Syntheses of New Open-Ring and *homo*-Epibatidine Analogues from Tropinone

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Epibatidine (**1**) (see Figure 1) is an alkaloid isolated from the skin of the Ecuadorian poisonous frog *Epipedobates tricolor*.[1] Epibatidine and its optical isomer exhibit powerful analgesic activity and high binding selectivity to nicotinic acetylcholine receptors but not to opioid receptors.[1,2] An unprecedented large number of syntheses of epibatidine have been described following its structural elucidation by Daly and co-workers in 1992.[3−5] More recently, efforts have been directed toward finding more selective nicotinic analgesics that have fewer toxicity and adverse side effects associated with the natural alkaloid. Some of these efforts have resulted in the syntheses of biologically active epibatidine analogues and epibatidine/anatoxin-a (**5**) hybrids.[5] Nonsymmetric *homo*-epibatidine[6] (**2**) and epiboxidine[7] (**3**) are azabicycloalkanes, the former possessing one more carbon than epibatidine and, in the latter, a methylisoxazole moiety replaces the 5-(2-chloropyridinyl) ring of epibatidine. UB-165 (**6**) is a hybrid of anatoxin-a and epibatidine, in which the acyl group of anatoxin-a is replaced by a 5-(2-chloropyridyl) ring.[8] ABT-594 (**4**) may be considered an open-ring analogue of epibatidine, in which a two atom linker connects the 5-(2-chloropyridinyl) ring with an azetidine ring.[9]

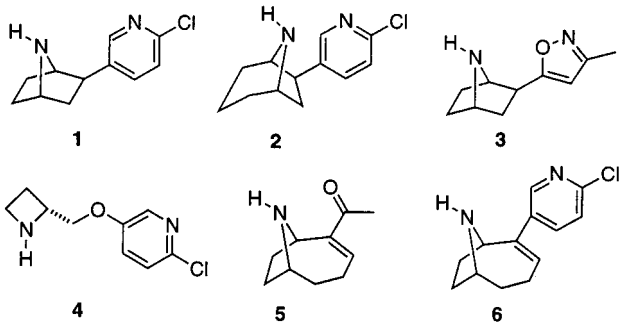

Figure 1.

We have recently reported the preparation of useful intermediates for the synthesis of epibatidine analogues, utilizing a microbial hydroxylation of unfunctionalized carbons with *Beauveria bassiana*.[10] Microbial hydroxylation of *N*-benzoyl tropane occurs on the methylene farthest away from the substituted nitrogen, producing symmetric *N*-benzoyl tropanol. However, it appeared to us that tropinone would be a better starting material than the hydroxylated metabolite for the synthesis of symmetric *homo*-epibatidine. In this paper, we describe the syntheses of new analogues of epibatidine readily prepared from tropinone (Schemes 1 and 2). These new analogues contain those structural features that make them potentially useful nicotinic analgesics: an azabicycloalkane or azabicycloalkene ring, a 5-(2-chloropyridinyl) ring, and a pyrrolidine ring connected to a 5-(2-chloropyridinyl) ring by two atoms.

Results and Discussion

Symmetric *homo*-epibatidine (**13**) and dehydro *homo*-epibatidine (**10**) were prepared from *N*-ethyl carbamate tropinone[7] (**7**) as illustrated in Scheme 1. Treatment of 2-chloro-5-iodopyridine[11] with *n*-butyllithium followed by addition of *N*-protected tropinone **7** gave recovered tropinone **7** (50% yield) and alcohol **8** in 44% yield. Addition

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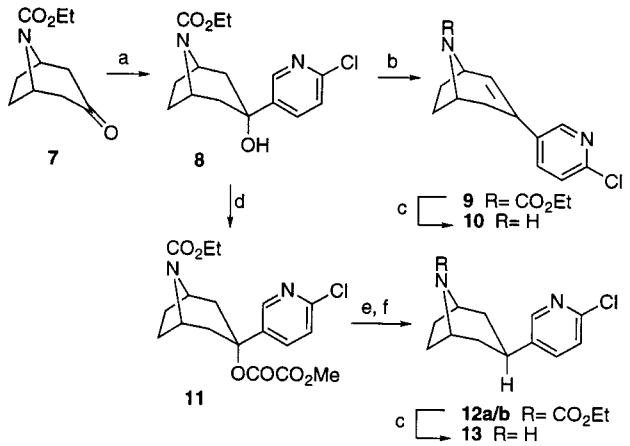
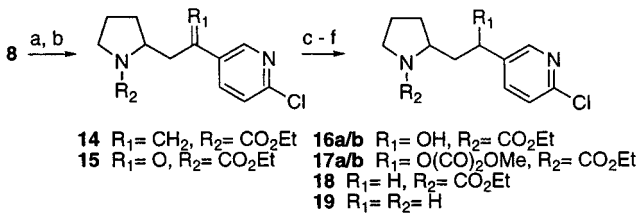
Scheme 1



Reagents: (a) 2-chloro-5-iodopyridine, *n*-BuLi, THF/Et_2O, then **7** in Et_2O, − 78 °C; (b) MsCl, Et_3N, DMAP, CH_2Cl_2, RT, 12 h; (c) concentrated HCl, 100 °C, 4 h; (d) $ClCOCO_2CH_3$, 2,6-lutidine, DMAP, CH_2Cl_2, RT, 12 h; (e) cat. AIBN, Bu_3SnH, toluene, 100 °C, 4 h; (f) KO-*t*-Bu, *t*-BuOH, 85 °C, 32 h.

Scheme 2



Reagents: (a) Et_3SiH/CF_3CO_2H (1:5), 80 °C, 8 h; (b) OsO_4, dioxane, H_2O, RT, then $NaIO_4$, 2 h; (c) $NaBH_4$, EtOH, 0 °C, 0.5 h; (d) $ClCOCO_2Me$, 2,6-lutidine, DMAP, CH_2Cl_2, RT, 12 h; (e) cat. AIBN, Bu_3SnH, toluene, 100 °C, 4 h; (f) concentrated HCl, 100 °C, 4 h.

of 2-chloro-5-lithiopyridine to *N*-protected tropinone **7** occurs stereoselectively on the *exo*-face of the tropinone. Efforts to improve the yield of the coupling product using cerium(III) chloride were unsuccessful.[12] Dehydroxylation of tertiary alcohol **8** was accomplished using the Dolan−MacMillan methodology[13] previously used by Trudell in a recent synthesis of epibatidine.[14] Alcohol **8** was treated with methyl oxalyl chloride to give methyl oxalate ester **11**, in 97%. An unseparable mixture of *endo*/*exo*-chloropyridinyl isomers (**12a**/**b**) was obtained when methyl oxalate ester **11** was treated with tributyltin hydride in boiling toluene (56%). The epimeric mixture affords solely the more thermodynamically stable *exo*-isomer **12a** when subjected to potassium *tert*-butoxide in boiling *tert*-butyl alcohol (50% yield). Deprotection under acidic conditions provided the desired symmetric epibatidine analogue **13** (63% yield). **10** was obtained in two steps from alcohol **8** (Scheme 1). Dehydration of alcohol **8** with methanesulfonyl chloride occurred in 96% yield, and subsequent treatment with hydrochloric acid gave the desired epibatidine/anatoxin-a analogue **10** (87% yield). Analogue **10** closely resembles the structure of anatoxin-a (**5**) and UB-165 (**6**). ^1H and ^{13}C NMR spectra of carbamates at

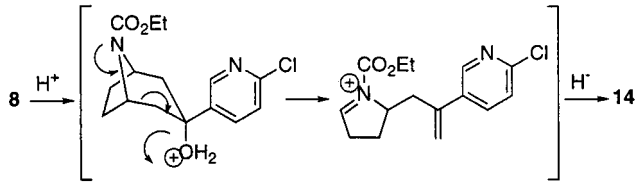


Figure 2.

room temperature showed a mixture of rotamers. NMR spectra of carbamates were simplified by recording the experiments at 335 K.

Tertiary benzyl alcohols are reported to undergo reduction to the corresponding hydrocarbon under ionic hydrogenation conditions (triethylsilane−trifluoroacetic acid).[15] Interestingly, when tertiary alcohol **8** was subjected to ionic hydrogenation conditions (Figure 2), we observed dehydration product **9** and opening of the bicyclic ring to form alkene **14** in a 1:1 ratio in high conversion (Scheme 2). A plausible mechanism for the ring opening of alcohol **8** is shown in Figure 2. This conversion begins with protonation of the alcohol, followed by formation of an iminium intermediate with loss of water. Pyrrolidine **14** is then formed by addition of a hydride to the double bond of the iminium intermediate. We noticed that the pyrrolidine olefinic product **14** could be a useful intermediate for the preparation of epibatidine analogues more closely related to nicotine and ABT-594 (**4**). Therefore, we undertook a synthetic approach to an "open-ring" analogue of epibatidine that contains a 5-(2-chloropyridinyl) ring connected by two carbon atoms to a pyrrolidine ring (Scheme 2).

Alkene **14** was oxidatively cleaved to ketone **15** in 77% yield, using sodium periodate−osmium tetroxide (Scheme 2).[16] Efforts to reduce ketone **15** using Clemmensen or Wolff−Kishner methods were not satisfactory. Thus, we decided to apply the Dolan−MacMillan protocol used previously. Reduction of ketone **15** with sodium borohydride gave a mixture of diastereomeric alcohols **16a**/**b** (1:2 ratio, 97% yield). Treatment of alcohols **16a**/**b** with methyl oxalyl chloride gave the corresponding methyl oxalate esters **17a**/**b** in 95%. Cleavage of methyl oxalates **17a**/**b** afforded pyrrolidine **18** in 67% yield. *N*-Deprotection was accomplished as previously described (77% yield). Analogue **19** possesses a pyrrolidine ring linked to a 5-(2-chloropyridyl) ring by a two-carbon spacer. Compound **19** is a new "open-ring" analogue of epibatidine and also could be considered an analogue that lacks the C1−C2 bond of epibatidine.

In summary, we have described a short synthesis of symmetric *homo*-**13**, dehydro *homo*-**10**, and open-ring analogues **19** of epibatidine all starting from tropinone. One common intermediate **8** was converted to an open-ring analogue via a novel ionic hydrogenation. The open-ring analogue of epibatidine closely resembles the structure of known natural and synthetic nicotinic agonists (such as epibatidine (**1**), nicotine, and ABT-594 (**4**)). The results of binding assays to nicotinic and muscarinic receptors for these analogues will be reported in due course.

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Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover apparatus and are not corrected. ^{1}H NMR spectra were recorded at 360 MHz and ^{13}C NMR spectra at 90 MHz. Experiments requiring anhydrous conditions were performed under a nitrogen atmosphere. All solvents and reagents were purchased from commercial sources and were used as received unless otherwise noted. THF and diethyl ether were distilled from potassium benzophenone. Thin-layer chromatography (TLC) was carried out on Merck silica gel F_{245} precoated plates; spots were visualized by dipping the plates in a *p*-anisaldehyde or phosphomolybdic acid staining solution. Column chromatography employed silica gel 60, mesh size 230−400. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN.

3-*exo*-5′-(2′-Chloropyridinyl)-8-(ethoxycarbonyl)-8-azabicyclo[3.2.1]octane (8). To a solution containing 1.56 g (6.67 mmol) of 2-chloro-5-iodopyridine in a mixture of 15 mL of Et_2O and 15 mL of THF cooled to − 78 °C was added 3.33 mL (6.67 mmol) of *n*-butyllithium (2 M in pentane). The solution was stirred at − 78 °C for 45 min. To the reaction mixture was added a solution containing 1.32 g (6.67 mmol) of *N*-ethyl carbamate tropinone (**7**) in 15 mL of THF, and it was stirred for 2 h. The reaction mixture was warmed to − 50 °C and stirred for 1 h. The reaction mixture was quenched with 25 mL of saturated NH_4Cl solution and warmed to room temperature. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under diminished pressure. The residue was purified by flash chromatography on a silica gel column (5 cm × 12 cm). Elution with 1:1 hexanes/ethyl acetate afforded recovered *N*-ethyl carbamate tropinone (**7**) as a colorless oil: 658 mg (50%). Further elution afforded **8** as a white solid: yield 920 mg (44%); R_f = 0.29 (1:1 hexanes/ethyl acetate); mp 130−131.5 °C; IR (KBr) 3447, 1762, 1440, and 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 335 K) δ 8.43 (1H, d, J = 2.4 Hz), 7.65 (1H, dd, J = 8.5, 2.4 Hz), 7.27 (1H, d, J = 8.5 Hz), 4.39 (2H, bs), 4.15 (2H, q, J = 7.2 Hz), 3.03 (1H, bs), 2.42−2.11 (4H, m), 2.06−1.83 (4H, m); ^{13}C NMR ($CDCl_3$, 335 K) δ 153.9 (CO), 149.6 (C), 146.5 (CH), 143.9 (C), 135.9 (CH), 123.7 (CH), 72.0 (C), 61.0 (CH_2), 53.1 (2CH), 44.1 ($2CH_2$), 27.9 ($2CH_2$), 14.7 (CH_3); EIMS 310 (M^+, 46), 68 (100). Anal. Calcd for $C_{15}H_{19}N_2ClO_3$: C, 57.97; H, 6.16; N, 9.01. Found: C, 57.87; H, 6.29; N, 8.79.

3-[5′-(2′-Chloropyridinyl)]-8-(ethoxycarbonyl)-8-azabicyclo[3.2.1]oct-2-ene (9). Methanesulfonyl chloride (20 μL, 0.27 mmol) was added to a stirred solution of 27.6 mg (0.09 mmol) of alcohol **8**, 25 μL (0.18 mmol) of triethylamine, and 2 mg of 4-(dimethylamino)pyridine (DMAP) in 2.0 mL of CH_2Cl_2. The solution was stirred for 12 h. The reaction mixture was diluted with 5 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. The solution was concentrated under diminished pressure to afford a residue that was purified by flash chromatography on a silica gel column (5 cm × 2.5 cm). Elution with 1:1 hexanes/ethyl acetate gave alkene **9** as a colorless oil: yield 24.9 mg (96%); R_f = 0.37 (3:2 hexanes/ethyl acetate); IR (film) 2980, 1697, 1352, and 1106 cm^{-1}; ^{1}H NMR ($CDCl_3$, 335 K) δ 8.36 (1H, d, J = 2.5 Hz), 7.60 (1H, dd, J = 8.5, 2.5 Hz), 7.27 (1H, d, J = 8.5 Hz), 6.50 (1H, d, J = 4 Hz), 4.59 (2H, bs), 4.15 (2H, q, J = 7.2 Hz), 3.08 (1H, bs), 2.22 (2H, m), 2.02 (2H, m), 1.72 (1H, m), 1.26 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 335 K) δ 153.6 (CO), 149.4 (C), 145.6 (CH), 134.4 (CH), 133.6 (C), 130.2 (CH), 129.5 (C), 123.2 (CH), 60.5 (CH_2), 52.6 (CH), 51.3 (CH), 35.1 (CH_2), 33.8 (CH_2), 29.3 (CH_2), 14.2 (CH_3); EIMS 292 (M^+, 23), 263 (95), 191 (100); HRMS calcd for $C_{15}H_{17}N_2O_2Cl$ 292.0979, found 292.1002.

Conversion of tertiary alcohol 8 to alkene 14 and dehydration product 9. 2-[2-5′(2′-Chloropyridinyl)-2-methylene-ethyl]-pyrrolidine-1-carboxylic Acid Ethyl Ester (14). A solution of 367 mg (1.18 mmol) of alcohol **8** in a mixture of 2.4 mL (15 mmol) of triethylsilane and 6 mL (75 mmol) of trifluoroacetic acid was heated at 80 °C for 8 h. To the solution was added 20 mL of CH_2Cl_2, and the mixture was washed successively with water, saturated $NaHCO_3$ and brine, then dried over Na_2SO_4. The solution was concentrated under diminished pressure to afford a residue that was purified by flash chromatography on a silica gel column (2.5 cm × 8 cm). Elution with 4:1 hexanes/ethyl acetate afforded alkene **14** as a viscous colorless oil: yield 161 mg (46%); R_f = 0.6 (1:1 hexanes/ethyl acetate); IR (film) 1696, 1419, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 335 K) δ 8.56 (1H, bs), 7.90 (1H, bs), 7.37 (1H, d, J = 7 Hz), 5.45 (1H, s), 5.24 (1H, s), 4.15 (2H, q, J = 7 Hz), 3.88 (1H, m), 3.37 (2H, m), 3.12 (1H, bd, J = 14 Hz), 2.42 (1H, dd, J = 14, 10 Hz), 1.96−1.70 (4H, m), 1.27 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 335 K) δ 155.8 (CO), 149.6 (C), 146.4 (CH), 141.2 (C), 137.4 (CH), 135.7 (C), 124.4 (CH), 117.6 (CH_2), 61.7 (CH_2), 56.2 (CH), 46.6 (CH_2), 39.3 (CH_2), 29.4 (CH_2), 23.1 (CH_2), 14.6 (CH_3); EIMS 296 (M^+ + 1, 0.95), 142 (100). Further elution afforded alkene **9** as a viscous colorless oil: 158 mg (46%).

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Supporting Information Available: Experimental procedures for compounds **10**−**13** and **15**−**19** and copies of ^{1}H and ^{13}C NMR spectra for compounds **10**, **13**, **14**, and **19**. This material is available free of charge from the Internet at http://pubs.acs.org.

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