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Synthesis of Semi-Rigid Analogs of Anabasine.

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Abstract: The synthesis of 3-(3-pyridyl)-2-azabicyclo[2.2.2]octane **1**, a semi-rigid analog of anabasine, is reported. This compound is prepared via Lewis acid promoted imino Diels-Alder reaction of 3-pyridine bismethylcarbamate **7** with 1,3-cyclohexadiene to form the rigid azabicyclic backbone. A 6-chloropyridyl analog **2** is also prepared. Hydrogenation and deprotection provide the desired substrates.

Rigid analogs of neurotransmitters are invaluable tools in helping to understand the relationship between neurotransmitter structure and function. Conformationally restricted molecules can provide an insight into the factors which are important for molecular recognition and binding. The tobacco alkaloids nicotine **3** and anabasine **4**, two of the earliest known insecticides,[1] are natural products which mimic the actions of the neurotransmitter acetylcholine. As such, these agonist have defined the nicotinic acetylcholine receptor (nAChr) in both invertebrate and vertebrate systems.[2] Agonists of the nAChr have been proported as therapies for disease states ranging from Alzheimer's and Parkinson's disease to Tourette's syndrome and schizophrenia.[3] Recently, alkaloids such as anatoxin-a **5**[4] and epibatidine **6**[5] have been shown to be potent agonists of the nAChr. Both of these molecules possess a secondary amine contained within a rigid azabicyclic framework. Pendant from this framework is a hydrogen-bond accepting group, either a carbonyl as in anatoxin-a **5** or a pyridine as in epibatidine **6**.

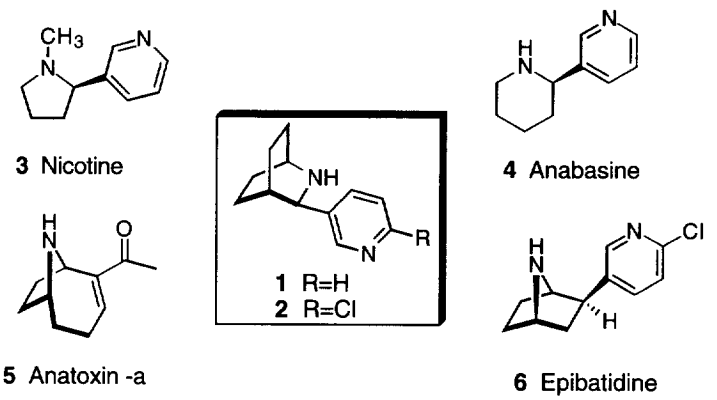
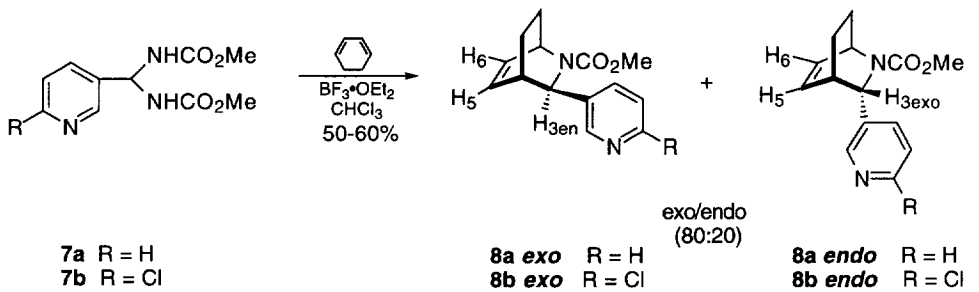


Figure 1.

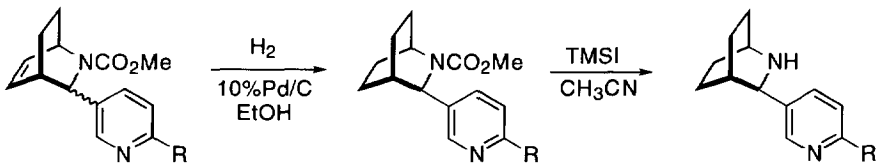
In this Letter, we wish to report the preparation of two semi-rigid azabicyclic analogs of the nicotinic receptor agonist anabasine, which we call bicycloanabasine **1** and chloro-bicycloanabasine **2**.[6] These molecules possess a core heterocyclic ring locked in a rigid azabicyclic skeleton as in **5** and **6**. The heterocycle (piperidine) must now assume a boat conformation, as opposed to the chair conformation normally found in **4**. The pendant hydrogen-bond accepting pyridine is located on the carbon adjacent to the piperidine nitrogen in the same spacial relationship as found in the natural products nicotine **3** and anabasine **4**.

Synthesis of these molecules utilizes the imino Diels-Alder reaction first pioneered by Merten[7] and Cava[8] and latter exploited by Quinn[9] in his synthesis of anabasine. Bisurethanes **7a,b** are prepared by condensation of the appropriately substituted pyridine-3-carboxaldehyde with two equivalents of methyl carbamate in the presence of an acid catalyst.[10] When a chloroform solution of the bisurethanes were refluxed with a five-fold excess of boron trifluoride etherate, the bisurethanes decompose to generate an iminium ion *in situ* , which condenses with 1,3-cyclohexadiene to provide 3-pyridyl-2-azabicyclo[2.2.2]octenes **8a,b** in 50-60% yield as a mixture of exo/endo isomers[11] (Scheme 1).



Scheme 1.

Analysis of the ^1H NMR spectra of the chromatographed reaction mixture indicates an 80:20 mixture of exo/endo cycloadducts. This assignment is based upon an analgous series of 3-phenyl cycloadducts prepared by Krow.[12] The major exo-pyridyl adducts for **8a** and **8b** have both olefinic resonances for H-5 and H-6 appearing at δ6.58. The minor endo cycloadducts show separate olefinic absorbances at δ6.58 for H-6 and 6.00 for H-5 consistent with shielding of the H-5 proton by the endo pyridyl group. Integration of the olefinic region permits determination of the exo/endo ratio as 80:20 (±2%) in favor of the exo isomer in both the pyridine and chloropyridine examples. Careful column chromatography provides early fractions of the pure exo isomers, while latter fractions are enriched with the minor endo adducts. Generally, however, the fractions are combined and hydrogenated (H_2/Pd/C) to give symmetrical **9a** (75%) and **9b** (85%)[13] (Scheme 2). The methyl carbamate protecting group is removed by treatment with an excess of iodotrimethylsilane (3 eq) in refluxing acetonitrile to give target substrates **1** (90%) and **2** (87%).[14]



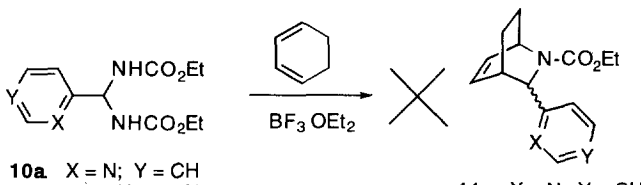
8a R = H
8b R = Cl

9a R = H (75%)
9b R = Cl (85%)

1 R = H (90%)
2 R = Cl (87%)

Scheme 2.

In an attempt to synthesize the 2- and 4-pyridyl regiosomers **11a** and **11b**, the bisethylcarbamates of 2- or 4-pyridine carboxaldehydes **10a** or **10b** were reacted in a similar fashion with cyclohexadiene (Scheme 3). Unfortunately, no traces of Diels-Alder adducts could be detected in the crude ^{1}H NMR spectra. Varying the solvent, reaction temperature, or amount of boron trifluoride etherate provided no improvement. As well, reaction of biscarbamate **7a** with cyclopentadiene did not occur under these reaction conditions. Rather, polymerization of the diene took place. Lower reaction temperatures result in recovery of the unreacted starting materials.



10a. X = N; Y = CH
10b. X = CH; Y = N

11a. X = N; Y = CH
11b. X = CH; Y = N

Scheme 3.

In summary, we have described the synthesis of rigid analogs of the nAChr agonist anabasine employing an imino Diels-Alder reaction. This method is presently limited to the synthesis of 3-substituted pyridines, as the other regioisomers failed to deliver the desired targets under the reaction conditions described.

References and Notes

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10. All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, high resolution mass spectrometry and/or combustion analysis.
11. A typical experimental procedure is as follows: The bisurethane **7b** (5.00g, 18.27 mmol) was suspended in 200 mL of chloroform and heated to reflux (solids dissolve). A solution of boron trifluoride etherate (12.96 g, 91.35 mmol, 11.2 mL, 5 eq) in 50 mL of chloroform was added dropwise over 15 minutes, followed by a chloroform solution (30 mL) of 1,3-cyclohexadiene (2.92 g, 36.54 mmol, 2 eq) dropwise over 15 minutes. The reaction was refluxed for 5 hours, then cooled and quenched by cautious addition of saturated aqueous sodium bicarbonate (100 mL). The layers were separated and the organic portion was washed with saturated $NaHCO_3$ (2 x 50 mL), water (2 x 50 mL), brine (1 x 100 mL), dried (Na_2SO_4) and the solvent removed to give a crude oil. Flash column chromatography (0-10% CH_3OH in CH_2Cl_2) provides early fraction of the pure exo-pyridyl cycloadduct **8b**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ8.31 (d, 1H, J = 1.5 Hz), 7.55 (dd, 1H, J = 8.2, 2.5 Hz), 7.34 (d, 1H, J = 8.2 Hz), 6.58 (m, 2H), 5.03 and 4.87 (two br s, 1H), 4.43 (br s, 1H), 3.71 and 3.51 (two br s, 3H), 2.73 (br s, 1H), 2.10-1.95 (br m, 1H), 1.45 (m, 2H), 1.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) 156.62, 149.76, 147.67, 136.13, 134.47, 133.19, 123.73, 58.32, 52.53, 46.98, 37.35, 25.36, 16.07. IR (film, cm^{-1}) 2950, 1705, 1440, 1380, 1100. HRMS calcd for $C_{14}H_{15}N_2O_2Cl$ 278.0822, found 278.0812. Characteristic resonances for the endo-isomer of **8b** are δ6.00 (m, 1H), 4.70 and 4.78 (two s, 1H), 2.85 (br s, 1H).
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13. For **9a**, ^{1}H-NMR (300 MHz, $CDCl_3$) δ8.51 (m, 2H), 7.56 (appt. dt, 1H, J = 2.1, 7.5 Hz), 7.25 (m, 1H), 4.86 and 4.79 (two br s, 1H), 4.33 and 4.18 (two s, 1H), 3.71 and 3.52 (two br s, 3H), 2.10-1.80 (br m, 5H), 1.66 (m, 2H), 1.33 (m, 2H).
14. For **1**, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.66 (d, 1H, J = 2.1 Hz), 8.46 (dd, 1H, J = 1.5, 4.6 Hz), 7.91 (dt, 1H, J = 8, 2 Hz), 7.27 (m, 1H), 4.36 (m, 1H), 4.36 (m, 1H), 3.49 (s, 1H), 3.07 (m, 1H), 2.14-1.69 (m, 6H), 1.53 (m, 2H), 1.32 (m, 1H).

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