, 5.85; N, 3.5%), δ ($CDCl_3$) 3.85 and 3.88 (each s, 6 H, 2 × OMe), 4.65 and 4.94 (each 1 H, d, *J* 15 Hz, ArCH_2·O), 5.23 (2 H, s, ArO·CH_2·O·CH_2), 5.95 and 5.98 (each 1 H, d, *J* 8 Hz, O·CH_2·O), and 6.30 and 6.51 (each 1 H, s, ArH); *m/e* 397 (M^+), 204, 192, and 162.

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