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A Novel Synthesis of Corgoine

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ABSTRACT

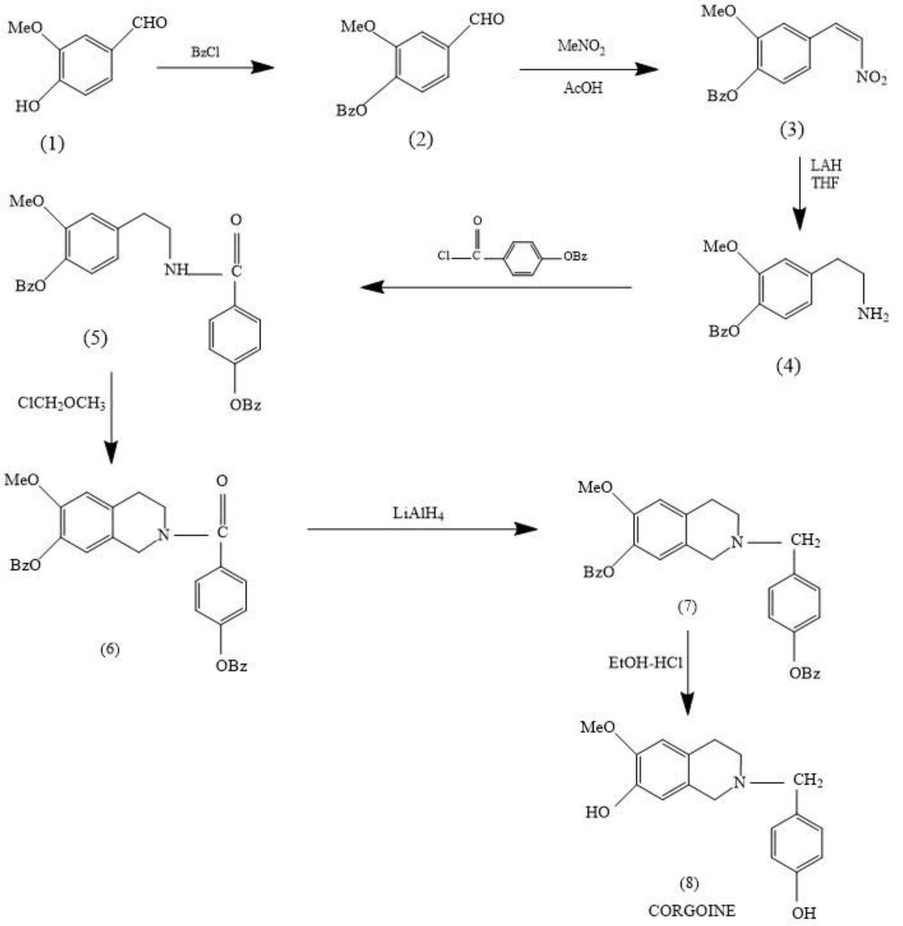
The synthesis of corgoine has been achieved through a novel synthetic route involving the condensation of N-(4-benzyloxy)benzoyl derivative of β-phenethyl amine with monochloromethyl ether, followed by reduction of condensation product with lithium aluminium hydride and debenzylation.

KEY WORDS: *Corgoine, Monochloromethylether, β-phenethylamine.*

Corgoine was isolated from Corydalis gortschakovii (Fam. Fumariaceae).[1]The alkaloid was assigned the structure (8) by NMR spectral comparison with the alkaloid Sendaverine. The structure (8) was finally confirmed by synthesis.[2-10]

In the present work,the synthesis of Corgoine has been achieved by condensation of N-(4-benzyloxy)benzoyl derivative of β-phenethyl amine with monochloromethyl ether, followed by reduction of the condensation product with Lithium aluminium hydride and debenzylation.

Vanillin (1) on benzylation with benzylchloride gave the O-benzyl vanillin (2) which on treatment with nitromethane gave 4-benzyloxy-3-methoxy- ω-nitro styrene(3). Lithium aluminium hydride reduction of (3) gave 2-(4'-benzyloxy-3'-methoxy phenyl)ethyl amine (4) which on treatment with 4-benzyloxy benzoyl chloride gave N-(4-benzyloxy)benzoyl derivative(5) of the amine(4), which was treated with monochloromethyl ether to give N-(4'-benzyloxy benzoyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydro isoquinoline (6).(6) On reduction with Lithium aluminium hydride followed by reflux with ethanol –HCl mixture gave Corgoine(8).



EXPERIMENTAL

(I) Synthesis of O-benzyl vanillin: (2)- A mixture of vanillin (1)(7.6 g), anh. potassium carbonate (5.0 g), benzyl chloride (4 mL), sodium iodide (0.4g) and ethanol (130 mL) was stirred and refluxed for 6 h. After cooling, the solvent was distilled out in vacuo and resulting oil poured into alkaline ice cold water (250 mL). The solid product was crushed under water, filtered and dried (Na_2SO_4). Recrystallisation from aq. ethanol gave O-benzyl vanillin (2).(9.6 g; 79.34%), m.p. 64-65^{0}C.

(Found C,74.2, H,5.96, O-19.8, $C_{15}H_{14}O_3$ requires C 74.5; H 5.78; O 19.9%)

(II) Synthesis of 4-benzyloxy-3-methoxy-ω-nitrostyrene:(3)-

A mixture of O-benzylvanillin (2) (9g), ammonium acetate (3g), nitromethane (15mL) and glacial acetic acid (25mL) was refluxed for 1.5 h. The crystals of the product which deposited on cooling were filtered, dried and recrystallised from ethanol to give the styrene (3) as yellow needles (8.47 g; 80%) m.p. 120-122^{0}C(lit[6],m.p. 121-123^{0}C).

(Found C:67.42; H: 5.25; N:4.90; $C_{16}H_{15}NO_4$ requires C:67.36; H:5.26; N:4.91%)

(III) Synthesis of 4-benzyloxy-3-methoxy-β-phenethylamine: (4)-

To a stirred suspension of lithium aluminium hydride (5.36g) in tetrahydrofuran was added the styrene(3) (8g), in portions, with ice bath cooling. The mixture was refluxed at 100^{0}C for 4 h, cooled, excess hydride was decomposed by addition of water and mixture was extracted with methylene dichloride. The extract was washed with 2N aq. sodium hydroxide, washed with water, dried (Na_2SO_4) and solvent removed to give the amine as oil(4) (5.62 g, 78%). The hydrochloride had m.p. 171-172^{0}C.

(IV) Synthesis of N-(4$^{'}$-benzyloxy benzoyl)-2-(4$^{'}$-benzyloxy-3’-methoxy phenyl) ethyl amine.(5):

To a stirred mixture of 2-(4$^{'}$-benzyloxy-3$^{'}$-methoxy phenyl) ethyl amine(4) (3.5g) in benzene (25mL) and 10% NaOH (60mL) a solution of p-benzyloxy benzoyl chloride (3.7g) in dry benzene (150mL) was slowly added and the stirring continued for 4h at room temperature. The benzene layer was then separated , washed with 1N HCl, water, dried (Na_2SO_4) and the solvent removed under reduced pressure to give (5) (4.7g; 74%),m.p. 179^{0}C

IR (KBr): 3330cm^{-1} (NH) and 1670cm^{-1} (C=O)

MS 467 (M^+)

(Found C: 77.22; H:6.37; N: 2.48. $C_{30}H_{29}O_4N$ requires C:77.08; H:6.21; N:2.30%)

(V) Synthesis of N-(4$^{'}$-benzyloxy)benzoyl-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline.(6):

A mixture of monochloromethyl ether (2g)in glacial acetic acid (20mL) was treated with N-(4$^{'}$-benzyloxy benzoyl)-2-(4’-benzyloxy-3’-methoxy phenyl) ethyl amine(5) (4g) at about 18^0 C for 24h. The excess solvent and reagent were removed under reduced pressure. The residue was washed with 20% ammonia solution extracted with ethyl acetate washed with water, dried (Na_2SO_4) and the solvent removed to afford(6) (3.03g, 74%), m.p. 145^{0}C

IR (KBr): 1656cm^{-1}

(Found C: 77.12; H: 5.92; $C_{31}H_{29}NO_4$ requires C: 77.66; H: 6.05%)

(VI) Synthesis of 7-benzyloxy-2-(4'-benzyloxy benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline(7):

The product (6) (2g) obtained in the previous step (step V) was added in portions to a well stirred suspension of lithium aluminium hydride (2g) in anh. THF (100mL) over a period of 45 min. The mixture was stirred and refluxed for 8h on a water bath. The mixture was cooled, and excess hydride was decomposed with moist ethyl acetate and the solution rendered alkaline with aq. sodium hydroxide solution. The organic layer which separated, was extracted with dilute hydrochloric acid and extracts were made alkaline to give the semisolid, which was taken in ether (200mL) and washed with water (2x200mL) and dried (Na_2SO_4). Removal of the solvent gave a solid which was recrystallised from n-hexane to give the tetrahydroisoquinoline derivative (7) as colourless needles. (1.4g; 72%) m.p. 106^0 C

IR (KBr): 2790, 2755cm^{-1}

(Found C: 80.0; H: 6.71; N: 3.01; $C_{31}H_{31}O_3N$ requires C: 79.97; H: 6.71; N: 3.01%)

(VII) Synthesis of 7-hydroxy-2-(4$^{'}$-hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Corgoine) (8):

The dibenzyl derivative (7) (1g) was refluxed with ethyl alcohol (30mL) and conc. HCl (20mL) for 3h. The reaction mixture was extracted with ether in order to remove neutral substance. The acidic layer formed above was basified with 25% ammonia solution and was extracted with benzene. The extract was dried on potassium carbonate and solvent removed in vacuo to give a solid. Recrystallisation from acetone. Pet. Ether gave Corgoine (8) as colourless needles (459mg; 75%) m.p. 191-192^{0}C .

UV $MeOH_{max}$ 227, 284nm

IR ($CHCl_3$); 3550cm^{-1} (-OH)

NMR: (CF_3COOH): δ6.74 (1H, s,C_8–H), 6.82 (1H, s, C_5–H); 7.09 (2H, d, J=8Hz; $C_{3'}$–H and $C_{5'}$–H); 7.42 (2H, d, J=8Hz; $C_{2'}$–H and $C_{6'}$–H)ppm.

(Found C: 71.70; H: 6.93; N: 4.79; $C_{17}H_{19}O_3N$ requires C: 71.56; H: 6.71; N: 4.91%)

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