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Synthesis of conformationally constrained spirodihydrofuropyridine analogues of epibatidine

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Abstract—Conformationally constrained spirofuropyridine analogues of epibatidine, *syn*-**2** and *anti*-**2**, in which the 7-azabicyclo[2.2.1]heptane system and the 2-chloropyridine ring are held rigidly with the shorter and longer N–N distances, respectively, were synthesized from *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one. The preliminary binding studies suggested that *syn*-**2** has stronger binding affinity for nAChRs than *anti*-**2**.

A new class of amphibian alkaloid, epibatidine (**1**), isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor* by Daly and co-workers,[1] has been reported to be a highly potent non-opioid analgesic agent with a potency 200-fold greater than that of morphine in mice. Recent studies have also shown that **1** is an extremely potent agonist of neuronal nicotinic acetylcholine receptors (nAChRs),[2] including α4/β2, the most predominant subtype in the central nervous system.[2a,3] Both natural (–)- and unnatural (+)-epibatidine possess high affinity for the α4/β2 nAChR with similar activity.[2b] However, interestingly, by attaching a methyl group to the 7-aza-position of epibatidine reduced effectivity of the (+)-enantiomer was observed, whereas the α4/β2 receptor does not distinguish between (–)-epibatidine and the corresponding *N*-methyl derivative, it is about 15-fold less sensitive to the (+)-enantiomer of *N*-methylepibatidine than to (+)-epibatidine.[4] Due to the novel structure and its remarkable analgesic activity, an unprecedented large number of syntheses of epibatidine have been described,[5] and recent efforts have been directed toward finding more selective analogues having lower toxicity and the adverse side effects associated with the natural alkaloid that preclude its use in human. Some of these efforts have resulted in the synthesis of several promising ligands for nAChRs,[6] but there is still a need for potent agents that would interact more selectively with the neuronal nicotinic receptors and display no or minimal side effects.

Molecular modeling studies have suggested that epibatidine adopts two local energy minimum conformations **1A** and **1B** (Fig. 1) by rotation around the bond between the two putative pharmacophore elements, the rigid 7-azabicyclo[2.2.1]heptane system and the 2-chloropyridine ring.[7] The first one corresponds to the case where the two nitrogens are on the same side of the molecule and the second when they are on opposite sides with internitrogen distance of ca. 4.5 and 5.5 Å, respectively.[7a,c] Even though the value of the N–N distance has been considered sufficiently important to justify pharmacophoric models, these conformers have quite similar energy and are separated by a very low barrier,[7a,8] and, thus, the optimal internitrogen distance question remains unanswered. To gain a better understanding of the conformation adopted on binding to the nAChRs, we were interested in studying rotationally locked analogues in which the important pharmacophores are held rigidly with the shorter and longer N–N distances corresponding to those in **1A** and **1B**.[9] In this paper we wish to disclose our results on the

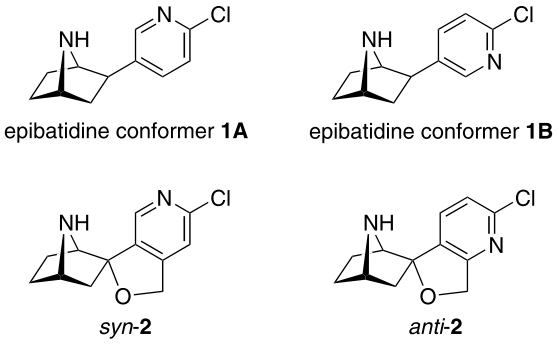

Figure 1. Epibatidine conformers **1A** and **1B**, and the corresponding analogues *syn*-**2** and *anti*-**2**.

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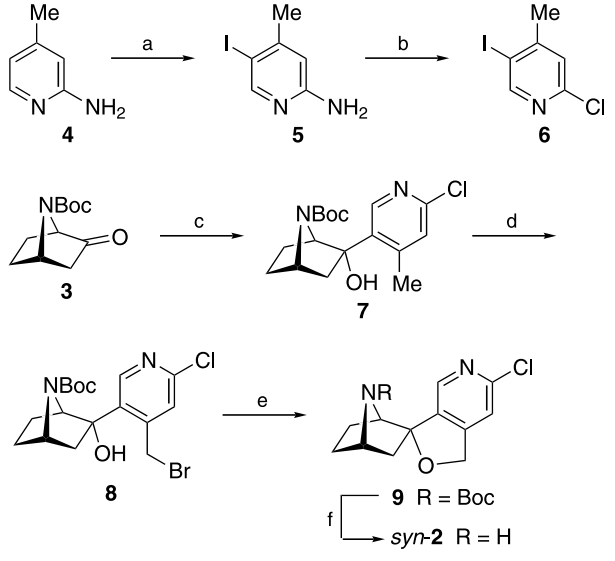
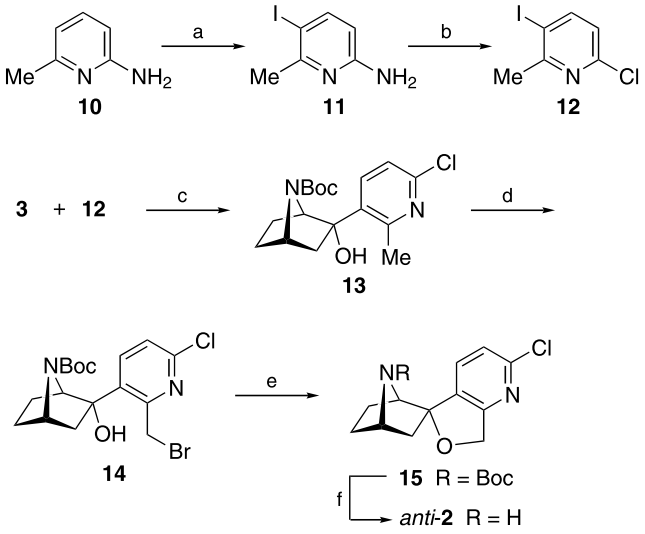
synthesis and nAChR binding properties of the conformationally constrained spirodihydrofuropyridine analogues of epibatidine, *syn*-**2** and *anti*-**2**, with shorter and longer internitrogen distances (Fig. 1).

The synthetic pathway for the preparation of *syn*-**2** is depicted in Scheme 1. Thus, 2-chloro-5-iodo-4-methylpyridine (**6**) was obtained starting from 2-amino-4-methylpyridine (**4**) by iodination (I_2, H_5IO_6)[6h] followed by chlorination via a diazotization procedure, ($NaNO_2$, concentrated HCl). Transmetalation of **6** with BuLi and addition to (±)-*N*-Boc-7-azabicyclo-[2.2.1]heptan-2-one (**3**)[5c,10] at −78°C (THF, 2 h) yielded exclusively the *endo*-alcohol **7** (86% yield). Bromination of **7** was performed by treatment with NBS in benzene under irradiation using a 150 W halogen lamp for 40 min to give the bromide **8** (56% yield), which was immediately exposed to the basic conditions (K_2CO_3, MeOH–THF) at room temperature to form the oxaspirocyclic compound **9** in 69% yield. Subsequent deprotection of the N-Boc group using trifluoroacetic acid (TFA) provided *syn*-**2**.

A rotationally constrained analogue with the longer internitrogen distance, *anti*-**2**, was also synthesized using a fundamentally similar protocol (Scheme 2). 6-Chloro-3-iodo-2-methylpyridine (**12**), available from 2-amino-6-methylpyridine (**10**) by iodination (I_2, H_5IO_6)[6h] followed by chlorination via a diazotisation procedure, was converted to the *endo*-alcohol **13** (90% yield) as a single isomer by treatment with BuLi followed by addition to the ketone **3**. While bromination of **13** using conditions (NBS, benzene, hν) similar to those described above for **7** resulted in a poor yield (ca. 8%) of the bromide **14** along with a complex mixture of products, the reaction proceeded smoothly upon treatment with NBS and benzoyl peroxide in refluxing benzene. Because the product **14** proved to be rather unstable at room temperature, after workup it was immediately subjected to basic treatment (K_2CO_3, MeOH–THF, rt) to provide the oxaspirocyclic compound **15** in 56% yield from **13**. Removal of the N-Boc protecting group with TFA afforded *anti*-**2**.



Scheme 1. *Reagents and conditions*: (a) I_2, H_5IO_6, H_2SO_4–AcOH–H_2O, 80°C (see Ref. 6h); (b) $NaNO_2$, HCl, rt, 78%; (c) **6**, BuLi, THF, −78°C, 85%; (d) NBS, benzene, h*v*, 56%; (e) K_2CO_3, MeOH–THF, rt, 69%; (f) CF_3CO_2H, CH_2Cl_2, rt, 70%.



Scheme 2. *Reagents and conditions*: (a) I_2, H_5IO_6, H_2SO_4–AcOH–H_2O, 80°C (see Ref. 6h); (b) $NaNO_2$, HCl, rt, 61%; (c) BuLi, THF, −78°C, 90%; (d) NBS, $(C_6H_5CO)_2O_2$, benzene, reflux; (e) K_2CO_3, MeOH–THF, rt, 56% from **13**; (f) CF_3CO_2H, CH_2Cl_2, rt, 81%.

Preliminary nAChR binding studies[11] showed that the spiro analogue with the shorter N–N distance, *syn*-**2**, has at least two-fold stronger binding affinity (IC_{50} = 409 nM, *K*i = 136 nM) for nAChRs than *anti*-**2** (IC_{50} = >1000 nM) containing the longer internitrogen distance.

In conclusion, we have developed a synthetic method to prepare the conformationally constrained spirodihydrofuropyridine analogues of epibatidine *syn*-**2** and *anti*-**2** with the shorter and longer internitrogen distances, respectively. The binding studies of these analogues imply that the epibatidine conformer with the shorter N–N distance is favoured for high affinity for the central nicotinic acetylcholine binding sites, which would provide some insight into the development of a rational approach for the design and preparation of new ligands selective for the central nAChRs. Further detailed binding studies with these compounds are currently under investigation.

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11. Binding assays were conducted in brain membranes of male Wistar rats by measuring the displacement of [^{3}H]cytisine.