The Synthesis of (+)- and (−)-Epibatidine

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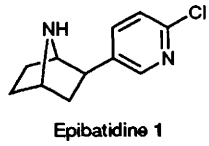
The synthesis of the alkaloid epibatidine {*exo*-2-(2-chloro-5-pyridyl)-7-azabicyclo[2.2.1]heptane} in enantiomeric form involving, as the critical step, reaction or 5-lithio-2-chloropyridine with *N-tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one is described.

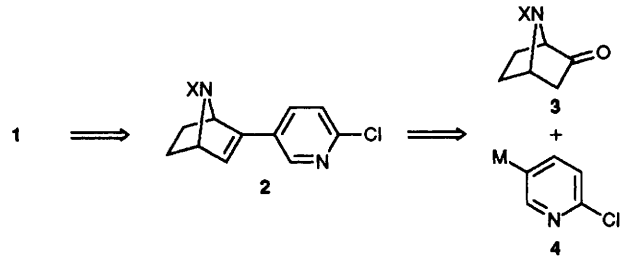
The isolation and structural elucidation of the alkaloid epibatidine **1** from the Ecuadoran poison frog, *Epipedobates tricolor*, was recently described by Daly *et al.*[1] Although apparently simple, the structure of epibatidine contains some unusual features. The natural occurrence of halogenopyridines is rare and this is the first natural product reported to contain the 7-azabicyclo[2.2.1]heptane ring system. The 2-chloro-5-pyridyl substituent is attached to the bicyclic system specifically in the *exo*-orientation and this may well be crucial for biological activity. We were intrigued by the remarkable analgesic properties of epibatidine. The compound is many times more potent than morphine in eliciting a Straub-tail reaction and in causing hot plate analgesia, and appears to operate *via* a non-opioid mechanism since naloxone, a general opioid antagonist, does not reverse the analgesic effects.[1] In view of these unusual observations we sought to carry out a more detailed pharmacological evaluation. Owing to the lack of material available from natural sources[2] and in the absence of a reported preparation,[3] a total synthesis of epibatidine was undertaken. Since the chirality of the natural material was not determined a racemic synthesis was investigated, with resolution to be carried out at a late stage.

Retrosynthetic analysis of the target suggested that a suitably protected 7-azabicyclo[2.2.1]hept-2-ene derivative **2** would be a valuable precursor (Scheme 1). Hydrogenation was projected to give a mixture of *exo*- and *endo*-derivatives which, it was proposed, could be converted to the desired, more thermodynamically stable *exo*-isomer by equilibration. It was further expected that alkene **2** would be obtained from the protected 7-azabicyclo[2.2.1]heptan-2-one **3** *via* condensation with a 5-metallo-2-chloropyridine species **4**.

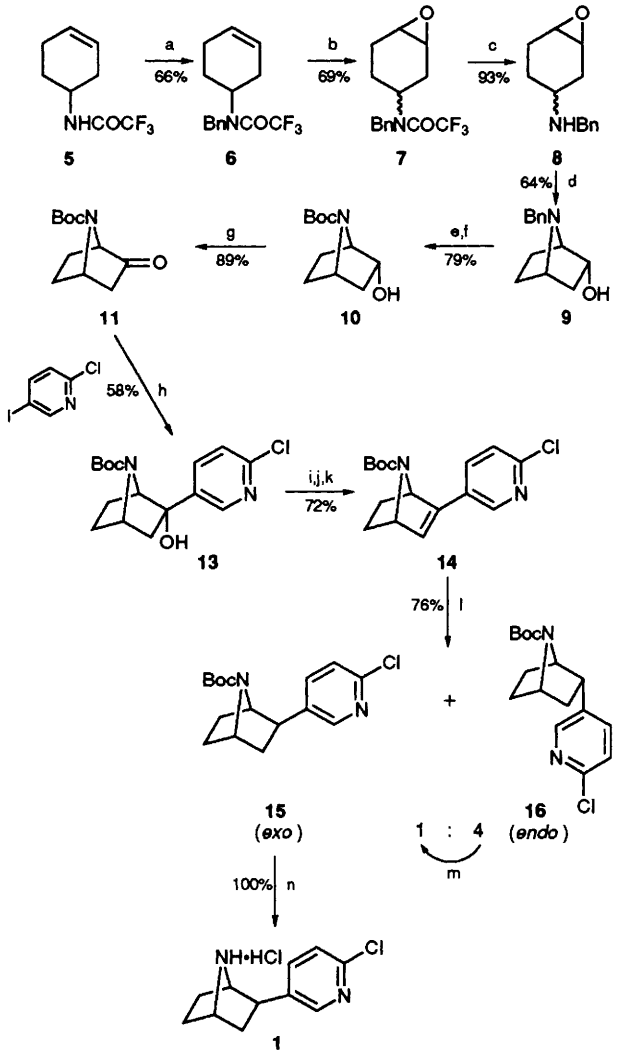
An efficient preparation of *endo*-7-methyl-7-azabicyclo[2.2.1]heptan-2-ol has previously been reported[4] and this methodology was utilised to prepare the 7-benzyl derivative **9**



Epibatidine **1**



Scheme 1 X = protecting group



Scheme 2 *Reagents and conditions* (Bn = $PhCH_2$): a, BnBr, DMF, Cs_2CO_3, 70 °C, 18 h; b, *m*-CPBA, CH_2Cl_2, room temp., 4 h; c, K_2CO_3, MeOH, H_2O, 3 days; d, *N*-methylpyrrolidinone, 180 °C, 18 h; e, H_2, 40 psi, 40 °C, EtOH, 5 mol l^{-1} HCl, $Pd(OH)_2$ on C (Pearlman's catalyst); f, $(Boc)_2O$, 1 mol l^{-1} NaOH, dioxane; g, $(COCl)_2$, Et_3N, Me_2SO, CH_2Cl_2; h, Bu^nLi (1 equiv.), Et_2O, tetrahydrofuran (THF), −70 °C; i, KH, THF, 0 °C to room temp. j, CS_2, MeI, 0 °C; k, toluene, 110 °C, l, PtO_2, H_2, 45 psi, EtOAc; m, Bu^tOH, Bu^tOK, 100 °C, 30 h; n, HCl, EtOAc

(Scheme 2). Benzylation of *N*-trifluoroacetylaminocyclohex-3-ene[5] **5** in dimethylformamide (DMF) with sodium hydride as base produced only a modest yield of the desired benzylated derivative. However, heating the trifluoroacetate **5** in DMF at 70 °C with the alkylating agent, in the presence of caesium, carbonate, afforded the benzylated derivative **6** in 66% yield. This material was treated with *m*-chloroperbenzoic acid (*m*-CPBA) to afford a mixture of epoxides **7**, which could be separated by column chromatography on silica gel, using diethyl ether–hexane as eluent, and the high-running material was shown to be the desired *trans*-product. Generally, however, the mixture was more conveniently partially purified to give a 69% yield of a 1 : 4 mixture of *cis–trans*-isomers. Mild base hydrolysis using potassium carbonate in methanol at room temperature then gave the amino epoxides **8** in 93% yield. Cyclisation of the *trans*-isomer was achieved in 64% yield by heating in *N*-methylpyrrolidinone at 180 °C for 18 h. At this stage the *N*-benzyl group was removed by hydrogenolysis (45 psi H_2) using Pearlman's catalyst in ethanol containing 5 mol l^{-1} hydrochloric acid (5% v/v). For efficient debenzylation, the hydrogenation was carried out at 40 °C for 3 h since at room temperature only 60% conversion to the amine occurred after 9h. *N*-Boc protection was then introduced using $(Boc)_2O$ in dioxane–sodium hydroxide solution at room temperature. The resulting alcohol **10** was subjected to Swern oxidation conditions to afford ketone **11** required for the key coupling reaction.

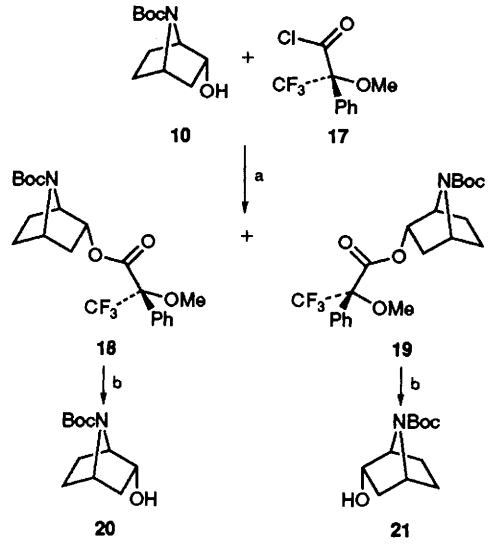
Whilst the 5-lithio derivative of 2-chloropyridine has not been previously reported, we expected that it could be generated by metallation of 2-chloro-5-iodopyridine **12**. Treatment of **12**[6] with Bu^nLi at −70 °C followed by quenching with ketone **11** afforded alcohol **13** in 58% yield. No products derived from metallation at other positions of the pyridine ring were detected. The tertiary alcohol obtained was converted to the *S*-methyl xanthate in quantitative yield by treatment with potassium hydride and subsequent quenching with carbon disulfide and methyl iodide. Thermolysis in toluene at reflux for 2 h resulted in smooth elimination of the xanthate to give the olefin **14** in 72% yield. Hydrogenation of **14** in ethyl acetate (40 psi H_2) using Adams' catalyst produced a 4 : 1 mixture of *endo–exo*-isomers from which the desired, more polar, *exo*-derivative **15** was isolated in 16% yield by column chromatography on silica gel with ethyl acetate–hexane as eluent. The undesired *endo*-isomer **16** was epimerised using potassium *tert*-butoxide in *tert*-butyl alcohol at reflux for 30 h to afford the *exo*-isomer in high overall yield.

^1H NMR spectroscopy was used to establish firmly the identity of the *exo*- and *endo*-isomers **15** and **16**. A 360 MHz, ^1H, 2D COSY experiment on the *exo*-isomer **15** showed that signals centred at δ 1.83 (m), 2.03 (dd, $J_{2endo,3endo}$ = 9.0 Hz, $J_{3exo,3endo}$ = 12.4 Hz) and 2.85 (dd, $J_{1,2endo}$ = 4.8 Hz, $J_{2endo,3endo}$ = 9.0 Hz) arise from the H_{3exo}, H_{3endo} and H_{2endo} protons, respectively. NOEs were observed between the H_{2endo} proton and the H_{3endo}, H_1, H_{6endo}, and the 4- and 6-pyridyl protons. A similar COSY experiment on the *endo*-isomer **16** showed that signals centred at δ 1.8 (m), 2.35 (m) and 3.46 (m) correspond to the H_{5exo}, H_{3exo} and H_{2exo} protons, respectively. A long-range coupling was observed between the H_{3exo} and H_{5exo} protons. NOEs were observed between the H_{2exo} proton and the H_{3exo}, H_1 and the 4- and 6-pyridyl protons.

Deprotection of the N-Boc *exo*-isomer **15** was achieved in quantitative yield using trifluoroacetic acid (TFA) at room temperature to afford racemic epibatidine† **1** as a colourless solid, which was characterised as the hemi-oxalate salt.‡ Using the above procedure racemic material could be obtained in multi-gram quantities.

† Structural confirmation was obtained by conversion to the *N*-diethyl acetyl derivative using acetic anhydride. This derivative was identical (^1H NMR; MS) with the *N*-acetyl derivative of epibatidine reported by Daly *et al.*[1]

‡ The hemi-oxalate salt was recrystallised from methanol–diethyl ether, m.p. 160–162 °C; ^1H NMR (360 MHz, CD_3SOCD_3) δ: 1.55–1.85 (5H, m), 2.18 (1H, dd, *J* 12.7 and 9.4 Hz), 3.20 (1H, dd, *J* 9.4 and 4.8 Hz), 4.08 (1H, s), 4.17 (1H, s), 7.46 (1H, d, *J* 8.3 Hz), 7.86 (1H, dd, *J* 8.3 and 2.4 Hz), 8.39 (1H, d, *J* 2.5 Hz). Satisfactory CHN analyses and mass spectral data were obtained.



Scheme 3 *Reagents*: a, 4-dimethylaminopyridine, CH_2Cl_2; b, KOH, EtOH

Semi-preparative, chiral HPLC was carried out on the Boc derivative **15** to afford the (+)- and (−)-isomers.§ Removal of the Boc group as described for the racemate **15** afforded milligram quantities of (+)- and (−)-epibatidine.¶

§ Resolution (600 μg per inj.) was achieved on a Chiralcel OD (250 mm × 10 mm id, 5 μm) column using 0.5% ethanol–hexane as eluent with a flow rate of 8 ml min^{-1}.

¶ (+)-Epibatidine·HCl, $[\alpha]_D^{24}$ + 34.7 (*c* 0.36, MeOH); m.p. 150 °C (decomp.); (−)-epibatidine·HCl, $[\alpha]_D^{24}$ −33.7 (*c* 0.16, MeOH); m.p. 130 °C (decomp.).

For the preparation of sufficient material for pharmacological evaluation a synthesis of the enantiomers was carried out. Resolution of alcohol **10** was achieved by formation of diastereoisomeric esters with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(−)-Mosher's acid chloride]. Crystallisation from hexane afforded a single diastereoisomer, m.p. 108–110 °C, in 37% yield based on **10**. Chromatographic purification of the mother liquors then afforded the other diastereoisomer in 38% yield. Deprotection of the esters **18** and **19** with potassium hydroxide in ethanol gave quantitative conversion to the enantiomeric alcohols **20** and **21** (Scheme 3). Each enantiomer was taken through the reaction sequence described above to afford gram quantities of the (+)- and (−)-isomers of epibatidine. The products were identical with the material obtained by preparative HPLC.

Pharmacological evaluation of the (+)- and (−)-enantiomers of epibatidine is currently underway.

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