

## A Facile Total Synthesis of ( $\pm$ )-Cherylline *via* an Aziridinium Intermediate

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The 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid, ( $\pm$ )-cherylline (1), has been synthesised by a ring-opening reaction of the quaternary aziridinium salt, followed by a cyclisation of the quinone methide.

Recently we reported<sup>1</sup> the synthesis of the 2-benzylisoquinoline alkaloids, sendaverine and corgoine, *via* a ring-opening reaction of quaternary aziridinium salts as a key step; the high reactivity of the aziridinium salts in this step arises from the release of the strain energy inherent in a small ring. In continuation of our work on the synthesis of various types of isoquinoline alkaloids using a quaternary aziridinium salt as a reactive intermediate, we have investigated the synthesis of the 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid, ( $\pm$ )-cherylline (1), isolated from *Crinum powellii* and other *Crinum* species by Brossi.<sup>2,3</sup>

A possible biosynthetic pathway for cherylline (1) involves a cyclisation of a quinone methide, as shown in Scheme 1, and Schwartz,<sup>4</sup> Evans,<sup>5</sup> and Kametani<sup>6</sup> have actually synthesised (1) by this route, independently.

Our design for the synthesis of (1) was based on the following considerations: (a) the facile ring opening of a quaternary aziridinium salt to give a carbon-extended amine, and (b) the cyclisation of a quinone methide, generated *in situ* during the above ring opening reaction, as shown in Scheme 2.

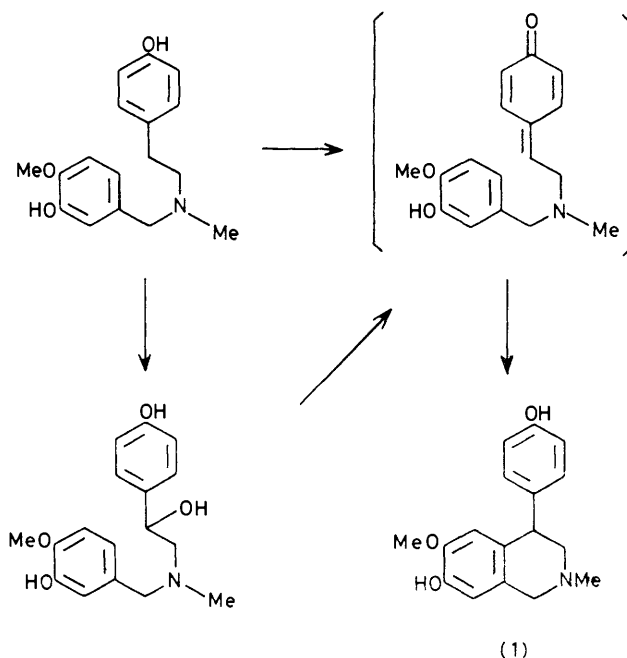
### Results and Discussion

The starting material for the synthesis of the dibenzyl diether (2) was prepared as follows. 3-Benzyloxy-4-methoxybenzaldehyde (4) was treated with hydroxylamine hydrochloride in the presence of sodium acetate in ethanol to give the oxime (5), whose reduction with lithium aluminium hydride in tetrahydrofuran afforded 3-benzyloxy-4-methoxybenzylamine (6) in 67.0% yield [from (4)]. Condensation of (6) with 4-benzyloxybenzaldehyde in refluxing benzene yielded the Schiff base (7) in quantitative yield. The conversion of compound (7) into the aziridine derivative (9) was initially attempted according to Hortman's procedure,<sup>7</sup> but difficulties were encountered. However, treatment of the Schiff base with an excess of methyl iodide in benzene yielded the quaternary immonium salt (8), which, without isolation, was treated with an excess of diazomethane and, subsequently, 1% methanolic hydrochloric acid to give di-*O*-benzylcherylline (3), presumably *via* the aziridinium salt (2) and the quinone methide, in 52.6% yield [from (7)]. Finally, di-*O*-benzylcherylline (3) was hydrolysed with 10% ethanolic hydrochloric acid to furnish ( $\pm$ )-cherylline, which was identical with an authentic specimen.<sup>6</sup>

### Experimental

I.r. spectra were obtained with a Hitachi 260-10 spectrophotometer, n.m.r. spectra with JEOL PMX-60 and JEOL JNM-FX 100 spectrometers (tetramethylsilane as internal reference), and mass spectra with JEOL JMS-D-300 spectrometers. Ether refers to diethyl ether throughout.

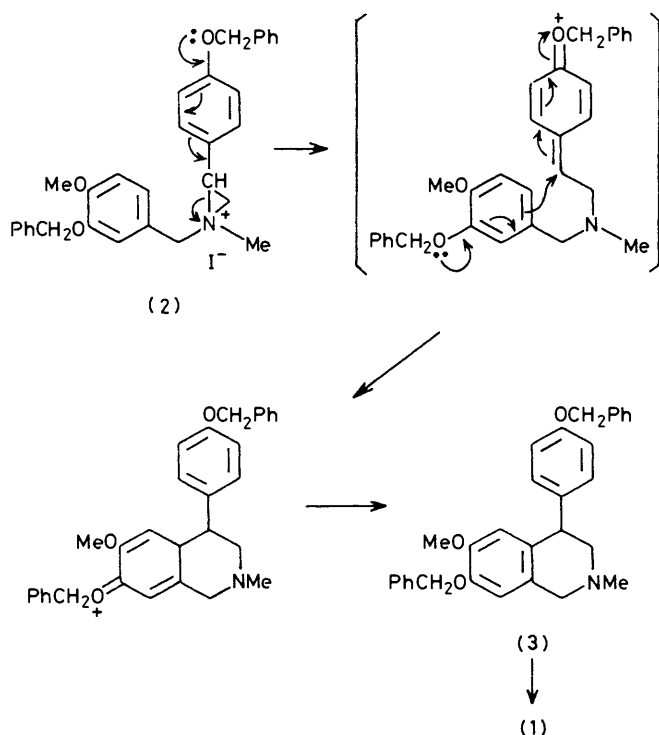
**3-Benzyloxy-4-methoxybenzaldehyde Oxime (5).**—A mixture of 3-benzyloxy-4-methoxybenzaldehyde (4) (2.4 g), hydroxyl-



Scheme 1.

amine hydrochloride (1 g), sodium acetate (2 g), and ethanol (40 ml) was heated under reflux for 1 h. After evaporation of the solvent, the residue was poured into water (40 ml), and the precipitated solid was filtered off to give the oxime (5) (2.5 g, 98.1%) as colourless needles, m.p. 96–97 °C (n-hexane) (Found: C, 70.5; H, 5.9; N, 5.3%;  $M^+$ , 257.1069.  $C_{15}H_{15}NO_3$  requires C, 70.0; H, 5.9; N, 5.45%;  $M$ , 257.1053);  $\nu_{\max}$  (CHCl<sub>3</sub>) 3 600 (OH), 1 600 and 1 580 cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>) 3.89 (3 H, s, OMe), 5.14 (2 H, s, OCH<sub>2</sub>Ph), 6.81–7.42 (8 H, m, ArH), 8.03 (1 H, s, CH=N), and 8.38 (1 H, br s, OH);  $m/e$  257 ( $M^+$ ).

**3-Benzyloxy-4-methoxybenzylamine (6).**—To a stirred suspension of lithium aluminium hydride (0.6 g) in tetrahydrofuran (THF) (10 ml) was added a solution of the oxime (5) (2.54 g) in THF (50 ml) during 0.5 h. After stirring for 3 h at ambient temperature, the excess of reagent was decomposed by addition of water, and the resulting mixture was filtered through a Celite pad. The filtrate was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to leave the residue which was purified by distillation to give the amine (6) (1.66 g, 68.3%), b.p. 192–194 °C at 4 mmHg;  $\nu_{\max}$  (CHCl<sub>3</sub>) 3 400, 3 250 (NH<sub>2</sub>), 1 600 and 1 595 cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>) 1.45 (2 H, s, NH<sub>2</sub>), 3.75 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>), 3.87 (3 H, s, OMe), 5.14 (2 H, s, OCH<sub>2</sub>Ph), 6.84–6.89 (3 H, m, ArH), and 7.29–7.45 (5 H, m, ArH);  $m/e$  243 ( $M^+$ ); it was crystallised as its hydrochloride, m.p. 253–254



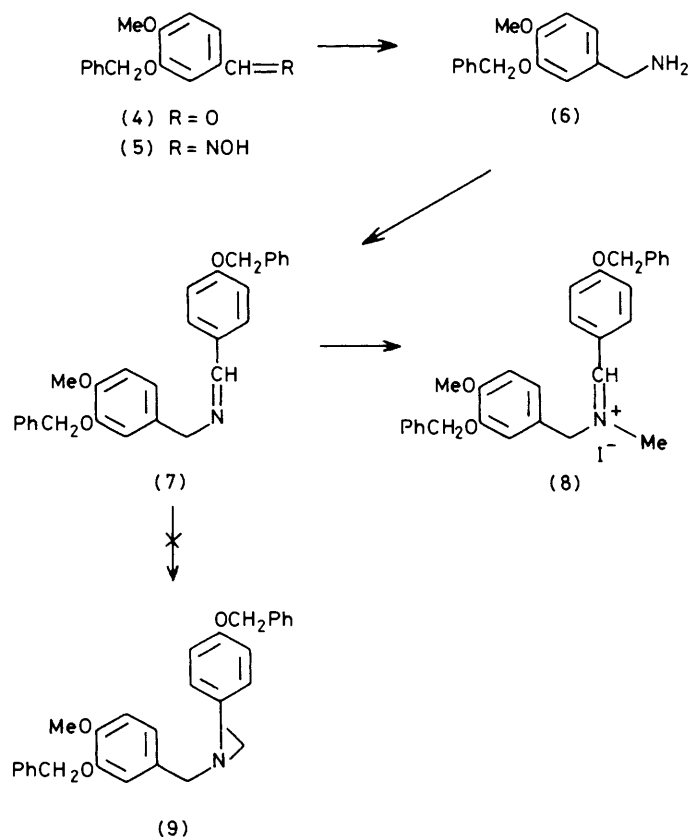
Scheme 2.

$^{\circ}\text{C}$  (ethanol) (Found: C, 64.2; H, 6.5; N, 4.85.  $\text{C}_{15}\text{H}_{18}\text{NO}_2\text{Cl}$  requires C, 64.4; H, 6.5; N, 5.0%).

**3-Benzoyloxy-N-(4-benzoyloxybenzylidene)-4-methoxybenzylamine (7).**—A solution of 3-benzoyloxy-4-methoxybenzylamine (6) (2.43 g) and 4-benzoyloxybenzaldehyde (2.12 g) in benzene (50 ml) was heated under reflux with Dean-Stark equipment for 3 h. Evaporation of the solvent afforded the Schiff base (7) (4.3 g, 98.4%) as colourless needles, m.p. 91–92  $^{\circ}\text{C}$  (n-hexane) (Found: C, 79.1; H, 6.15; N, 3.05%;  $M^+$ , 437.1979.  $\text{C}_{29}\text{H}_{27}\text{NO}_3$  requires C, 79.6; H, 6.2; N, 3.2%;  $M$ , 437.1990);  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 640 ( $\text{C}=\text{N}$ ), 1 600 and 1 575  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 3.86 (3 H, s, OMe), 4.66 (2 H, br s,  $\text{NCH}_2\text{Ar}$ ), 5.09 (2 H, s,  $\text{OCH}_2\text{Ph}$ ), 5.13 (2 H, s,  $\text{OCH}_2\text{Ph}$ ), 6.86–6.89 (3 H, m, ArH), 6.99 (2 H, d,  $J$  8.8 Hz, ArH), 7.67 (2 H, d,  $J$  8.8 Hz, ArH), 7.23–7.40 (10 H, m, ArH), and 8.23 (1 H, br s,  $\text{CH}=\text{N}$ );  $m/e$  437 ( $M^+$ ).

**The Quaternary Salt (8).**—A solution of the Schiff base (7) (1 g) and methyl iodide (3 g) in benzene (50 ml) was heated under reflux for 20 h. Evaporation of the solvent gave the quaternary salt (8) as a brown gum;  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 685 ( $\text{N}=\text{C}$ ) and 1 590  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 3.45 (3 H, s, NMe), 3.79 (3 H, s, OMe), 5.13 (2 H, s,  $\text{OCH}_2\text{Ph}$ ), 5.22 (2 H, s,  $\text{OCH}_2\text{Ph}$ ), 5.29 (2 H, br s,  $\text{NCH}_2\text{Ar}$ ), 6.79 (2 H, d,  $J$  8.6 Hz, ArH), 8.06 (2 H, d,  $J$  8.6 Hz, ArH), and 9.94 (1 H, br s,  $\text{N}=\text{CH}$ ); it was not stable enough to give a satisfactory microanalysis and was used for the next reaction without purification.

**Di-O-benzylcherylline (3).**—To a solution of the quaternary salt (8) obtained above, in chloroform (60 ml), was added an excess of diazomethane in ether and the resulting mixture was left at 5  $^{\circ}\text{C}$  for 12 h. After evaporation of the solvent and the excess of reagent, the residue was dissolved in methanol and concentrated hydrochloric acid (99 : 1 v/v; 100 ml) and the



Scheme 3.

mixture was heated under reflux for 3 h. Evaporation of the solvent afforded the residue, which was basified with 10% ammonium hydroxide and extracted with methylene dichloride. The organic layer was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to leave the gum, which was subjected to column chromatography on silica gel. Elution with methylene dichloride gave di-O-benzylcherylline (3) [0.56 g, 52.6% from (7)] as colourless needles, m.p. 144–145  $^{\circ}\text{C}$  (methanol-ether) [lit.,<sup>6</sup> 144–145  $^{\circ}\text{C}$ ];  $\delta$  ( $\text{CDCl}_3$ ) 2.38 (3 H, s, NMe), 2.46 (1 H, dd,  $J$  8.5 and 11.5 Hz, 3- $\text{CH}_2$ ), 2.95 (1 H, dd,  $J$  5.6 and 11.5 Hz, 3- $\text{CH}_2$ ), 3.51 (2 H, br s, 1- $\text{CH}_2$ ), 3.65 (3 H, s, OMe), 4.08 (1 H, dd,  $J$  8.5 and 5.6 Hz, 4-CH), 5.04 (2 H, s,  $\text{OCH}_2\text{Ph}$ ), 5.11 (2 H, s,  $\text{OCH}_2\text{Ph}$ ), 6.37 (1 H, s, ArH), 6.58 (1 H, s, ArH), 6.89 (2 H, d,  $J$  8.9 Hz, ArH), 7.10 (2 H, d,  $J$  8.9 Hz, ArH), and 7.29–7.45 (10 H, m, ArH); these data are identical with those reported.

**( $\pm$ )-Cherylline (1).**—A solution of di-O-benzylcherylline (3) (465 mg) in ethanol and concentrated hydrochloric acid (1 : 1 v/v, 50 ml) was heated under reflux for 4 h. After removal of the solvent, the residue was basified with 10% ammonium hydroxide and extracted with ethyl acetate. The extract was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to afford ( $\pm$ )-cherylline (1) (140 mg, 49.1%) as colourless needles, m.p. 216–218  $^{\circ}\text{C}$  (chloroform-methanol) [lit.,<sup>6</sup> 216–218  $^{\circ}\text{C}$ ];  $\delta$  ( $\text{CD}_3\text{COCD}_3$ ) 2.31 (3 H, s, NMe), 2.44 (1 H, dd,  $J$  7.6 and 11.2 Hz, 3- $\text{CH}_2$ ), 2.83 (1 H, dd,  $J$  5.4 and 11.2 Hz, 3- $\text{CH}_2$ ), 3.47 (2 H, s, 1- $\text{CH}_2$ ), 3.60 (3 H, s, OMe), 4.01 (1 H, dd,  $J$  5.4 and 7.6 Hz, 4-CH), 6.37 (1 H, s, ArH), 6.55 (1 H, s, ArH), 6.73 (2 H, d,  $J$  8.5 Hz, ArH), and 7.03 (2 H, d,  $J$  8.5 Hz, ArH), identical with an authentic sample.<sup>6</sup>

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