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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—DXCI†

TOTAL SYNTHESIS OF (±)-CHERYLLINE AND CORGOINE THROUGH QUINONOID INTERMEDIATES

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Abstract—Acid catalysed cyclisation of N - (4' - benzyloxy - β - methoxyphenethyl) - 3 - benzyloxy - 4 - methoxy - N-methylbenzylamine (**18**) gave (±)-cherylline (**1**), one of the *Amaryllidaceae* alkaloids. Fusion of 4-hydroxybenzyl alcohol (**22**) with 1,2,3,4-tetrahydroisoquinoline (**24**) also gave corgoine (**5**).

Cherylline, an *Amaryllidaceae* alkaloid, has been isolated from several *Crinum* species, and assigned the structure (**1**),[1] which was synthesised by two groups.[2,3] On the other hand, corgoine (**5**) has been isolated from *Corydalis gortschakovii*[4] and assigned structure (**5**) by NMR spectral comparison with the known alkaloid, sendaverine (**6**).[5] Since both alkaloids have been synthesised through quinonoid intermediates, we now wish to report a facile total synthesis of (±)-cherylline (**1**) by intramolecular coupling of quinonoid intermediate (**21**) and a simple synthesis of corgoine by intermolecular coupling of intermediate (**23**).

4 - Benzyloxy - α,β - dibromoethylbenzene (**12**), obtained by addition of 1 equivalent of bromine to 4 - benzyloxystyrene (**9**), was converted to 4 - benzyloxy - β - methoxyphenethyl bromide (**14**). Fusion of the bromide (**14**) with 3 - benzyloxy - 4 - methoxy - N - methylbenzylamine (**16**) gave the tertiary amine (**18**), m.p. 90–91°, whose cyclisation followed by debenzylation afforded (±)-cherylline (**1**) in 56% yield. This was identical with an authentic (±)-cherylline in its IR and NMR spectra. We also synthesised cherylline analogues (**3** and **4**) by the same routes.

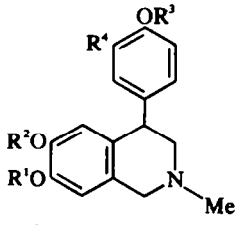
Secondly, corgoine was synthesised by a simple method; a mixture of 1,2,3,4 - tetrahydro - 7 - hydroxy - 6 - methoxyisoquinoline (**24**) and 4 - hydroxybenzyl alcohol (**22**) was heated under a current of nitrogen to give corgoine (**5**) in 44% yield, which was identical with the natural corgoine by direct comparisons of spectroscopic data. This reaction mechanism would proceed through a quinonoid intermediate (**23**), leading to the formation of **5** by attack with nitrogen of the isoquinoline nucleus.

†Part DXC, *Heterocycles* **3**, 29 (1975).

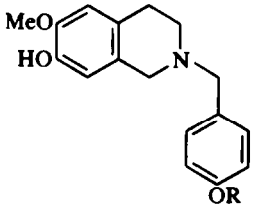
EXPERIMENTAL

IR spectra were taken with a type 215 Hitachi recording spectrometer, mass spectra were with a Hitachi RMU-7 mass spectrometer, and NMR spectra were with a Hitachi H-60 spectrometer using TMS as an internal standard.

4 - *Benzyloxy - α - hydroxyethylbenzene* (**8**). To a stirred soln of **7** (10 g) in MeOH (300 ml) was added in small portions $NaBH_4$ (3·4 g) during 1 h. After stirring for 2 h the solvents were evaporated to give a residue, which was extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to leave a solid (9 g), which was recrystallised from ether–hexane to give **8** as colourless needles, m.p. 85–86° (Found: C, 79·41; H,

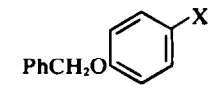


1: $R^1 = R^3 = R^4 = H$; $R^2 = Me$
2: $R^1 = R^3 = CH_2Ph$; $R^2 = Me$; $R^4 = H$
3: $R^1 = R^3 = H$; $R^2 = Me$; $R^4 = OMe$
4: $R^1 + R^2 = -CH_2-$; $R^3 = R^4 = H$

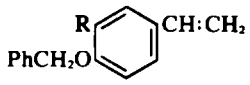


5: R = H
6: R = Me

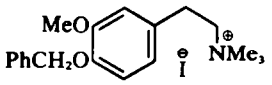
SCHEME 1



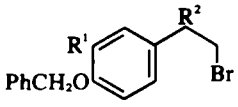
7: X = CO . Me
8: X = CH(OH) . Me



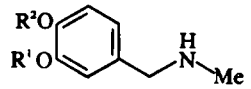
9: R = H
11: R = OMe



10

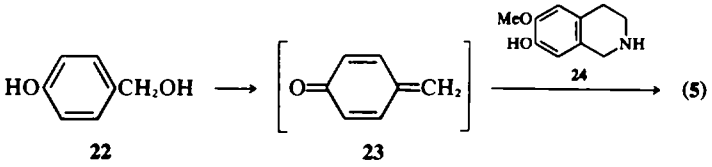


12: R^1 = H; R^2 = Br
13: R^1 = OMe; R^2 = Br
14: R^1 = H; R^2 = OMe
15: R^1 = R^2 = OMe

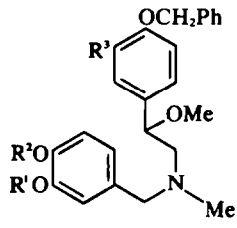


16: R^1 = CH_2Ph; R^2 = Me
17: $R^1 + R^2$ = $-CH_2-$

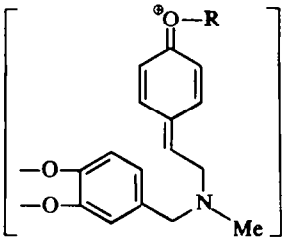
SCHEME 2



22 **23** **24** **(5)**



18: R^1 = CH_2Ph; R^2 = Me; R^3 = H
19: R^1 = CH_2Ph; R^2 = Me; R^3 = OMe
20: $R^1 + R^2$ = $-CH_2-$; R^3 = H



21

SCHEME 3

7·38. $C_{15}H_{16}O_2$ requires: C, 78·92; H, 7·06%); ν max ($CHCl_3$) 3430 cm^{-1} (OH).

4-Benzyloxystyrene (**9**). To a stirred soln of **8** (7 g) in pyridine (28 ml) was added dropwise $SOCl_2$ (4 g) during 5 min under cooling with ice. After stirring for 1 h at room temp, the mixture was gently refluxed for 65 min. After evaporation of the solvent, the residue was poured into H_2O and extracted with ether. The extract was washed with 5% NaOH, 5% HCl and H_2O, dried over Na_2SO_4, and evaporated to leave an orange solid (2 g), which was recrystallised from hexane to give colourless prisms, m.p. 68–69° (Found: C, 85·27; H, 6·53. $C_{15}H_{14}O$ requires: C, 85·68; H, 6·71%); ν max ($CHCl_3$) 1620 and 980 cm^{-1}.

4 - Benzyloxy - α,β - dibromoethylbenzene (**12**). To a stirred soln of (**9**) (0·5 g) in CCl_4 (20 ml) was added dropwise a soln of Br_2 (0·38 g) in CCl_4 (10 ml) during 10 min at 10°. After stirring for 15 min at room temp, the solvent was evaporated to leave **12** (0·85 g) as a solid, which was used for the following reaction without purification, because of the unstability of the product.

3 - Benzyloxy - 4 - methoxy - N - methylbenzylamine (**16**). A soln of O-benzylisovanillin (40 g) and $MeNH_2$ (13 g) in EtOH (150 ml) was heated at 80–90° under 5 atm of H_2 pressure for 5 h, and, after cooling at room temp, $NaBH_4$ (6·3 g) was added in small portions during 1·5 h. After stirring for 14 h the solvent was evaporated to leave a residue, to which H_2O (500 ml) was added and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and evaporated to leave **16** (34 g) as a solid, whose hydrochloride was recrystallised from MeOH to give **16** as colourless needles, m.p. 209–211° (Found: C, 65·42; H, 7·04; N, 4·72. $C_{16}H_{19}NO_2 \cdot HCl$ requires: C, 65·41: H, 6·86; N, 4·77%); τ (CCl_4), 5·06 (2H, s, OCH_2Ph), 6·29 (3H, s, OCH_3), 6·50 (2H, s, NCH_2Ph), 7·71 (3H, s, NCH_3), 8·68 br (1H, s, NH).

4 - Benzyloxy - β - methoxyphenethyl bromide (**14**). A mixture of **12** (0·7 g), $NaHCO_3$ (0·4 g), MeOH (50 ml) and H_2O (2 ml) was refluxed for 19 h. After evaporation of the solvent, the residue was extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to leave a solid, which was recrystallised from hexane to give **14** (0·4 g) as colourless needles, m.p. 56–57·5° (Found: C, 60·45; H, 5·45. $C_{16}H_{17}BrO_2 \cdot 0{\cdot}1C_6H_{14}$ requires: C, 60·45; H, 5·62%); τ (CCl_4) 2·86, 3·18 (4H, AA'BB' pattern, J 8·5 Hz, 2-H, 6-H, 3-H, and 5-H), 5·01 (2H, s, OCH_2Ph), 5·81 (1H, t, J 6 Hz, PhCHOMe), 6·80 (3H, s, OCH_3).

N - (4' - Benzyloxy - β - methoxyphenethyl) - 3 - benzyloxy - 4-methoxy - N - methylbenzylamine (**18**). A mixture of **16** (0·64 g) and **14** (0·4 g) was heated at 100° for 3·5 h in a current of N_2. The mixture was suspended in H_2O and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to leave a pale yellow syrup, which was triturated with ether to give a solid (0·45 g), which was recrystallised from ether–hexane to give **18** as colourless needles, m.p. 90–91° (Found: C, 77·09; H, 7·19; N, 2·76. $C_{32}H_{35}NO_4$ requires: C, 77·23; H, 7·09; N, 2·82%); τ

($CDCl_3$) 2·50–3·24 (17H, m, ArH), 4·95, 5·03 (4H, each s, 2 × OCH_2Ph), 5·78 (1H, q, *J* 5 and 7 Hz, PhCHOMe), 6·20 (3H, s, OCH_3), 6·54 (2H, s, $PhCH_2N$–), 6·82 (3H, s, OCH_3), 7·20–7·70 (2H, m, NCH_2CH), 7·78 (3H, s, NCH_3).

(±) - O,O - *Dibenzylcherylline* (**2**). A mixture of **18** (360 mg), D - camphor - 10 - sulfonic acid (9·65 g), H_2O (20 ml), and EtOH (15 ml) was refluxed for 9 h. After evaporation of EtOH, the aqueous layer was basified with sat $NaHCO_3$ aq, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to leave a yellow viscous syrup, which was triturated with ether to give a solid, which was recrystallised from MeOH–ether to give **2** (190 mg) as colourless needles, m.p. 144–145°. (Found: C, 80·40; H, 6·84; N, 2·70. $C_{31}H_{31}NO_3$ requires: C, 79·97; H, 6·71; N, 3·01%); τ ($CDCl_3$) 2·55–2·83 (10H, m, ArH), 2·92, 3·16 (4H, AA'BB' pattern, *J* 8·5 Hz, 2'-H, 6'-H, 3'-H and 5'-H), 3·45 (1H, s, 8-H), 3·64 (1H, s, 5-H), 4·94, 5·01 (4H, each s, 2 × OCH_2Ph), 5·89 (1H, q, *J* 5 and 7 Hz, 4-H), 6·40 (3H, s, OCH_3), 6·49 br (2H, s, 1-H), 6·90–7·80 (2H, m, 3-H), 7·65 (3H, s, NCH_3).

(±)-*Cherylline* (**1**). (a) A soln of **18** (250 mg) in EtOH (15 ml) and conc HCl (10 ml) was refluxed for 1·5 h. After evaporation of the solvent, the residue was dissolved in H_2O and the resulting soln was washed with ether. The aqueous layer was basified with conc NH_4OH and extracted with $CHCl_3$. The extract was washed with sat NaCl aq, dried over Na_2SO_4, and evaporated to leave a solid, which was recrystallised from $CHCl_3$ to give **1** (80 mg) as colourless needles, m.p. 216–218° (lit.[2] m.p. 215–216°), which was identical with an authentic sample, ν max (KBr) 3450 cm^{-1} (OH), τ (CD_3COCD_3), 3·00, 3·32 (4H, AA'BB' pattern, *J* 8·5 Hz, 2'-H, 6'-H, 3'-H, and 5'-H), 3·49 (1H, s, 8-H), 3·68 (1H, s, 5-H), 6·12 (1H, q, *J* 5 and 7 Hz, 4-H), 6·42 (3H, s, OCH_3), 6·52 (2H, br s, 1-H), 7·00–7·74 (2H, m, 3-H), 7·70 (3H, s, NCH_3), *m/e* 285 (M^+), 242, 241, 225, 211.

(b) A soln of **2** (35 mg) in EtOH (20 ml) and conc HCl (15 ml) was refluxed for 4 h. After evaporation of the solvent, the residue was basified with 5% NH_4OH and extracted with EtOAc. The extract was washed with sat NaCl aq, dried over Na_2SO_4, and evaporated to leave a residue, which was recrystallised from MeOH–$CHCl_3$ to give **1** (10 mg) as colourless needles, m.p. 216–218°, identical in all respects with the material as mentioned above.

4 - *Benzyloxy* - 3 - *methoxy* - N,N - *dimethylphenethylamine methiodide* (**10**). A mixture of 4 - benzyloxy - 3 - methoxyphenethylamine (10 g), MeI (25 g), $NaHCO_3$ (12 g), and MeOH (100 ml) was stirred for 22 h at room temp. After removal of the inorganic material the solvent was evaporated to leave a yellow solid, which was recrystallised from MeOH to give **10** (8·5 g) as colourless prisms, m.p. 180–182°. (Found: C, 53·50; H, 6·29; N, 3·17. $C_{19}H_{26}INO_2$ requires: C, 53·39; H, 6·13; N, 3·28%).

4 - *Benzyloxy* - 3 - *methoxystyrene* (**11**). A mixture of **10** (8·5 g), KOH (25 g), EtOH (50 ml), and H_2O (50 ml) was refluxed for 4·5 h. After cooling, the mixture was poured into H_2O and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and evaporated to leave a solid, which was recrystallised from hexane to give **11** (4·2 g) as colourless needles, m.p. 55–56°. (Found: C, 80·20; H, 6·75. $C_{16}H_{16}O_2$ requires: C, 79·97; H, 6·71%); ν max ($CHCl_3$) 1622 cm^{-1}.

4 - *Benzyloxy* - α,β - *dibromo* - 3 - *methoxyethylbenzene* (**13**). To a stirred soln of **11** (1 g) in CCl_4 (30 ml) was added dropwise a soln of Br_2 (0·67 g) in CCl_4 (24 ml) during 20 min at 10°. After stirring for 15 min at room temp, the solvent was evaporated to leave **13** (1·6 g) as a solid, which was used for the following reaction without purification because of the unstability of the product.

4-*Benzyloxy* - 3,β - *dimethoxyphenethyl bromide* (**15**). A mixture of **13** (1 g), $NaHCO_3$ (1 g), MeOH (50 ml), and H_2O (2 ml) was refluxed for 24 h. After evaporation of the solvent, the residue was extracted with ehter. The extract was washed with sat NaCl aq, dried over Na_2SO_4, and evaporated leave a solid, which was recrystallised from hexane to give **15** (0·6 g) as colourless prisms, m.p. 78–79°. (Found: C, 58·61; H, 5·62. $C_{17}H_{19}BrO_3$ requires: C, 58·13; H, 5·45%), τ ($CDCl_3$) 4·90 (2H, s, OCH_2Ph), 5·72 (1H, t, *J* 6 Hz, PhCH), 6·14 (3H, s, OCH_3), 6·55 (2H, d, *J* 6 Hz, CH_2Br), 6·72 (3H, s, OCH_3).

N - (4' - *Benzyloxy* - 3' - *methoxy* - β - *methoxyphenethyl*) - 3 - *benzyloxy* - 4 - *methoxy* - N - *methylbenzylamine* (**19**). A mixture of **16** (257 mg) and **15** (175 mg) was heated at 100° for 6 h in a current of N_2. The mixture was suspended in H_2O and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to leave a solid, which was recrystallised from ether to give **19** (180 mg) as colourless needles, m.p. 95–96°. (Found: C, 74·78; H, 6·87; N, 2·75. $C_{33}H_{37}NO_5$ requires: C, 75·12; H, 7·07; N, 2·65%); τ ($CDCl_3$) 2·45–3·30 (16 H, m, ArH), 4·95 (4H, s, 2 × OCH_2Ph), 5·80 (1H, q, *J* 5 and 8 Hz, PhCHOMe), 6·20 (6H, s, 2 × OCH_3), 6·54 (2H, s, $PhCH_2N$–), 6·82 (3H, s, OCH_3), 7·82–7·95 (2H, m, NCH_2CH), 7·75 (3H, s, NCH_3).

1,2,3,4 - *Tetrahydro* - 7 - *hydroxy* - 4 - (4' - *hydroxy* - 3' - *methoxyphenyl*) - 6 - *methoxy* - 2 - *methylisoquinoline* (**3**). A soln of **19** (400 mg) in EtOH (20 ml) and conc HCl (15 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in H_2O, and the soln washed with ether. The aqueous layer was basified with conc NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to leave a brown solid which was recrystallised from benzene–$CHCl_3$ to give **3** (175 mg) as colourless needles, m.p. 185–187°. (Found: C, 68·72; H, 6·69. $C_{18}H_{21}NO_4$ requires: C, 68·55; H, 6·71%); ν max ($CHCl_3$) 3550 cm^{-1}, (OH), τ ($CDCl_3$) 3·30–3·75 (5H, m, ArH), 5·87 (1H, q, *J* 5 and 8 Hz, 4-H), 6·28, 6·42 (6H, each s, 2 × OCH_3), 6·80–7·70 (2H, m, 3-H), 7·61 (3H, s, NCH_3), *m/e* 315 (M^+), 272, 271, 257, 255, 241.

3,4 - *Methylenedioxy* - N - *methylbenzylamine* (**17**). A mixture of piperonal (25 g) 30% methylamine (44 ml) and EtOH (100 ml) was heated at 80–90° under 8 atm of H_2 pressure for 5 h, and after cooling at room temp, $NaBH_4$ (6·05 g) was added in small portions during 1 h. After the addition had been completed, stirring was continued for 2 h. The solvent was distilled off under reduced pressure and H_2O (100 ml) was then added to the residue, and the soln extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and evaporated to afford a brown liquid (25·9 g), which was distilled to yield a colourless liquid (19·7 g), bp_3 98–100°, τ (CCl_4) 3·27 (1H, s, ArH), 3·38 (2H, s, ArH), 4·18 (2H, s, OCH_2O), 6·45 (2H, s, $PhCH_2N$), 7·67 (3H, s, NCH_3), 8·75 (1H, s, NH). Recrystallisation of the oxalate from EtOH gave colourless needles, m.p. 178–179°. (Found: C, 52·06; H, 5·14; N, 5·53. $C_9H_{11}NO_2 \cdot (COOH)_2$ requires: C, 51·76; H, 5·14; N, 5·49%).

N - (4' - *Benzyloxy* - β - *methoxyphenethyl*) - N - *methyl* - 3,4-*methylenedioxybenzylamine* (**20**). A mixture of **14** (1·37 g) and **17** (1·41 g) was heated on a water-bath for 4 h under a current of N_2. The mixture was then poured into H_2O and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and evaporated to give a brown syrup (2·51 g) which was purified by column chromatography with $CHCl_3$ as eluant to yield a yellow syrup (1·78 g), τ (CCl_4) 2·70–2·90 (5H, m, $C_6H_5CH_2O$), 2·94 (2H, d, *J* 8·5 Hz, 2'-H, 6'-H), 3·22 (2H, d, *J* 8·5 Hz, 3'-H and 5'-H), 3·36 (1H, s, ArH), 3·44 (2H, s, ArH), 4·26 (2H, s, OCH_2O), 5·08 (2H, s, OCH_2Ph), 5·88 (1H, t, *J* 6·5 Hz, PhCHOMe), 6·62 (2H, br s, $PhCH_2N$), 6·90 (3H, s, OCH_3), 7·80 (3H, s, NCH_3). Recrystallisation of the oxalate of **20** from EtOH afforded colourless prisms, m.p. 186–187°. (Found: C, 65·40; H, 5·92; N, 2·88. $C_{25}H_{27}NO_4$, $(COOH)_2$ requires: C, 65·44; H, 5·90; N, 2·83%).

1,2,3,4 - *Tetrahydro* - 4 - (4' - *hydroxyphenyl*) - N - *methyl* - 6,7 - *methylenedioxyisoquinoline* (**4**). A soln of **20** (784 mg) in EtOH (8 ml) and conc HCl (8 ml) was refluxed for 3 h. After evaporation of the solvent, the residue was poured into H_2O and the soln was made alkaline with conc NH_4OH and extracted with $CHCl_3$. The

extract was washed with H_2O, dried over Na_2SO_4, and evaporated to afford a brown solid, which was recrystallised from EtOAc to yield yellow prisms (205 mg), m.p. 238–239·5° (Found: C, 71·96; H, 6·40; N, 4·63. $C_{17}H_{17}NO_3$ requires: C, 72·06; H, 6·05; N, 4·94%); τ (DMSO-d_6) 3·02 (2H, d, J 8 Hz, 2'-H, 6'-H), 3·32 (2H, d, J 8 Hz, 3'-H, 5'-H), 3·38 (1H, s, 8-H), 3·76 (1H, s, 5-H), 4·12 (2H, s, OCH_2O), 6·04 (1H, t, J 6 Hz, 4-H), 7·70 (3H, s, NCH_3).

Corgoine (**5**). A mixture of *isoquinoline* **24** (90 mg) and **22** (62 mg) was heated at 150–160° for 30 min in a current of N_2. The mixture was purified by preparative TLC to give **5** (58 mg), which was recrystallised from MeOH–ether to give colourless needles, m.p. 190–191° (lit.[4] m.p. 190–191°), whose hydrochloride was recrystallised from MeOH–ether to give colourless prisms, m.p. 239–240°. (Found: C, 63·24; H, 6·33; N, 4·32. $C_{17}H_{19}NO_3 \cdot HCl$ requires: C, 63·60; H, 6·26; N, 4·35%); ν max (KBr) 3450 cm^{-1} (OH), τ (CF_3CO_2H), 2·58, 2·91 (4H, AA'BB' pattern, J 8 Hz, 2'-H, 6'-H, 3'-H and 5'-H), 3·18 (1H, s, 5-H), 3·26 (1H, s, 8-H), 6·05 (3H, s, OCH_3).

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