

NOVEL ($\pm$)-1-PHENYLTETRAHYDROISOQUINOLINES AND 1-PHENYLISOQUINOLINES:
POTENTIAL INTERMEDIATES IN ALKALOID SYNTHESIS

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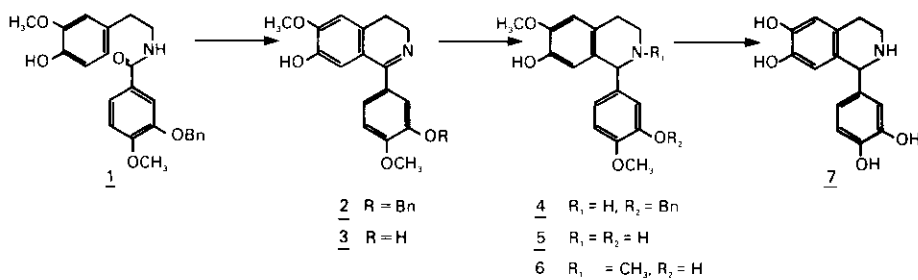
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Abstract - Synthesis of several novel ($\pm$)-1-phenyltetrahydroisoquinolines and 1-phenylisoquinolines, structurally related to the 1-benzylisoquinoline alkaloids norreticuline, reticuline, tetrahydropapaveroline and papaverine, by the Bischler-Napieralski route is reported.

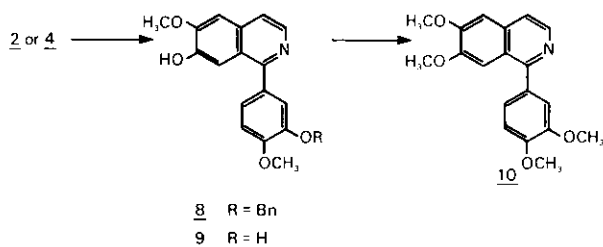
1-Benzyl substituted isoquinolines represent a well known group of natural alkaloids, are endogenous precursors in biosynthesis, and intermediates in synthesis of many polycyclic isoquinoline alkaloids. The corresponding 1-phenyl congeners are relatively rare among natural products, and limited at present to a few alkaloids isolated from plants of the family of Orchidaceae.²⁻⁵ We now report synthesis and characteristic properties of racemic 1-phenyl-substituted analogs of ($\pm$)-norreticuline, ($\pm$)-reticuline, ($\pm$)-tetrahydropapaveroline and papaverine. Although ($\pm$)-1-phenyltetrahydroisoquinoline 7 was readily available by a Pictet-Spengler synthesis,⁶ further conversion into other analogs such as 5 seemed complicated because of the extreme sensitivity of 7 to autoxidation, suggesting that 5 might better be available by the Bischler-Napieralski route. This has now been accomplished from benzamide 1 prepared by conventional chemistry, affording by cyclization with phosphorous oxychloride in acetonitrile 3,4-dihydroisoquinoline 2.⁷ Conversion of O-benzyl protected isoquinoline 2 into diphenol 5 was accomplished by acid hydrolysis, affording first 3, and 5 after reduction of 3 with sodium borohydride in methanol. Compound 5 also was obtained by reduction of 2 with sodium borohydride followed by hydrolysis of 4 with acid.

Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.

O-Demethylation of 5 with refluxing 48% HBr afforded tetraphenol 7, an analog of ($\pm$)-tetrahydropapaveroline. Treatment of 3 with methyl iodide in methanol, followed by reduction of the quaternary methoiodide with sodium borohydride, gave N-methylated diphenol 6, a C-nor analog of ($\pm$)-reticuline.



Aromatization of dihydroisoquinoline 2 over Pd/C catalyst in refluxing toluene^{8,9} proved difficult, and was better accomplished with tetrahydroisoquinoline 4, affording isoquinoline 8 as minor, and diphenol 9 as the major reaction product. Although considerable amounts of by-products were formed in the aromatization, phenylisoquinolines 8 and 9 could readily be obtained by chromatographic separation. Diphenol 9 upon treatment with an ethereal solution of diazomethane in methanol afforded the known tetramethylether 10, a C-nor analog of papaverine.¹⁰ Synthetic utility of tetrahydroisoquinoline 5 and isoquinoline 9 for preparing polycyclic isoquinoline alkaloids is being investigated.



EXPERIMENTAL SECTION

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed in the Laboratory of Analytical Chemistry (Dr. David Johnson). Silica gel 60 (230-400 mesh) from Aldrich Chemical Co. was used for chromatography with a flash-chromatography column. Chemical ionization (CI) mass spectra (m/e) were obtained by using a Finnigan-1015D spectrometer. $^1\text{H-NMR}$ spectra were determined by using a Varian XL-300 spectrometer with Me_4Si as an internal standard (δ in ppm, J in Hz). UV-spectra were measured using a Hewlett-Packard 8450A UV-VIS spectrometer.

Preparation of N-(4-Hydroxy-3-methoxyphenethyl)-4-methoxy-3-benzyloxybenzamide (1):

To a solution of 3-benzyloxy-4-methoxybenzoyl chloride (2.7g; 10 mmol) in CHCl_3 , was added 4-hydroxy-3-methoxyphenethylamine (1.67 g; 10 mmol), Na_2CO_3 (1.06 g) and water (2 ml). The mixture was stirred at room temperature for 18 h. Then the inorganic salt was removed by filtration and the organic filtrate was washed with water, dried and concentrated to give a white solid. Recrystallization from $\text{CHCl}_3/\text{Et}_2\text{O}$ gave 2 as a white solid (3.5 g, 86%); mp $98-100^\circ\text{C}$; $^1\text{H-NMR}$ (CDCl_3): δ 2.8 (t, $J=7.5$ Hz, 2H, CH_2), 3.6 (m, 2H, HNCH_2), 3.8 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 5.15 (s, 2H, OCH_2), 6.0 (bt, 1H, NH), 6.7-7.5 (m, 10H, Ar); CI-MS m/e 408 ($\text{M}^+ + 1$).

Preparation of 3,4-Dihydro-6-methoxy-7-hydroxy-1-(3-benzyloxy-4-methoxyphenylisoquinoline) (2):

To a solution of 1g (2.5 mmol) of 1 in 10 ml of MeCN was added 1 ml of POCl_3 under Ar atmosphere. After initial exothermic reaction ceased, the reaction mixture was refluxed at $85-100^\circ\text{C}$ for $1\frac{1}{2}$ h under Ar. Then the mixture was concentrated and basified with conc. aq. NH_3 . A yellow solid precipitated and was filtered, washed with water and dried. Recrystallization from $\text{HOAc}/\text{H}_2\text{O}$ afforded 2 (900 mg; 95%); mp $153-154^\circ\text{C}$; $^1\text{H-NMR}$ (CD_3OD): δ 3.1 (bs, 2H, $\text{CH}_2\text{-CH}_2\text{N}$), 3.95 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 3.9 (m, 2H, N-CH_2), 5.2 (s, 2H, OCH_2) 6.9-7.5 (m, 10H, Ar); CI-MS m/e 390 ($\text{M}^+ + 1$).

Preparation of 1,2,3,4-Tetrahydro-6-methoxy-7-hydroxy-1-(3-hydroxy-4-methoxyphenylisoquinoline) (5):Method A

A suspension of benzyloxyisoquinoline 2 (600 mg; 1.5 mmol) in 6N HCl (20 ml) was refluxed for $2\frac{1}{2}$ h. Then the reaction mixture was cooled and basified with conc. aq. NH_3 . A yellow solid precipitated and was filtered, washed with water and dried. Recrystallization from $\text{MeOH}/\text{Et}_2\text{O}$ afforded 3,4-dihydroisoquinoline 3 (450 mg; 97%); mp 193°C ; $^1\text{H-NMR}$ (CDCl_3): δ 2.8 (t, $J = 7.5$ Hz,

2H, $\text{CH}_2\text{-CH}_2\text{N}$), 3.7 (t, $J = 7.5$ Hz, 2H, NCH_2), 3.9 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.8-7.1 (m, 5H, Ar); CI-MS m/e 300 ($M^+ + 1$). To a solution of 3,6-dihydroisoquinoline 3 (299 mg; 0.1 mmol) in MeOH (20 ml), was added NaBH_4 (120 mg) in small portions at 0-5°C. The reaction mixture was brought to room temperature and stirred for 1 h. Then the mixture was concentrated, diluted with water and extracted with CHCl_3 . The organic layer was washed with water dried and concentrated to afford a white solid. Recrystallization from $\text{CHCl}_3/\text{Et}_2\text{O}$ gave 5 as a white solid (187 mg; 62%); mp 185-186°C; $^1\text{H-NMR}$ (CDCl_3): δ 2.6-3.2 (m, 6H, $\text{CH}_2\text{-CH}_2$ and OH), 3.85 (s, 3H, OCH_3), 4.9 (s, 1H, NCH), 6.3 (s, 1H, Ar), 6.55 (s, 1H, Ar), 6.75 (m, 3H, Ar); CI-MS m/z 302 ($M^+ + 1$); UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm(ϵ): 284(11612), 234(sh) (21505).

Method B

To a solution of 3,4-dihydroisoquinoline 2 (1g; 2.5 mmol) in methanol (20 ml), was added NaBH_4 (700 mg) in small portions at 0-5°C. The reaction mixture was brought to room temperature and stirred for 2 h. The mixture was concentrated, acidified with 2N HCl and then basified with conc. aq. NH_3 . A solid precipitated and was filtered and dried. Recrystallization from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ gave 4 as a white solid (950 mg; 95%); mp 137-138°C; $^1\text{H-NMR}$ (CDCl_3): δ 2.6-3.2 (m, 5H, $\text{CH}_2\text{-CH}_2$ and OH), 3.9 (s, 6H, OCH_3), 4.9 (s, 1H, NCH), 5.1 (s, 2H, OCH_2), 6.3 (s, 1H, Ar), 6.6 (s, 1H, Ar), 6.8 (s, 3H, Ar), 7.3 (m, 5H, Ar); CI-MS m/z 392 ($M^+ + 1$). A suspension of tetrahydroisoquinoline, 4, (900 mg; 2.3 mmol) in 6N HCl (10ml) was refluxed for 2 h. The mixture was cooled, basified with conc. aq. NH_3 and extracted with CHCl_3 . The organic layer was washed with water, dried and concentrated to give a solid. Recrystallization from $\text{CHCl}_3/\text{Et}_2\text{O}$ afforded 5 as a white solid (500 mg; 72%); mp 185-186°C and identical with material prepared by Method A. An analytical sample was made by converting the free base 5 into its hydrochloride salt; mp 261-262°C; Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_4\text{Cl}$: C, 60.44; H, 5.96; N, 4.14; Cl, 10.49. Found: C, 60.38; H, 5.99; N, 4.06; Cl, 10.56%.

Preparation of 1,2,3,4-Tetrahydro-6-methoxy-2-methyl-7-hydroxy-1-(3-hydroxy-4-methoxyphenyl)-isoquinoline (6):

To a solution of 3,4-dihydroisoquinoline, 3, (1.99g; 6.6 mmol) in 40 ml of methanol, was added 2 ml of MeI. The reaction mixture was kept at room temperature for 18 h. The mixture was concentrated and dry ether was added. A pale yellow solid (mp 143°C) precipitated and was filtered. It was directly used for the next reaction. To a solution of the quaternary salt (1.5 g) in MeOH (10 ml), was added NaBH_4 (700 mg) at 0-5°C. The mixture was stirred at room temperature for 2 h. The mixture was concentrated, acidified with 2N HCl and basified with conc. aq. NH_3 . The mixture was extracted with CH_2Cl_2 . The extract was washed with water, dried and concentrated to give a solid.

Recrystallization from MeOH/Et₂O gave 6 as a white solid (1.2g; 57%); mp 160-161°C; ¹H-NMR (CDCl₃): δ 2.2 (s, 3H, NCH₃), 2.5-3.2 (m, 4H, CH₂-CH₂), 3.8 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 4.0 (s, 1H, NCH), 6.2 (s, 1H, Ar), 6.5 (s, 1H, Ar), 6.75 (m, 3H, Ar); CI-MS m/z 316 (M⁺+1); UV λ_{max}^{MeOH} nm (ε): 282 (20145), 234 (sh) (38349). An analytical sample was made by converting the free base 6 into its hydrochloride salt; mp 180°C; Anal. Calcd. for C₁₈H₂₂NO₄Cl 1½ H₂O: C, 57.06; H, 6.65; N, 3.69; Cl, 9.39. Found: C, 56.82; H, 6.79; N, 3.62; Cl, 9.33%.

Preparation of 1,2,3,4-Tetrahydro-6,7-dihydroxy-1-(3,4-dihydroxyphenylisoquinoline) (7):

A solution of tetrahydroquinoline, 5, (130 mg; 0.43 mmol) in 2 ml of 48% HBr was refluxed for 2h under Ar. The reaction mixture was evaporated to dryness to give a foamy solid. Recrystallization from acetone gave tetrahydroxyisoquinoline (7), as its hydrobromide salt which was identical with that obtained by Pictet-Spengler reaction of 3,6-dihydroxyphenylethylamine with 3,6-dihydroxybenzaldehyde;⁶ mp 207°C; ¹H-NMR (D₂O): δ 2.72-3.44 (m, 4H, CH₂-CH₂), 5.44 (s, 1H, NCH), 6.32-6.92 (m, 5H, Ar); CI-MS m/e 274 (M⁺+1); UV λ_{max}^{MeOH} nm(ε): (free base) 286 (7587), 230(sh) (12594); Anal. Calcd. for C₁₅H₁₆NO₄Br·1½ H₂O: C, 47.25; H, 5.02; N, 3.67; Br, 20.96. Found: C, 47.14; H, 5.41; N, 3.41; Br, 20.57%.

Preparation of 7-Hydroxy-6-methoxy-1-(3-benzyloxy-4-methoxyphenylisoquinoline) (8) and

7-Hydroxy-6-methoxy-1-(3-hydroxy-4-methoxyphenylisoquinoline) (9):

To a hot solution of tetrahydroisoquinoline 4, (1.8 g; 4.6 mmol) in 30 ml of toluene, was added 2.0 g of 10% Pd/C. The reaction mixture was refluxed for 18 h. Then the catalyst was filtered off and washed with CHCl₃. The filtrate was concentrated and passed through a column of silica gel. Elution with CHCl₃/MeOH (1%) gave a colorless solid. Recrystallization from MeOH/Et₂O gave 8 as a colorless solid (70 mg; 4%); mp 176-177°C; ¹H-NMR (CDCl₃): δ 3.9 (s, 3H, OCH₃), 4.05 (s, 3H, OCH₃), 5.15 (s, 2H, OCH₂), 6.95-7.45 (m, 11H, Ar), 8.4 (d, J = 7.0 Hz, 1H, Ar); CI-MS m/e 388 (M⁺+1). Further elution with CHCl₃/MeOH (3%) gave a yellow solid. Recrystallization from CHCl₃/Et₂O gave 9 as a yellow solid (500 mg; 36%); mp 125-126°C; ¹H-NMR (CDCl₃): δ 3.9 (s, 3H, OCH₃), 4.05 (s, 3H, OCH₃), 4.05 (s, 3H, OCH₃), 6.85-7.55 (m, 6H, Ar), 8.35 (d, J = 7.0 Hz, 1H, Ar); CI-MS m/e 298 (M⁺+1); UV λ_{max}^{MeOH} nm (ε): 335 (14012), 289 (12314), 237 (61910). An analytical sample was made by converting the free base 9 into its hydrochloride salt; mp 231-233°C; Anal. Calcd. for C₁₇H₁₆NO₄Cl·1.1H₂O: C, 58.04; H, 4.87; N, 3.98; Cl, 10.07. Found: C, 58.17; H, 5.20; N, 3.97; Cl, 10.05%.

Preparation of 6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-isoquinoline, (10):

To a solution of isoquinoline, 9, (500 mg, 1.6 mmol) in MeOH (5 ml), was added a solution of CH_2N_2 (400 mg) in ether and stirred at room temperature for 18 h. The reaction mixture was concentrated and passed through a column of silica gel. Elution with $\text{CHCl}_3/\text{MeOH}$ (1%) gave a solid.

Recrystallization from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ afforded 10 as a white solid (300 mg; 55%); mp 153-154°C; (reported¹⁰ mp 154°C). $^1\text{H-NMR}$ (CDCl_3): δ 3.9 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 7.0-7.5 (m, 6H, Ar), 8.45 (d, $J = 7.0\text{Hz}$, 1H, Ar); CI-MS m/e 326 ($\text{M}^+ + 1$).

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