

Synthesis of Benzyloisoquinoline Derivatives

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4-Benzyloxy-3-methoxyphenethylamine (1) on formylation with ethyl formate gave N-formyl-7-benzyloxy-6-methoxyphenethylamine (2) which on Bischeler-Napieralski cyclization with phosphorus oxychloride followed by methylation with methyl iodide furnished 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline methiodide (4). The base catalysed condensation of 4 with 2-methoxy-6-nitrotoluene (5) afforded 7-benzyloxy-6-methoxy-1-(2-nitro-6-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (6). On hydrogenation with zinc and sulphuric acid, 6 gave 7-benzyloxy-6-methoxy-1-(2-amino-6-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (7). Pschorr cyclization of 7 furnished three compounds, 1-benzyloxy-2,8-dimethoxyaporphine (8), 1-hydroxy-2,8-dimethoxyaporphine (9) and 7-benzyloxy-6-methoxy-1-(2-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (10).

TREATMENT of 4-benzyloxy-3-methoxyphenethylamine (1)¹ with ethyl formate gave N-formyl-7-benzyloxy-6-methoxyphenethylamine (2) which showed the expected C=O and NH bands in its spectrum† at 1650 and 3250, respectively. Bischeler-Napieralski cyclization of 2 with phosphorus oxychloride afforded 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline hydrochloride which on quaternization with methyl iodide furnished 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline methiodide (4). In its pmr spectrum† the methyl and methoxy protons appeared as singlets at 6.70 and 6.34, respectively. The methylenes of positions 3 and 4 were observed as a pair of triplets at 6.45 ($J=8.00$ Hz) and 7.24 ($J=8.00$ Hz) while the benzyloxymethylene protons showed a singlet at 5.95. The proton of position 1 appeared as singlet at 2.09 and the remaining aromatic protons resonated between 2.98-3.56.

Condensation² of 4 with 5 in presence of sodium ethoxide gave 7-benzyloxy-6-methoxy-1-(2-nitro-6-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (6). The ir spectrum exhibited NO_2 bands at 1350 and 1500. The nmr spectrum showed an upfield singlet for N-methyl and other singlets for two methoxy protons at 7.68, 6.30 and 6.17, respectively. The two benzyloxy methylene protons were observed as singlet at 5.15. The rest of the methylenes and methine protons appeared as multiplet between 6.00-7.52. The remaining aromatic protons resonated between 2.50-3.22.

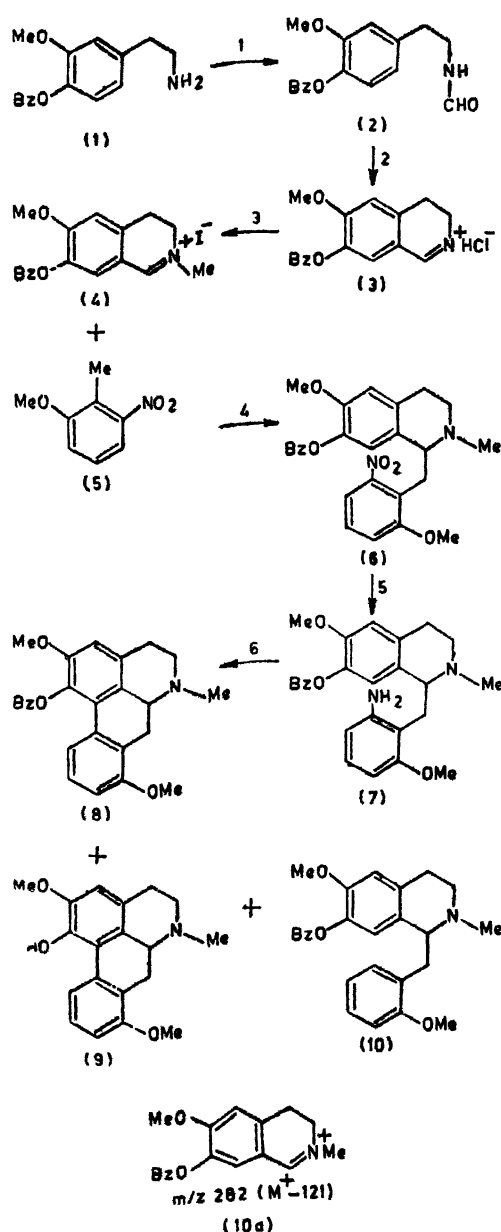
Hydrogenation³ of 6 with zinc and sulphuric acid gave 7 which showed the desired NH_2 band at 3340 in its spectrum. In the pmr spectrum the methyl and methoxy protons singlets appeared at 7.57, 6.25 and 6.18, respectively. The benzyloxy methylene and the rest of the methylenes and methine protons were observed at 5.10 and 6.00-7.36, respectively. The remaining aromatic protons appeared as multiplets between 2.50-3.83.

Pschorr cyclization of 7 afforded 1-hydroxy-2,8-dimethoxyaporphine (9). In the ir spectrum, a band for phenolic hydroxy group appeared at 3550. Its uv spectrum showed a band at 270 nm. On addition of a drop of 10% NaOH solution, this band shifted to 280 nm showing the presence of a phenolic-hydroxy function. In the pmr spectrum, methyl and methoxy protons singlets appeared at 7.43, 6.15 and 6.13, respectively. The methylenes and methine protons resonated between 6.08-7.50. The aromatic protons of positions C-3, C-9, C-10 and C-11 appeared as singlet, doublet, multiplet and doublet, respectively at 3.43, 3.18 ($J=9.0$ Hz), 2.72 and 1.80 ($J=9.0$ Hz). In the mass spectrum the molecular ion peak was observed at m/z 311 (M^+).

One of the products of the reaction was 1-benzyloxy-2,8-dimethoxyaporphine (8). Its methyl and methoxy protons singlets at 7.48, 6.19 and 6.17 were observed in its pmr spectrum. The benzyloxy methylene and methylenes and methine protons resonated at 5.34 and 6.00-7.50. The aromatic protons of positions C-3, C-9, C-10 and C-11 appeared at 3.41, 3.22 ($J=9.0$ Hz), 2.80 and 2.00 ($J=9.0$ Hz), respectively as singlet, doublet, multiplet and doublet. The remaining five aromatic protons appeared as singlet at 2.79. In the mass spectrum, the expected molecular ion peak was observed at m/z 401 (M^+).

Another product was 7-benzyloxy-6-methoxy-1-(2-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (10). In its pmr spectrum the methyl, methoxy and benzyloxy methylene protons appeared as singlets at 7.52, 6.31, 6.26 and 4.19, respectively. The other methylenes, methine and aromatic protons resonated between 6.13-7.50 and 2.45-3.80, respectively. The fragment ion at m/z 282 (10^+ , M^+-121) was in accordance with the isoquinolinium ion of 10.

† PMR chemical shifts in τ -scale and ir ν_{max} in cm^{-1} .



Reagents: 1. HCO_2Et ; 2. $\text{POCl}_3/\text{MeON}$; 3. $\text{MeI}/\text{C}_6\text{H}_6$; 4. EtONa ; 5. $\text{Zn}/\text{H}_2\text{SO}_4$; 6. $\text{NaNO}_2/\text{Zn}, \text{H}_2\text{SO}_4$.

Experimental

N-Formyl-7-benzyloxy-6-methoxyphenethylamine (2): A solution of 1 (19.2 g; 0.0747 mole) in HCO_2Et (200 ml) was refluxed at $70-80^\circ$ for 8 hr to afford the crude product which was purified by column chromatography over silica gel using C_6H_6 -EtOAc as eluent to give 2 as an oil (10.8 g; 0.0307 mole), yield 50.72%. (Found: C, 71.7; H, 6.82; N, 5.17. $\text{C}_{17}\text{H}_{19}\text{NO}_3$ requires C, 71.57; H, 6.71; N, 4.19%).

7-Benzyloxy-6-methoxy-3,4-dihydroisoquinoline hydrochloride (3): A mixture of 2 (2.7 g; 0.0094

mole), MeCN (75 ml) and distilled POCl_3 (7 ml) was heated at $80-90^\circ$ for 1 hr and stirred for another 4 hr to afford 3 as an oil (2.8 g; 0.0093 mole), yield 98.03%.

7-Benzyloxy-6-methoxy-3,4-dihydroisoquinoline methiodide (4): The free base from 3 in dry C_6H_6 (10 ml) was treated with MeI for 24 hr. The separated oil was warmed and cooled to give 4 (1.5 g; 0.0030 mole), yield 72.67%, m.p. $180-82^\circ$ (C_6H_6 - C_6H_{14}). (Found: C, 52.82; H, 4.82; N, 3.41. $\text{C}_{18}\text{H}_{20}\text{NO}_2\text{I}$ requires C, 52.81; H, 4.88; N, 3.42%).

7-Benzyloxy-6-methoxy-1-(2-nitro-6-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (6): A mixture of 4 (4.5 g; 0.0101 mole) and 2-nitro-6-methoxytoluene⁴ (5) (3.9 g; 0.0233 mole) was added to a solution of NaOEt [prepared by addition of Na metal (1.5 g) in absolute EtOH (60 ml)]. The reaction mixture was warmed for 15 min and kept for 2 days. It was then poured on crushed ice and extracted with EtOAc (6×25 ml). The organic layer was washed (H_2O), dried (anhyd. Na_2SO_4) and solvent removed to give a crude mixture which was purified by column chromatography over silica gel using C_6H_6 -EtOAc as eluent to afford unreacted 5 (2.5 g; 0.0149 mole) and 6 (2.4 g; 0.0050 mole), yield 36.73% as an oil. (Found: C, 69.10; H, 6.30; N, 5.87. $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_6$ requires C, 69.63; H, 6.29; N, 6.25%).

7-Benzyloxy-6-methoxy-1-(2-amino-6-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (7): A solution of 6 (4.4 g; 0.0098 mole) in MeOH (120 ml) was reduced with zinc dust (15 g) and 4 N H_2SO_4 (100 ml). It was basified with ammonia and extracted with EtOAc (6×30 ml). The organic layer was washed (H_2O), dried (anhyd. Na_2SO_4) and solvent removed to afford the crude product (3.1 g) which was purified by dry column chromatography on neutral alumina using C_6H_6 -EtOAc-Et₃NH (70 : 26 : 4) as eluent to give 7 as oil (2.3 g; 0.0055 mole), yield 99.99%. (Found: C, 74.00; H, 7.30; N, 6.67. $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_3$ requires C, 74.61; H, 7.22; N, 6.69%).

Pschorr cyclization of (7): A solution of the foregoing amine (7) (2.1 g; 0.0050 mole) in MeOH (30 ml) and 2 N H_2SO_4 (30 ml) cooled to 0° was treated with a solution of NaNO_2 (3 g) in H_2O (20 ml). It was stirred for 30 min and heated at $80-90^\circ$ for 30 min. To this hot solution, zinc dust (10 g) and 10 N H_2SO_4 (16 ml) was added and heated for another 30 min. The acidic solution was basified with ammonia and extracted with EtOAc (8×25 ml). The organic layer was washed (H_2O), dried (anhyd. Na_2SO_4) and solvent removed to afford the crude mixture which was separated by dry column chromatography over silica gel using EtOAc as eluent to afford 1-hydroxy-2,8-dimethoxyaporphine (9) [(140 mg; 0.0004 mole), yield 8.96%, hydrobromide, m.p. 238° (dec). (Found: C, 58.80; H, 5.32; N, 3.57. $\text{C}_{19}\text{H}_{22}\text{NO}_3\text{Br}$ requires C, 58.31; H, 5.37; N, 3.58%)] ; 1-benzyloxy-2,8-dimethoxyaporphine (8) [(84.8 mg; 0.0002 mole), yield 4.20%.

(Found : C, 77.72 ; H, 6.69 ; N, 3.47. $C_{26}H_{27}NO_8$ requires C, 77.80 ; H, 6.73 ; N, 3.49%) and 7-benzyl-oxy-6-methoxy-1-(2-methoxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (10) [(121 mg ; 0.0003 mole), yield 5.98%, m.p. 94°. (Found : C, 77.30 ; H, 7.38 ; N, 3.14. $C_{26}H_{29}NO_8$ requires C, 77.39 ; H, 7.24 ; N, 3.47%)].

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