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A Novel Route For Synthesis Of N-(3',4'-DIMETHOXY-β-PHENETHYL)-6,7-DIMETHOXY-1,2,3,4-Tetrahydroisoquinoline Alkaloid.

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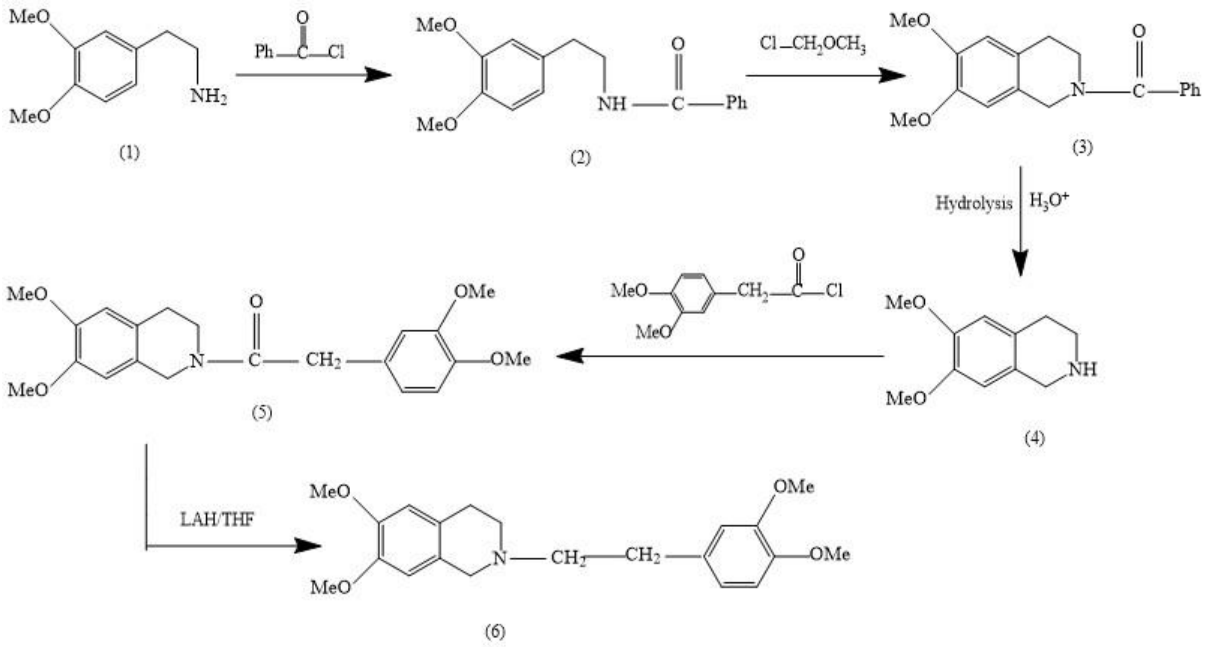
ABSTRACT
A new synthesis of N-β-phenethyl-1,2,3,4-tetrahydroisoquinoline alkaloid is achieved. N-benzoylated amine on treatment with monochloromethylether gave N-benzoyl-3,4-dimethoxy-1,2,3,4-tetrahydroisoquinoline which on acid hydrolysis followed by condensation with 3,4-dimethoxyphenyl acetyl chloride gave N-(3',4'-dimethoxyphenyl) acetyl -6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline which on reduction gave N-(3,4-dimethoxy-β-phenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.
KEY WORDS*-1,2,3,4-tetrahydroisoquinoline, Monochloromethylether, β-phenethylamine.*

A new synthesis[1-5] of N-(3',4'-dimethoxy-β-phenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline alkaloid has been achieved according to the reaction sequence as shown in the scheme below.



I. EXPERIMENTAL

I. Synthesis of N-benzoyl-2-(3',4'-dimethoxyphenyl) ethylamine(2):
To a stirred mixture of 2-(3',4'-dimethoxyphenyl) ethylamine(1) (10g) in benzene (50mL) and 10% NaOH (150mL) was added benzoyl chloride (8mL) in small portions of 0.5mL each with cooling in water. The stirring continued for 4h at room temperature. The benzene layer was then separated, washed with 1N HCl, dried (Na_2SO_4) and the solvent removed under reduced pressure to give (2) (11.38g, 72.25%) m.p. 93^0C. IR(KBr): 3320cm^{-1} (NH); 1630cm^{-1} (C=O)
(Found C: 70.2; H: 6.1; N: 5.1; $C_{17}H_{19}NO_3$ requires C: 71.57; N: 4.9; H: 6.67%)

II. Synthesis of N-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline(3):
A mixture of monochloromethyl ether (4g) in glacial acetic acid (30mL) was treated with N-benzoyl-2-(3',4'-dimethoxy phenyl) ethyl amine(2) (10g) at about 18^0C for 18h. The excess solvent and reagent were removed

under reduced pressure. The residue was washed with 20% NH_3 solution, extracted with ethyl acetate, washed with water, dried (Na_2SO_4) and the solvent removed to afford (3) (7.8g; 74.85%).
m.p. 106^0C.
(Found C: 71.8; H: 6.52; N: 4.81; O: 16.2; $N_{18}H_{19}NO_3$ requires C: 72.7; H: 6.3; N: 4.7; O: 16.16%)

III. Synthesis of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline(4):
N-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline(3) (7g) was refluxed with 60% H_2SO_4 (35mL) for thirty minutes, cooled and filtered. The filtrate was rendered alkaline with 15% NaOH solution, cooled and extracted with ether. The extract was evaporated under reduced pressure to give 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4) (3.72g; 81%) as colourless prism (crystallised from isopropanol) m.p. 83^0C. The hydrochloride had m.p. 252^0C.
IR($CHCl_3$): 3285 (NH)

IV. Synthesis of N-(3',4'-dimethoxyphenyl) acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline(5):
To a stirred mixture of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline(4) (1.75g) in benzene (15mL) and 20% NaOH (10mL) was added 3,4-dimethoxyphenyl acetyl chloride (2g) in small portions, with cooling. The stirring continued for 2.5h 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) as a gummy solid(5) (2.75g; 68.2%).
IR($CHCl_3$) 1650cm^{-1}
NMR ($CDCl_3$) δ: 3.66-4.10 (12H, bs, 4x-OCH_3) 6.66-6.88 (4H, m, Hx Ar-H) MS m/e 371(M^+)
(Found C: 67.68; H: 6.61; O: 21.2; $C_{21}H_{25}O_5N$ requires C: 67.80; H:6.6; O: 21.5%)

V. Synthesis of N-(3',4'-dimethoxy-β-phenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline(6):
To a suspension of Lithium aluminium hydride (3.5g) in tetrahydrofuran (10mL), a solution of (5) (2.0g) in tetrahydrofuran (6mL), was added in portions with stirring and cooling. The mixture was refluxed on a water bath for 6h. After cooling the mixture was diluted with dropwise addition of water and the gel which formed was separated. The filtrate was extracted with ethylacetate, washed with water and dried (Na_2SO_4). Removal of the solvent in vacuo gave the isoquinoline (6) (1.1g 57%)
(Found C: 70.2; H: 7.69; N: 3.72; $C_{21}H_{27}O_4N$ requires C: 70.5; H: 7.5; N: 3.8%)
m.p. 85-89^0C.
The hydrochloride had m.p. 129^0C

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