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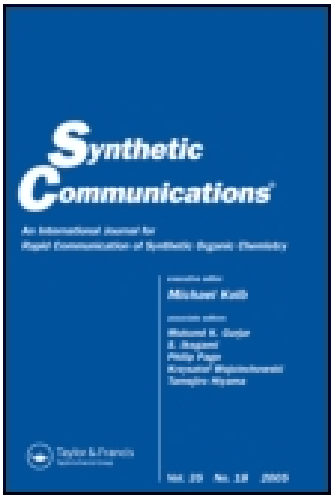

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Synthesis of Anabaseine and Anabasine Derivatives: Structural Modifications of Possible Nicotinic Agonists

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Abstract: Coupling nicotinoyl chloride with 3,4-dimetoxyphenethylamine under Bischler-Napieralski cyclization afforded the isoquinoline (**4**) in good yield. This latter was used as starting material to obtain with only hydrobromic acid a product with demethylation at the position 7 (**5**). In addition, treatment of (**4**) with $NaBH_4$/MeOH gave 6,7-dimetoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**6**) and unexpectedly, under mild reduction of the pyridine moiety with H_2/PtO_2/AcOH/, gave 6,7-dimetoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**7**) as the title compound. The unusual chemical reactivity of **4** onto acidic conditions and catalytic hydrogenation allowed us to obtain anabaseine and anabasine derivatives under mild conditions.

Keywords: anabaseine, anabasine, 1-(pyridin-3-yl)isoquinoline, nicotinic acetylcholine receptor

INTRODUCTION

Nicotine (**1**), as a main component of cigarette smoke, affects organisms through nicotinic acetylcholine receptors. In addition to the central nervous

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system, nicotine is known to affect many other tissues such as the respiratory tract, skin, hematological cells, and vascular and immune tissues.[1,2] Thus, nicotinic acetylcholine receptors (nAChRs) play an important role in the mediation of synaptic signals in the nervous systems of animals.[3] At the molecular level, anabaseine (**2**) differs from nicotine and anabasine (**3**) by having a tetrahydropyridyl ring whose imine double bond is electronically conjugated with the 3-pyridyl ring (Fig. 1). This causes its two rings to be approximately coplanar in their relative orientation, whereas the two rings in the tobacco alkaloids nicotine and anabasine are almost perpendicular to each other.[4,5]

The syntheses of anabaseine consist of CsF on CaO-catalyzed cyclization of aromatic amides,[6] from 2-piperidone aminal and a nicotinic acid derivatives via acid-catalyzed rearrangement of a nicotinoylpiperidone salt,[7] and by α-alkylation of (*E*)-N-(1-(pyridin-3-yl)ethylidene)propan-2-amine with ethylenetetramethyldisilyl-protected ω-bromoamines, followed by ring closure.[8] On the other hand, anabasine derivatives have been synthesized from racemic 2-hydroxymethyl–piperidine, racemic pipecolic acid, or (*S*)-(-)-piperidine-1,2-dicarboxylic-acid-1-tert-Bu ester,[9] and recently through the cyclodehydration of achiral or racemic aryl-δ-oxoacids with (*R*)-phenylglycinol to give (-)-anabasine.[10] Theoretical and molecular modeling studies have been conducted among anabaseine analogues to provide valuable tools for nAChR drug-receptor structure–function relationships.[11] The position of a benzylidene moiety attachment to anabaseine analogues has effects on the potency of this class of agonists in practical drug design against Alzheimer's disease.[12] The annulation of a rigid system into the tetrahydropyridyl ring such as substituted benzene ring with electron-donating groups would help to improve the pharmacological properties of this type of alkaloid with simple structural modifications.

In this communication, we describe the formation of 6-methoxy-7-hydroxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline (**5**), 6,7-dimethoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**6**), and 6,7-dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**7**) starting from 6,7-dimethoxy-1-(pyridine-3-yl)-3,4-dihydroisoquinoline (**4**) (Scheme 1).

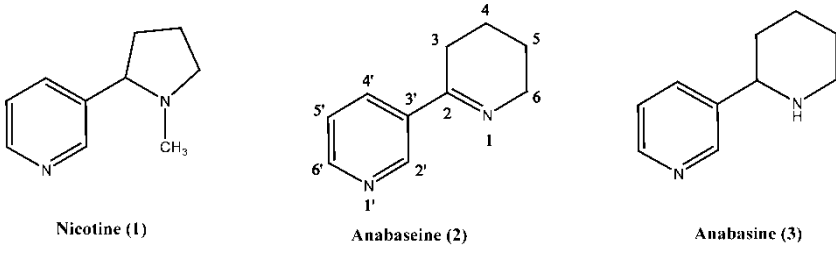

Figure 1. Nicotine (1), Anabaseine (2), Anabasine (3).

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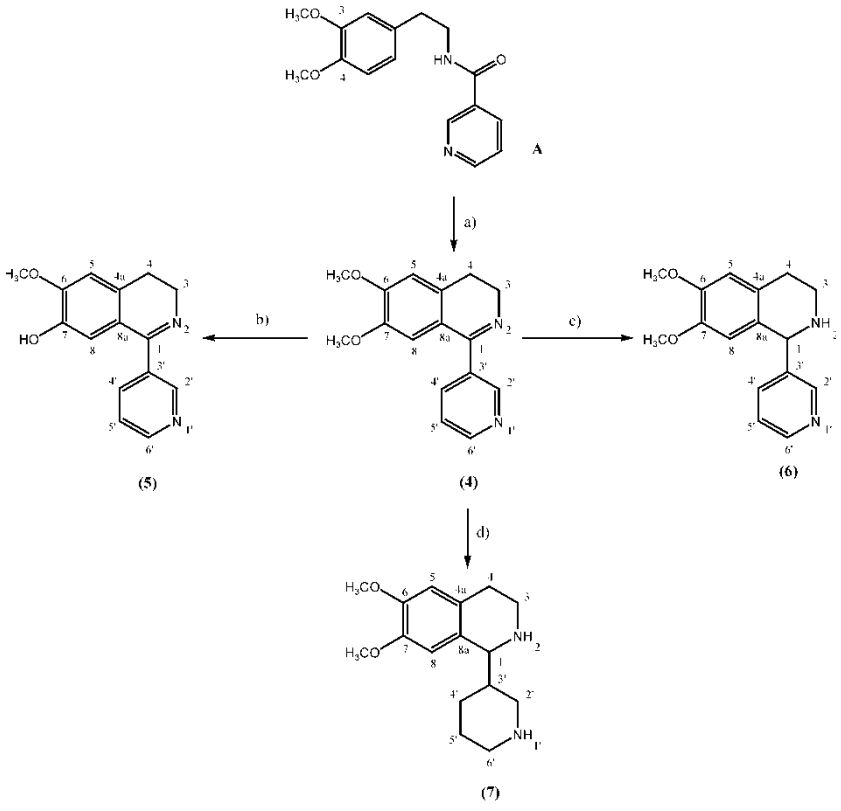

a) $POCl_3$/toluene/reflux; b) 50% HBr/AcOH/100°C, 1 h; c) $NaBH_4$/MeOH/r t; d) H_2/PtO_2/AcOH/r t, 1 h.

Scheme 1. Reagents and experimental conditions.

RESULTS AND DISCUSSION

The reaction between 3,4-dimethoxyphenethylamine and nicotinoyl chloride afforded the corresponding amide that, without further purification, was used through the standard Bischler–Napieralski reaction to give (**4**) in good yield.[13] Because this precursor can be obtained in an efficient way, the synthesis of anabaseine derivatives was carried out to study the reactivity of this type of heterocycle under acidic and reductive conditions. Thus, the demethylation of the methoxyl groups by heating with HBr/AcOH should give a catechol derivative as the main compound. This reaction induced by HCl or HI has been described in isoquinoline derivatives, for instance, as potential antidepressant drugs.[14] However, (**4**) unexpectedly afforded a product characterized as 6-methoxy-7-hydroxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline (**5**). The partial hydrolysis of the methoxyl group at C-7 was observed in the hydrolysis of the methoxyl group at C-1 in aporphines as nornuciferina,[15] being possibly attributable to steric hindrance between the

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pyridine ring and the isoquinoline framework. In this sense, the chemical shifts of the *O*-7-CH_3 and *O*-6-CH_3 groups at δ 3.73 and 3.94 ppm, respectively, indicated to us a shield evident for the first one. This could be attributed to the loss of the anisotropic effect from the aromatic ring on the methoxyl group at C-7, probably due to the lack of coplanarity between both, and the proximity and rotation of the pyridine ring at C-1. On the other hand, several reduction methods were used to explore the reactivity of (**4**) under reductive conditions. Using $NaBH_4$ in MeOH as solvent afforded 6,7-dimethoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**6**) in high yield, and this was an effective way to obtain anabasine derivatives. However, the mild catalytic hydrogenation under PtO_2 as catalyst to gave a product characterized as 6,7-dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**7**), which presented the complete reduction of both the pyridine ring and the imine bond. This unusual hydrogenation has been described by us in a small group of isoquinoline alkaloids called "oxoisoaporphines," whose reactivity has been determined either by the partial or total unsaturation of the isoquinoline skeleton.[16] Therefore, the formation of a single product under mild hydrogenation conditions using the Adam's catalyst would be useful for the preparation of piperidine derivatives attached to substituted isoquinolines at C-1.

EXPERIMENTAL

Melting points were determined on a Reichert-Jung Galen III Kofler hot stage and are uncorrected. Column chromatography was performed on Merck silica gel 60, 230–400 mesh, and thin-layer chromatography (TLC) was performed on Merck silica gel G. Mass spectra of high and low resolution were carried out on the Micromass Autospec-Q and HP-5988A spectrometers, respectively. The infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. NMR spectra were recorded in $CDCl_3$ using a Bruker AMX 300 instrument operating at 300.13 MHz (^{1}H) or 75.48 MHz (^{13}C).

All solvents and reagents were obtained from either Aldrich Chemical Co. or Merck. Methanol, dichloromethane, tetrahydrofuran, and diethyl ether were dried using standard procedures.

Synthesis of *N*-(3,4-dimethoxyphenethyl)nicotinamide (A)

Nicotinoyl chloride (1 g, 5.51 mmol) was added into a mixture of THF (40 mL) and 40 mL of 10% aqueous NaOH solution in an ice bath with stirring. Later on, 3,4-dimethoxyphenethylamine (0.92 mL, 5.51 mmol) dissolved in 20 mL of THF was added dropwise to the mixture during 1 h. The formed white precipitate was filtered off, and the ether layer of the filtrate was evaporated to leave the residue. The precipitates and the residue were combined and dissolved in CH_2Cl_2. The organic solution was washed

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successively with 10% aqueous HCl solution, 10% aqueous NaOH solution, and water and dried over Na_2SO_4. Removal of the solvent by evaporation left the residue, which was purified by column chromatography on silica gel (eluted by CH_2Cl_2 containing 5% MeOH) to give the corresponding benzamide derivative **A** (1.33 g, 85%) as brownish oil.

^{1}HNMR δ ($CDCl_3$, ppm): 2.88 (t, $J = 8.4$ Hz, 2H, CH_2), 3.71 (t, $J = 8.1$ Hz, 2H, CH_2), 3.83 (s, 3H, *O*-4-CH_3), 3.85 (s, 3H, *O*-3-CH_3), 6.39 (bs, 1H, N-H), 6.73–6.83 (m, 3H, H-1, H-4, H-5), 7.36 [dd, J (4,5) = J (5,6) = 6.0 Hz, 1H, H-5′], 8.06 [dd, J (4,5) = 11.7 Hz; J (4,6) = 2.7 Hz, 1H, H-4′], 8.67 [dd, J (6,5) = 5.7 Hz; J (6,4) = 2.0 Hz, 1H, H-6′], 8.87 [d, J (2,4) = 1.2 Hz, 1H, H-2′]. ^{13}C-NMR δ ($CDCl_3$, ppm): 35.08, 41.27, 55.81, 55.86, 111.36, 111.79, 120.64, 123.53, 130.29, 130.99, 135.14, 147.51, 147.77, 149.10, 152.01, 165.45. IR (KBr, ν, cm^{-1}): 3055 (N-H), 1653 (NC═O). EI-MS (m/z): 286.25 (M^+, 100). EI-HRMS calcd. for $C_{16}H_{18}N_2O_3$ 286.1317; found 286.1317.

Synthesis of 6,7-Dimethoxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline (4)

N-(3,4-Dimethoxyphenethyl)nicotinamide (**A**) (6.7 g, 23.4 mmol) was dissolved in 30 mL of toluene and heated with $POCl_3$ (30 mL) at 130°C for 3 h. The solvent and the excess reagent were removed by evaporation in vacuum, and the residual reagent was decomposed by adding MeOH and 10% HCl aq. The acidic solution was washed once with Et_2O, made alkaline with 10% NH_4OH aq., and extracted with CH_2Cl_2. The extract was washed with H_2O and dried, and the solvent was evaporated. The residue was purified by column chromatography on silica gel (eluted by CH_2Cl_2 containing 10% MeOH). Recrystallization from cyclohexane gave 4.74 g (75%) of **4** as brownish needles.

^{1}H-NMR δ ($CDCl_3$, ppm): 2.74 (t, $J = 7.4$ Hz, 2H, H-4), 3.73 (s, 3H, *O*-7-CH_3), 3.83 (t, $J = 7.4$ Hz, 2H, H-3), 3.94 (s, 3H, *O*-6-CH_3), 6.70 (s, 1H, H-8), 6.79 (s, 1H, H-5), 7.37 [dd, J (4,5) = 7.3 Hz; J (5,6) = 4.9 Hz, 1H, H-5′], 7.94 [dd, J (4,5) = 7.8 Hz; J (4,6) = 1.8 Hz, 1H, H-4′], 8.68 [dd, J (6,5) = 4.8 Hz; J (6,4) = 1.5 Hz, 1H, H-6′], 8.83 [d, J (2,4) = 1.3 Hz, 1H, H-2′]. ^{13}C-NMR δ ($CDCl_3$, ppm): 25.82, 47.74, 56.04, 56.16, 110.48, 110.87, 120.97, 123.16, 132.50, 134.77, 136.17, 147.31, 149.78, 150.29, 151.28, 164.36. IR (KBr, ν, cm^{-1}): 1636 (C═N). Mp 117–118°C. EI-MS (m/z): 268.20 (M^+, 100). EI-HRMS calcd. for $C_{16}H_{16}N_2O_2$ 268.1211; found 268.1208.

Synthesis of 6-Methoxy-7-hydroxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline (5)

A solution of **4** (1.2 g, 4.48 mmol) was dissolved over a 50% AcOH/HBr mixture and heated with stirring at 100 °C for 1 h under an Ar atmosphere.

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Later on, the organic residue was washed with a 20% $NaHSO_3$ solution, the pH was adjusted at 8 with NH_4OH, and the residue was extracted with CH_2Cl_2. The extracts were then dried with Na_2SO_4 and concentrated in vacuum to be subjected to silica-gel flash chromatography eluted with dichloromethane–methanol 9:1 (v/v) to afford (**5**) (0.680 g, 67%) as yellow needles.

^{1}HNMR δ ($CDCl_3$, ppm): 2.67 (t, $J = 7.6$ Hz, 2H, H-4), 3.71 (t, $J = 7.6$ Hz, 2H, H-3), 3.85 (s, 3H, *O*-6-CH_3), 6.59 (s, 1H, H-8), 6.95 (s, 1H, H-5), 7.50 [dd, J (4,5) = 7.9 Hz; J (5,6) = 4.9 Hz, 1H, H-5′], 7.90 [dd, J (4,5) = 8.1 Hz; J (4,6) = 2.0 Hz, 1H, H-4′], 8.66 [dd, J (6,5) = 4.8 Hz; J (6,4) = 1.6 Hz, 1H, H-6′], 8.68 [d, J (2,4) = 1.6 Hz, 1H, H-2′], 9.20 (bs, 1H, OH). ^{13}C NMR δ ($CDCl_3$, ppm): 25.53, 47.61, 56.16, 111.77, 114.77, 120.89, 123.66, 130.63, 134.64, 136.51, 145.14, 149.61, 150.50, 150.54, 164.07. IR (KBr, ν, cm^{-1}): 3427, 1297 (OH), 1639 (C=N). Mp 114–115°C. EI-MS (m/z): 254.25 (M^+, 100). EI-HRMS calcd. for $C_{15}H_{14}N_2O_2$ 254.1055; found 254.1128.

Synthesis of 6,7-Dimethoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (6)

A suspension of (**4**) (0.375 g, 1.39 mmol) in methanol (50 mL) was carried out in an ice-water bath at 0°C. After 5 min, $NaBH_4$ (2 g, 52.6 mmol) was added in portions, resulting in effervescence and solution of the material. This suspension was stirring for 20 min and diluted with water. After adjusting the pH at 8–9 with AcOH solution, the mixture was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluted by CH_2Cl_2 containing 10% MeOH) to give 0.310 g (83%) of (**6**) as brownish oil.

^{1}H NMR δ ($CDCl_3$, ppm): 2.74–2.91 (m, 2H, H-4), 3.06–3.17 (m, 2H, H-3), 3.61 (s, 3H, *O*-7-CH_3), 3.85 (s, 3H, *O*-6-CH_3), 5.07 (s, 1H, H-1), 6.15 (s, 1H, H-8), 6.62 (s, 1H, H-5), 7.22 [dd, J (4,5) = 7.7 Hz; J (5,6) = 4.9 Hz, 1H, H-5′], 7.53 [d, J (4,5) = 7.8 Hz, 1H, H-4′], 8.51 [d, J (6,5) = 4.1 Hz, 1H, H-6′], 8.54 [d, J (2,4) = 1.1 Hz, 1H, H-2′]. ^{13}C NMR δ ($CDCl_3$, ppm): 29.00, 41.70, 55.86, 55.89, 58.80, 110.60, 111.60, 123.50, 127.70, 128.40, 136.40, 140.00, 147.30, 147.90, 149.00, 150.30. IR (KBr, ν, cm^{-1}): 3384, 1520 (NH). EI-MS (m/z): 270.25 (M^+, 100). EI-HRMS calcd. for $C_{16}H_{18}N_2O_2$ 270.0429; found 270.0433.

Synthesis of 6,7-Dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (7)

A solution of (**4**) (0.3 g, 1.12 mmol) dissolved in AcOH (50 mL) was hydrogenated at 80 psi over PtO_2 (100 mg) as catalyst at room temperature for 24 h. The colorless solution was diluted with 100 mL of water, neutralized with

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NH_4OH, and extracted with CH_2Cl_2 (200 mL). The organic extract was dried over Na_2SO_4 and concentrated to dryness, and the residue was subjected to flash column chromatography on silica gel and eluted with 90:10 CH_2Cl_2–MeOH (v/v) to give **7** (0.102 g, 33% yield) as a brownish amorphous solid.

^{1}H NMR δ ($CDCl_3$, ppm): 1.81 (m, 4H, H-4′/H-5′), 2.35 (m, 2H, H-3′), 2.57 (m, 4H, H-2′/H-6′), 2.57–2.72 (m, 2H, H-4), 2.86–3.13 (m, 2H, H-3), 3.80 (s, 3H, *O*-7-CH_3), 3.87 (s, 3H, *O*-6-CH_3), 3.99 (m, 1H, H-1), 6.52 (s, 1H, H-5), 6.70 (s, 1H, H-8). ^{13}CNMR δ ($CDCl_3$, ppm): 24.63, 27.82, 29.45, 40.16, 42.23, 45.39, 45.98, 55.77, 56.05, 58.26, 109.05, 111.70, 128.11, 128.40, 2 × 147.30. IR (KBr, ν, cm^{-1}): 3437, 1521 (NH). Mp 112–113 °C. EI-MS (m/z): 276.20 (M^+, 100). EI-HRMS calcd. for $C_{16}H_{24}N_2O_2$ 276.1837; found 276.1911.

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