An Improved Synthesis of 5,6,7,8-Tetrahydro-1,7-naphthyridine - A Conformationally-Restricted Analog of 2-(3-Pyridyl)ethylamine

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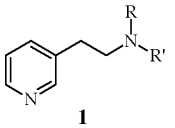
Received October 23, 2000

The 5,6,7,8-tetrahydro-1,7-naphthyridine (**7**) pharmacophore has the potential to serve as a conformationally-locked analog of the pharmacologically active 2-(3-pyridyl)ethylamine (**1**) core structure. This paper describes the synthesis of 5,6,7,8-tetrahydro-1,7-naphthyridine (**7**) *via* a five-step sequence, which affords a significant improvement over previously reported syntheses.

J. Heterocyclic Chem., **38**, 535 (2001).

Introduction.

The 2-(3-pyridyl)ethylamine pharmacophore (**1**) has been documented to possess a range of pharmacological activities, including potent binding to members of the dopaminergic [1] and cholinergic [2] receptor families. Of particular interest is the suggestion that **1** is bioisosteric to the 3-hydroxyphenylethylamine pharmacophore found in many dopamine agonists [1]. This replacement of 3-hydroxyphenyl with pyridyl could potentially lead to agents with improved pharmacokinetic properties, given the low bioavailability and short *in vivo* half-lives associated with the former functionality. In addition, replacement of the aromatic ring of phenylethylamines with the 3-pyridyl functionality has been shown to improve aqueous partitioning [3], thus improving the "drug-like" potential of the resultant analogs. Though pharmacological studies have been carried out on compounds in which the 2-(3-pyridyl)ethylamine pharmacophore is constrained within a pyrido[3,4-*d*]azepine ring [2], there have not been any reports on analogs containing conformationally restrained 5,6,7,8-tetrahydro-1,7-naphthyridine (**7**) core structure.



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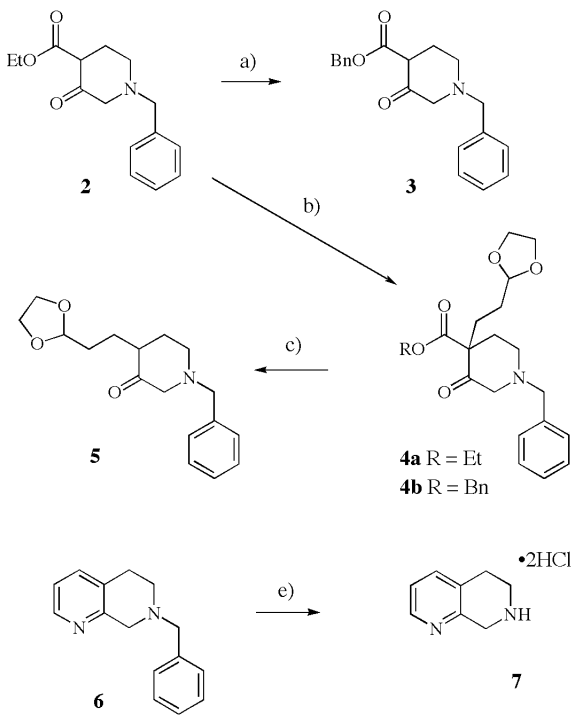
To date there have been only two reported syntheses of the 5,6,7,8-tetrahydro-1,7-naphthyridine (**7**) [4] or its *N*-benzyl derivative **6** [5], both of which are based on elaboration of a 2,3-disubstituted pyridine core. The first of these routes relies upon a partial reduction of 1,7-naphthyridine that affords a 1:1 mixture of **7** and 1,2,3,4-tetrahydro-1,7-naphthyridine, which require separation by preparative gas chromatography or multiple thin-layer chromatographies [4]. Preparation of the requisite 1,7-naphthyridine proceeds *via* a six-step synthesis in a low overall yield (<10%). The other reported synthesis [5] of a 5,6,7,8-tetrahydro-1,7-naphthyridine core proceeds *via* a nine-step sequence, affording **6** in low overall yield.

Scheme I



In contrast to the previously reported syntheses of **7**, the approach described herein (Scheme I) is based on appending the pyridine ring to a commercially available 3-piperidone (**2**). This was envisioned to occur through incorporation of a three-carbon aldehyde equivalent into the 4-position of the piperidone backbone followed by decarboxylation and cyclization/aromatization with *N*-hydroxylamine to from the tetrahydronaphthyridine core (**6**). Towards this end, alkylation of the β-ketoester **2** with 2-(2-bromoethyl)-1,3-dioxolane afforded **4a** in 55% yield, along with 12% of the corresponding *O*-alkylated product. Attempts to hydrolyze and decarboxylate **4a** under a variety of conditions (*e.g.* NaOH, LiCl/H_2O or $MgCl_2$/HMPA) afforded a significant number of side products in addition to desired ketone **5**. Presumably, formation of the undesired reaction products is at least in part mediated *via* a reverse Dieckmann reaction.

As a means of circumventing this problem, benzyl ester **3** was prepared (92%) by transesterification of **2** catalyzed by 4-dimethylaminopyridine [6]. Alkylation of the potassium enolate of **3** with the dioxolane-based bromide afforded **4b** in 65% yield. Selective hydrogenolysis (Pd/carbon, 15 p.s.i. H_2 in ethyl acetate) of the benzyl ester followed by concomitant decarboxylation produced ketodioxolane **5**. Cyclodehydration of this 1,5-dicarbonyl equivalent with hydroxylamine hydrochloride in either acetic acid [7] or ethanol [8] provided the tetrahydronaphthyridine nucleus. From a limited set of experiments, heating in ethanol at 70 °C for 16 hours afforded the highest yield (34%) of **6**. Finally, *N*-debenzylation was achieved by hydrogenolysis (Pd/carbon) in acidic methanol to afford the dihydrochloride salt of 5,6,7,8-tetrahydro-1,7-naphthyridine (**7**) in 78% recrystallized yield.

In summary we have developed a five-step synthesis of 5,6,7,8-tetrahydro-1,7-naphthyridine, which provides improved access to this conformationally-restrained, pharmacophore structure and its corresponding *N*-substituted derivatives.

EXPERIMENTAL

General.

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H nmr spectra were recorded on a Varian Inova 400 MHz Spectrometer. Low resolution mass spectral data were obtained on a Micromass ZMD2000 utilizing flow injection and APcI ionization. Microanalyses were obtained from Schwarzkopf Microanalytical Laboratory, Inc. Silica gel column chromatography was performed on a Biotage® Flash 40i chromatography module. All commercial reagents were used without further purification.

1-Benzyl-3-piperidone-4-carboxylic Acid Benzyl Ester (**3**).

A stirred solution of 1-benzyl-3-piperidone-4-carboxylic acid ethyl ester (**2**) (23.3 g, 89 mmol) [9], benzyl alcohol (45 mL) and 4-dimethylaminopyridine (1.1 g, 8.9 mmol) in toluene (400 mL) was heated at reflux temperature for 48 hours, with an additional portion of 4-dimethylaminopyridine (1.1 g, 8.9 mmol) being added at the 24 hour time point. The solvent and excess benzyl alcohol were removed by distillation under reduced pressure (5 - 10 Torr). The resulting oil was purified by elution through a pad of silica gel (400 g) employing 5% ethyl acetate/hexanes to afford the title compound as a yellow oil, 26.6 g (92%). ^{1}H nmr (deuteriochloroform): δ 2.38 (t, 2H, CH_2), 2.59 (t, 2H, CH_2), 3.11 (s, 2H, CH_2-N), 3.61 (s, 2H, CH_2-N), 5.20 (s, 2H, O-CH_2), 7.31-7.35 (m, 10H, Ar-H), 11.82 (s, 0.3H, enol); ms (CI) m/z 324 (M+1, 100%).

Anal. Calcd. for $C_{20}H_{21}N_1O_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.17; H, 6.71; N, 4.38.

1-Benzyl-4-(2-[1,3]dioxolan-2-yl-ethyl)-3-piperidone-4-carboxylic Acid Benzyl Ester (**4b**).

To a cooled (0 °C), stirred solution of 1-benzyl-3-piperidone-4-carboxylic acid benzyl ester (**3**) (13.6 g, 42.0 mmol) in dimethylformamide (84 mL) was added potassium tert-butoxide (5.2 g, 46.2 mmol). After 5 minutes, the cooling bath was removed and the resulting solution was allowed to stir at ambient temperature for an additional 30 minutes. Freshly distilled 2-(2-bromoethyl)-1,3-dioxolane (15.2 g, 84.1 mmol) and sodium iodide (3.2 g, 21.0 mmol) were added and the resulting mixture was heated at 80 °C for 2 hours. After cooling, the reaction mixture was diluted with ethyl ether (1 L), washed with water (3 x 50 mL), brine (50 mL), dried over sodium sulfate and concentrated *in vacuo* to afford a brown oil. Chromatography through a pad of silica gel (300 g) employing a gradient of 5% to 20% ethyl acetate/hexanes afforded the title compound as a golden oil, 11.5 g (65%). ^{1}H nmr (deuteriochloroform): δ 1.51-1.72 (m, 4H, CH_2-CH_2), 1.95 (dt, 1H, CH_2), 2.57-2.70 (m, 3H, CH_2, CH_2), 3.02 (AB quartet, 2H, CH_2-N, J = 15.8, Δν = 66.0 Hz), 3.44 (AB quartet, 2H, CH_2-N), 3.78-3.92 (AB pattern, 4H, O-CH_2CH_2-O), 4.81 (t, 1H, O-CH-O), 5.13 (AB quartet, 2H, O-CH_2), 7.20-7.33 (m, 10H, Ar-H); ms (CI) m/z 424 (M+1, 100%). This compound slowly polymerizes (~20% degradation after 1 month at 5 °C) to an insoluble white solid/red oil mixture.

1-Benzyl-4-(2-[1,3]dioxolan-2-yl-ethyl)-3-piperidone (**5**).

A slurry of 1-benzyl-4-(2-[1,3]dioxolan-2-yl-ethyl)-3-piperidone-4-carboxylic acid benzyl ester (**4b**) (1.3 g, 3.1 mmol) and 10% palladium-on-carbon (0.65 g) in ethyl acetate (15 mL) was treated with 15 p.s.i. of hydrogen on a Parr® apparatus for 2 hours. The reaction slurry was filtered through a short pad of Celite®, washing with dichloromethane and ethyl acetate. The filtrate was concentrated *in vacuo* to afford the title compound as a tan oil, 0.73 g (82%). This material was utilized in the next reaction without further purification. ^{1}H nmr (deuteriochloroform): δ 1.33-1.42 (m, 1H, CH_2), 1.57-1.71 (m, 3H, CH_2, CH_2), 1.90-2.03 (m, 1H, CH_2), 2.04-2.09 (m, 1H, CH_2), 2.24-2.32 (m, 1H, CH_2), 2.42-2.48 (m, 1H, CH_2), 2.89-2.94 (m, 1H, CH), 3.19 (AB quartet, 2H, CH_2-N, J = 13.7, Δν = 157.3 Hz), 3.56 (s, 2H, CH_2-N), 3.77-3.97 (AB pattern, 4H, O-CH_2CH_2-O), 4.83 (t, 1H, O-CH-O), 7.22-7.32 (m, 5H, Ar-H); ms (CI) m/z 290 (M+1, 100%).

7-Benzyl-5,6,7,8-tetrahydro-1,7-naphthyridine (**6**).

A slurry of 1-benzyl-4-(2-[1,3]dioxolan-2-yl-ethyl)-3-piperidone (**5**) (0.73 g, 2.5 mmol) and hydroxylamine hydrochloride (1.8 g, 25 mmol) in anhydrous ethanol (25 mL) was stirred at 70 °C for 16 hours. The resulting brown solution was cooled, concentrated *in vacuo*, diluted with half-saturated aqueous sodium carbonate and extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting brown oil was chromatographed on a Biotage® Flash 40S eluting with a gradient of 0%-1.5% methanol in dichloromethane to afford the title compound as a golden oil, 0.19 g (34%). ^{1}H nmr (deuteriochloroform): δ 2.74 (t, 2H, CH_2-pyridyl), 2.87 (t, 2H, CH_2-N), 3.72 (s, 2H, CH_2-N), 3.74 (s, 2H, CH_2-N), 7.03-7.06 (m, 1H, pyridyl-H), 7.23-7.40 (m, 6H, Ar-H and pyridyl-H), 8.33 (d, 1H, pyridyl-H); ms (CI) m/z 325 (M+1, 100%).

The bis-hydrochloride salt was recyrstallized from methanol/ethyl acetate; mp 231-233 °C (significant darkening of solid above 225 °C); ^{1}H nmr (methanol-d_4): δ 3.43 (br t, 2H, CH_2-pyridyl), 3.78 (br s, 2H, CH_2-N), 4.66 (s, 2H, CH_2-N), 4.71 (s, 2H, CH_2-N), 7.53-7.55 (m, 3H, Ar-H), 7.66-7.69 (m, 2H, Ar-H), 7.89 (dd, 1H, pyridyl-H), 8.39 (d, 1H, pyridyl-H), 8.73 (d, 1H, pyridyl-H), 9.78 (br s, 2H, HCl).

Anal. Calcd. for $C_{15}H_{18}N_2Cl_2$: C, 60.62; H, 6.10; N, 9.42. Found: C, 60.44; H, 6.13; N, 9.42.

5,6,7,8-Tetrahydro-1,7-naphthyridine, Bis-hydrochloride (**7**).

A slurry 7-benzyl-5,6,7,8-tetrahydro-1,7-naphthyridine (**6**) (170 mg, 0.76 mmol) and 10% palladium-on-carbon (0.85 mg) in methanol (4 mL)/4 *N* HCl in dioxane (0.8 mL) was treated with 50 p.s.i. of hydrogen on a Parr® apparatus for 6 hours. The reaction slurry was filtered through a short pad of Celite®, washed with methanol and concentrated *in vacuo*. The resulting solids were azeotroped with toluene (2x) and dried *in vacuo* (0.1 torr) to afford an off-white solid. Recrystallization from methanol/ethyl acetate and drying *in vacuo* (0.1 torr, 60 °C) afforded the title compound, 123 mg (78%), mp 251-253 °C (significant darkening of solid above 180 °C). Alternatively, **7** can be prepared by palladium-on-carbon catalyzed hydrogenolysis of **6** in the presence of di-*t*-butyl dicarbonate (MeOH, 50 p.s.i. H_2) and subsequent N-BOC cleavage with methanol/HCl in ~90% overall yield. ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.09 (t, 2H, Ar-CH_2), 3.36-3.38 (m, 2H, CH_2-N), 4.38 (s, 2H, pyridyl-CH_2-N), 7.58 (dd, 1H, pyridyl-H), 8.01 (d, 1H, pyridyl-H), 8.57 (d, 1H, pyridyl-H), 10.12 (br s, 2H, HCl); ms (CI) m/z 135 (M+1, 100%).

Anal. Calcd. for $C_8H_{12}N_2Cl_2 \cdot 0.25H_20$: C, 45.41; H, 5.95; N, 13.24. Found: C, 45.15; H, 6.04; N, 12.98. A portion of the dihydrochloride salt was free-based (CH_2Cl_2/aq. Na_2CO_3) and the ^{1}H nmr spectrum of the isolated oil was consistent with that previously reported [4].

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[9] The free base was obtained from the corresponding hydrochloride salt (Aldrich Chemical Co.) by partitioning between ethyl acetate and half-saturated aqueous sodium bicarbonate, drying the organic phase over sodium sulfate and concentrating *in vacuo* to afford a brown oil.