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Synthesis of Epibatidine Homologues: Homoepibatidine and Bis-Homoepibatidine

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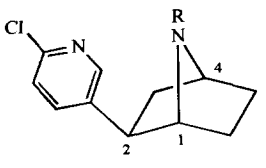
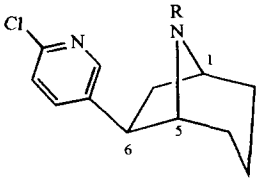
Abstract Synthetic approaches are described leading to homoepibatidine and bis-homoepibatidine which are based, respectively, on the tropane (8-azabicyclo[3.2.1]octane) and homotropane (9-azabicyclo-[4.2.1]nonane) ring systems. Epoxy- tropanes and -homotropanes (which are readily available from simple cyclic dienes) are convenient precursors for the azabicyclic alkenes needed for the key reductive coupling with pyridine derivatives. Copyright © 1996 Elsevier Science Ltd

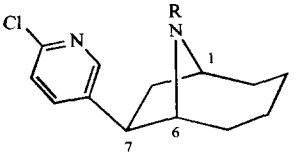
Epibatidine (**1a**) was first isolated in 1992 from the skin of the Ecuadorian poison frog *epipedobates tricolor*.[1] The recognition of the remarkable analgesic properties of (**1a**) immediately sparked off synthetic interest of such intensity that over a dozen syntheses have already appeared.[2] The compound is unusual in containing a chloropyridyl group but is also the first known alkaloid to be based on the azanorbornane (7-azabicyclo[2.2.1]heptane) ring system. We have long been intrigued by the unusual nature of the bridging nitrogen in derivatives of the 7-azabicyclo[2.2.1]heptane skeleton as shown, for example, by the exceptionally high barrier to inversion at nitrogen[3,4] and by the dramatic deshielding of the bridging nitrogen in the ^{15}N NMR spectra of a wide range of derivatives when compared with other cyclic and bicyclic amines.[5] Preliminary nitrogen NMR results from epibatidine itself show unexpected temperature-dependent behaviour but have not yet been fully evaluated.[6] Our work in tropanes[7] and homotropanes[8] suggests that the unusual inversion and spectroscopic properties associated with the bridging nitrogen of azanorbornanes may not be carried up the homologous series to any great extent. We wished to synthesise homoepibatidine (**2a**) and *bis*-homoepibatidine (**3a**) not only to compare and contrast their pharmacological properties as a function of increased flexibility in the bicyclic framework, but also to investigate in detail the spectroscopy, conformational behaviour, and nitrogen inversion of derivatives including the N-alkyl compounds (**2c, 3c**) and a wider range of analogues. We report here the synthesis of the key compounds (**2a,b**) and (**3a,b**).[9]



(1a) R=H, epibatidine
(1b) R=CO_2Me



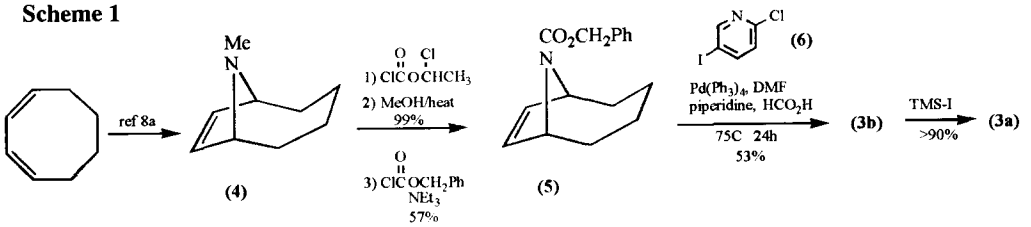
(2a) R=H, homoepibatidine
(2b) R=CO_2CH_2Ph
(2c) R=alkyl



(3a) R=H, *bis*-homoepibatidine
(3b) R=CO_2CH_2Ph
(3c) R=alkyl

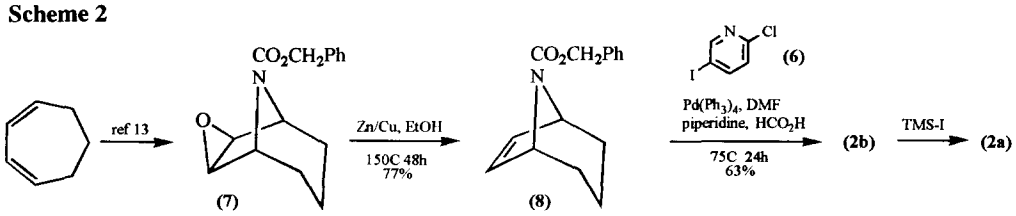
Our initial approach to (**2**) and (**3**) was based on the use of Pd-catalysed reductive Heck-type coupling.[2b] In preliminary work, the N-protected precursor (**5**) was obtained from (**4**)[8a] by demethylation with α-chloroethyl chloroformate followed by treatment with benzyl chloroformate and triethylamine (scheme 1). An alternative strategy is considered below. Coupling[6b] of (**5**) with the iodo-pyridine (**6**)[2b] provided the N-benzyloxycarbonyl derivative of *bis*-homoepibatidine (**3b**) in yields of over 50%.[10a] The ^{1}H NMR (table) and ^{13}C NMR spectra of (**3b**) showed two sets of signals due to the presence of two rotamers about the N-CO bond; irradiation of the signal due to H_7 led to only slight sharpening of H_6, leaving a sharp doublet, $J_{5exo,6}$ = 6.3 Hz. The small coupling between the bridgehead (H_6) and α-pyridyl (H_7) protons [$J_{6,7endo}$ < 2 Hz] confirmed that H_7 was indeed *endo*- and that the coupling reaction had given the *exo*- (β-) isomer (**3b**).[10] Deprotection with trimethylsilyl iodide gave *bis*-homoepibatidine (**3a**) in > 90% yield (scheme 1). ^{1}H NMR data for (**3a**) are summarised in the table.

Scheme 1



The synthesis of homoepibatidine (**2a**) using the reductive coupling approach requires 6,7-dehydro-tropanes but simple derivatives are not readily available.[11] Our own, otherwise successful, route to tropanes gave poor yields when applied to the synthesis of nortrop-6-ene.[7a] However, a very recent report of deoxygenation of the 6,7-epoxytropane scopolamine[12a] coupled with our recent synthesis of *exo*- and *endo*-epoxytropanes from cyclohepta-1,3-diene[13] opened up the route shown in scheme 2.

Scheme 2



The epoxide provides convenient and effective protection for the 6,7-dehydro- linkage; deoxygenation of the epoxide (**7**)[13] with a zinc-copper couple in ethanol[12b] gave the N-protected nortrop-6-ene (**8**) in good yield (scheme 2). The coupling reaction then gave (**2b**) in 63% yield[10] after chromatography. The ^{1}H NMR spectra for (**2b**) (table) showed similar features to those described for (**3b**); there was no detectable spin interaction between H_5 and $H_{6\text{-endo}}$ confirming the *exo*- stereostructure.[15] The ^{13}C NMR spectrum also showed a duplication of peaks due to the presence of two rotamers. Deprotection of (**2b**) gave (**2a**) smoothly.

Table Selected ^{1}H NMR data for epibatidine, homologues, and N-protected derivatives

(1b) [2b]	(2b) [a,b]	(3b) [a,b]	(1a) [2b]	(2a)	(3a)
H_4 4.44 brt	H_1 4.53 brd 4.47 brd	H_1 4.66 brt 4.58 brt	H_4 3.84 t (3.5)	H_1 3.70 m	H_1 3.9 m
$H_{3,5,6}$ 1.5 - 1.9 m 2.03 dd (12.0, 8.5)	$H_{2\text{-}4}$ 1.2 - 1.9 m H_{7endo} 2.28 m H_{7exo} 1.95 m	$H_{2\text{-}5,8}$ 1.4 - 1.8 m 2.0 - 2.30 m	$H_{3,5,6}$ 1.5 - 1.72 m 1.94 dd (12.2, 9.1)	$H_{2\text{-}4,7}$ 1.5 - 1.9 m H_{7endo}- 2.24 dd (13.2, 9.4)	$H_{2\text{-}5,8}$ 1.5 - 1.9 m 2.1 m
H_1 4.20 brs	H_5 4.22 brs 4.12 brs	H_6 4.31 brd (6.3) 4.20 brd (6.3)	H_1 3.60 brs	H_5 3.34 brs	H_6 3.48 br dd (5.3, 2.0)
H_{2endo} 2.89 dd (9.1, 5.0)	H_{6endo} 3.21 dd (9.4, 4.7)	H_{7endo} 3.19 m	H_{2endo} 2.79 dd (8.8, 5.3)	H_{6endo} 3.16 dd (9.1, 5.0)	H_{7endo} 3.10 brddd (~9.2, 6.6, 2.0)
pyridine ring 8.22 d (2.5) 7.60 dd (8.2, 2.5) 7.23 d (8.2)	pyridine ring 8.20 br 7.47, 7.40 dd (8.2, 2.5)[c] 7.20, 7.13 d (8.2)[c]	pyridine ring 8.21 brd (~2.4) 7.73 [c] 7.4 [c]	pyridine ring 8.27 d (2.5) 7.76 dd (8.4, 2.5) 7.24 d (8.4)	pyridine ring 8.28 d (2.5) 7.75 dd (8.2, 2.5) 7.23 d (8.2)	pyridine ring 8.25 d (2.5) 7.66 d (8.2, 2.5) 7.27 d (8.2)
	benzyl CH_2 5.20 AB (12.4) 5.16 AB (12.4)	benzyl CH_2 5.17 AB (12.3) 5.13 AB (12.3)			

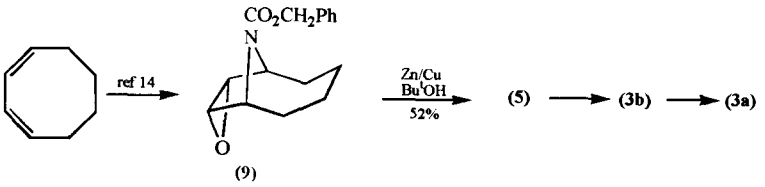
a. Spectra in $CDCl_3$; data shown as δ, multiplicity, (J Hz). J values differ across the series; relative values are supported by MM calculations.

b. Some signals are duplicated and/or broadened due to the presence of two rotamers about the N-CO bond.

c. Signals partially hidden beneath aryl signals; δ values extracted using HH COSY spectrum and homonuclear spin-decoupling experiments.

The ready availability of the N-protected 7,8-epoxyhomotropanes[14] from cycloocta-1,3-diene offered an effective alternative route to the key precursor **(5)** (scheme 3); the *endo*- epoxide **(9)** was selected for initial studies although the *exo*-epoxide or a mixture of stereoisomers can be used. Deoxygenation provided **(5)**[12b,c] and thence **(3b)** and **(3a)**.

Scheme 3



We are currently extending these studies to include N-methyl derivatives and analogues containing different substitution patterns in the pyridine ring. Other approaches also under active investigation are based on ring opening of the more reactive[13,14] *endo*-6,7- epoxytropanes and *endo*-7,8-epoxyhomotropanes with metallo-pyridines and also the incorporation of pyridyl substituents into monocyclic precursors[13,14] prior to the bicyclisation step.

We hope to report on the pharmacological properties[16] and spectroscopic behaviour of **(2)**, **(3)**, and analogues in due course.

References and Notes

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2. **a.** Early syntheses include: Broka, C.A.; *Tetrahedron Letters*, **1993**, *34*, 3251; Fletcher, S.R.; Baker, R.; Chambers, M.S.; Hobbs, S.C.; Mitchell, P.J. *J.Chem.Soc.Chem.Commun.*, **1993**, 1216; Corey, E.J.; Huang, D.F.; Shen, T.Y. *Tetrahedron Letters*, **1993**, *34*, 4477; Loh, T.E.; AchyuthaRao, S.; Daley, D.C.; Sarshar, S. *J.Org.Chem.*, **1993**, *58*, 5600 and reference 2b. Other syntheses published since 1993 are listed in a very recent paper: Xu, R.; Chu, G.; Bai, D. *Tetrahedron Letters*, **1996**, *37*, 1463.
   b. Clayton S.C.; Regan, A.C. *Tetrahedron Letters*, **1993**, *34*, 7493.
3. Lehn, J.M. *Fortschr.Chem.Forsch.*, **1970**, *15*, 311; Lambert, J.B. 'Topics in Stereochemistry', Allinger, N.L. and Eliel, L. Eds.; Wiley-Interscience: New York, **1971**, Vol.6; Jennings, W.B.; Worley, S.D. *J.Chem.Soc.Perkin Trans. 2*, **1980**, 1512 and references cited in these papers.
4. **a.** N-Alkyl derivatives: see Davies, J.W.; Durrant, M.L.; Walker, M.P.; Belkacemi, D.; Malpass, J.R. *Tetrahedron*, **1992**, *48*, 861, and references therein.
   b. N-Chloro derivatives: see Durrant, M.L.; Malpass, J.R. *Tetrahedron*, **1995**, *51*, 7063; Davies, J.W.; Durrant, M.L.; Walker, M.P.; Malpass, J.R. *Tetrahedron*, **1992**, *48*, 4379 and references to the work of others therein (e.g. footnote 4e in the first reference under **4b**).
   c. X-ray crystallographic studies: Davies, J.W.; Malpass, J.R.; Fawcett, J.; Prouse, L.J.S.; Lindsay, R.; Russell, D.R. *J.Chem.Soc.Chem.Commun.*, **1986**, 1135.
5. ^{15}N NMR studies in azanorbornanes, tropanes and homotropanes: Belkacemi, D.; Davies, J.W.; Malpass, J.R.; Naylor, A.; Smith, C.R. *Tetrahedron*, **1992**, *48*, 10161.
6. **a.** Initial ^{14}N NMR studies on epibatidine in $CDCl_3$ solution showed a relatively sharp signal at -70 ppm, tentatively assigned to the pyridyl nitrogen, together with broad (> 40 ppm) signals in the -70 ppm and -300 ppm region which only appeared at temperatures above 310K. On addition of trifluoracetic acid at 233K, only the signal at ca. -70 ppm was visible; however, a broad signal at ca. -300 ppm developed at 298K. [All spectra measured at 21.688 MHz; chemical shifts relative to external nitromethane = 0.] Further studies are in progress. We thank Dr. G. Griffith for measurement of N NMR spectra.
   b. We are very grateful to Dr. Andrew Regan (University of Manchester) for the loan of a sample of epibatidine and for advice on conditions for Pd-catalysed coupling reactions.
7. **a.** Tropanes and 6,7-dehydro- derivatives: Naylor, A.; Howarth, N.; Malpass, J.R. *Tetrahedron*, **1993**, *49*, 451. **b.** 1-Hydroxy-derivatives: Justice, D.E.; Malpass, J.R. *J.Chem.Soc.Perkin Trans.1.*, **1994**, 2559.
8. **a.** Homotropanes, 7,8-dehydrohomotropanes, and 1-alkyl derivatives: Smith, C.R.; Justice, D.E.; Malpass, J.R.; *Tetrahedron*, **1993**, *49*, 11037. **b.** 1-Hydroxyhomotropanes, nor-, and 7,8-dehydro-derivatives: Smith, C.R.; Justice, D.E.; Malpass, J.R.; *Tetrahedron*, **1994**, *50*, 11039.
9. Routes to **(2)** and **(3)**, NMR spectra of **(3a)** and **(3b)** and preliminary ^{14}N and ^{15}N NMR studies on epibatidine were presented at the Hong Kong International Symposium on Heterocyclic Chemistry in August 1995. [Abstract OP 17, p. 41]
10. **a.** Yields in this work are not yet optimised. **b.** In the reductive coupling reaction in the homotropane system, a small amount of a minor isomer was isolated from one reaction (performed at higher temperature) and shows the characteristics expected of the *endo*- stereoisomer of **(3b)**. Very minor products in the tropane series have still to be investigated.
11. See, for example, Woolley, J.G. *Rodd's Chemistry of Carbon Compounds, Supplement to Second Edition*, Vol. IV, Part B. **1985**, Chapter 11.
12. **a.** Bremner, J.B.; Smith, R.J.; Tarrant, G.J. *Tetrahedron Letters*, **1996**, *37*, 97. We thank Professor Bremner for a preprint of this paper and for helpful discussions. **b.** Conditions and yields for these reactions are still being improved; the deoxygenation of **(7)** proceeded more slowly than that of **(9)**. **c.** Some opening of the epoxide occurred from time to time when this reaction was performed in ethanol. This could be avoided by the use of t-butanol as solvent.
13. Justice, D.E.; Malpass, J.R. *Tetrahedron Letters*, **1995**, *36*, 4689.
14. Justice, D.E.; Malpass, J.R. *Tetrahedron Letters*, **1995**, *36*, 4685.
15. MS,^{13}C & HH COSY NMR spectra were in accord with the proposed structures.
16. N.B. Following acceptance of our manuscript, we received a copy of a very recent paper which describes the synthesis of homoepibatidine in 8 steps from 6β-hydroxytropinone; the compound is reported to show potent analgesic activity in hot-plate assays: Xu, R.; Bai, D.; Chu, G.; Tao, J.; Zhu, X. *Bioorg.Med.Chem.Lett.* **1996**, *6*, 279.

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