Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 3, pp. 279-282, 1996

0960-894X/96 $15.00 + 0.00

S0960-894X(96)00005-4

Synthesis and Analgesic Activity of Epibatidine Analogues

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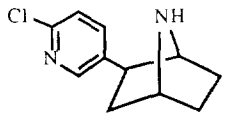
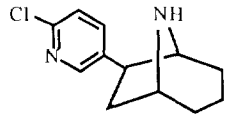
Abstract: Two epibatidine analogues with different skeleton were synthesized and their analgesic activity was evaluated. Compound **2** which has the 8-azabicyclo[3.2.1]octane ring system showed potent analgesic activity in hot -plate assay.

Epibatidine (**1**), the first alkaloid with a 7-azabicyclo[2.2.1]heptane ring system, was isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and co-workers.[1] It was reported to be a highly potent, non-opioid analgesic and nicotinic acetylcholine receptor agonist.[2-4] Due to its remarkable biological activity and unique structure, epibatidine has attracted a great deal of biological[2-9] and synthetic studies[10-22]. Up to now, over ten research papers about the synthesis of epibatidine and its analogues have been published. But all the analogues reported so far have the same basic skeleton, 7-azabicyclo[2.2.1]heptane ring system, as epibatidine itself. Recently we have also been involved in the synthesis of epibatidine and its analogues.[23] In this paper we wish to disclose our results about the synthesis and biological evaluation of two analogues of epibatidine, homoepibatidine **2** and deethylene epibatidine **3**.



epibatidine (**1**)



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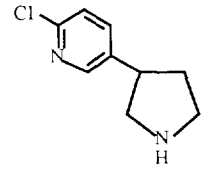
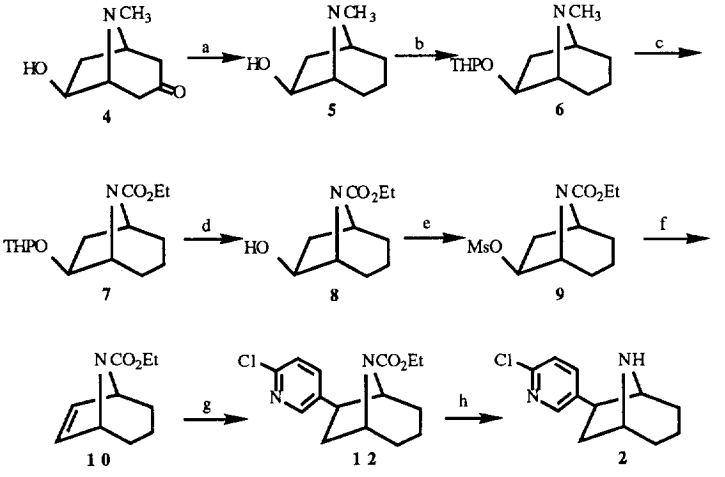


3

The synthesis of homoepibatidine **2** was summarized in Scheme 1. The commercially available 6β-hydroxytropinone (**4**) was used as a starting material. Wolff Kischner reduction of **4** by the method of Jones and Pinder[24] gave 6β-tropanol **5** (68.2%). Protection of the hydroxy group in **5** as THP ether followed by demethylation of **6** by treatment with ethyl chloroformate[25] afforded the carbamate **7** (90.3% overall yield from **5**). Deprotection of **7** with ethanol in the presence of PPTS yielded alcohol **8** (97.2%), which was mesylated to

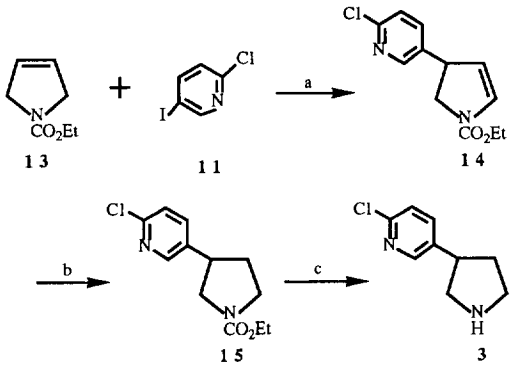
furnish mesylate **9** (92.6%). The elimination of mesylate **9** was accomplished by treatment with 1eq. of DBU in collidine at reflux, yielding the olefin **10** (79.3%). 2-Chloro-5-iodopyridine (**11**), the other component for the coupling, could be easily prepared in two steps from 2-aminopyridine according to the literature.[26] The crucial reductive coupling reaction between compound **10** and **11** was carried out in a solution of DMF containing piperidine, formic acid and the palladium catalyst formed *in situ* from palladium (II) acetate and triphenylphosphine.[13,27] The desired coupled product **12** was obtained in good yield (75.1%). Finally, cleavage of the carbamate in **12** with TMSI gave the target molecule **2** (93.2%). The assignment of the stereochemisty of **2** was made on the basis of the lack of a coupling between H-1 and H-2 in the ^1H NMR spectrum,[28] implying a dihedral angle close to 90°, which is only consistent with the *exo*-isomer.

Scheme 1



(a) i) 85% $NH_2NH_2{\cdot}H_2O$; ii) KOH; (b) DHP, TsOH, CH_2Cl_2; (c) $ClCO_2Et$, K_2CO_3, $CHCl_3$; (d) EtOH, PPTS; (e) MsCl, pyridine; (f) DBU, collidine; (g) 2-chloro-5-iodo-pyridine, $Pd(OAc)_2$, Ph_3P, HCO_2H, piperidine; (h) Me_3SiI, $CHCl_3$.

Scheme 2



(a) $Pd(OAc)_2$, KOAc, n-Bu_4NBr; (b) 10% Pd-C, EtOH, H_2; (c) Me_3SiI, $CHCl_3$.

The synthesis of deethylene epibatidine **3** was outlined in Scheme 2. The synthesis started with the protected 3-pyrroline **13**, which could be easily prepared from pyrrole in two steps by reduction with zinc and protection of the amine as carbamate.[29] Palladium-catalyzed allylic arylation of **13** with **11** by Larock's method[30] furnished the unstable cross-coupling product **14**, which was immediately hydrogenated to give the pyrrolidine derivative **15** (62.2% overall yield from **13**). Removal of the carbethoxy group in **15** with TMSI afforded the target compound 3-(2'-chloro-5'-pyridyl)-pyrrolidine (**3**) (94.3%).[31]

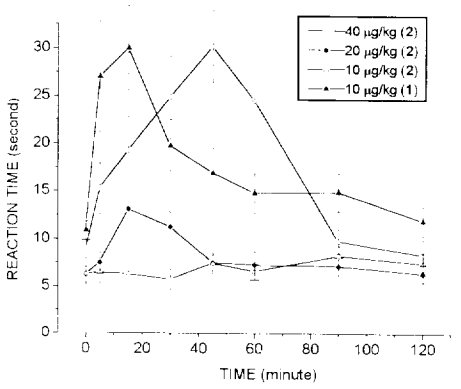


Fig. 1. Analgetic activity of homoepibatidine(2) in mice using hot-plate assay. Each value is mean ± standard error (n=10 animals).

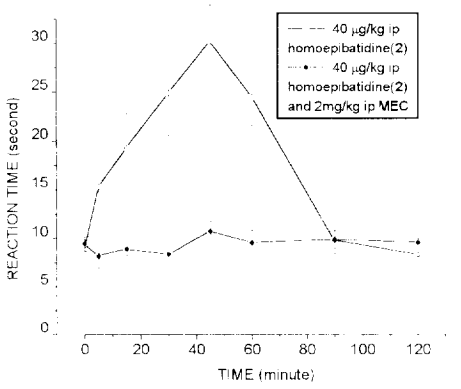


Fig. 2. Effect of nicotinic antagonist on homoepibatidine (2)-elicited analgesia in mice. 2 was administered 5 min after mecamylamine(MEC).

The analgesic activity of analogues **2** and **3** was evaluated using hot-plate assay and compared with (±) epibatidine, which was synthesized in our laboratory.[23] At a dose of 10 μg/kg, (±) epibatidine caused significant analgesia upon i.p. in mice. Compound **2**, with a LD_{50} of about 1mg/kg in mice, caused a marked analgesic effect at a dose of 40 μg/kg (Figure 1) comparable to that elicited by 10 μg/kg racemic epibatidine. Compound **3** is much less potent and caused analgesia at high dose (10 mg/kg). The analgesia elicited by compound **2** was abolished by the nicotinic receptor antagonist mecamylamine (Figure 2), suggesting the possible involvement of nicotinic receptor.

Acknowledgements. We acknowledge the financial support of this work by the National Key Laboratory of New Drug Research.

References and Notes

1. Spande, T.F.; Garraffo, H.M.; Edwards, M.W.; Yeh, H.J.C.; Pannel, L.; Daly, J.W. *J. Am. Chem. Soc.* **1992**, 114, 3475.
2. Li, T.; Qian, C.; Eckman, J.; Huang, D.F.; Shen, T.Y. *Bioorg. Med. Chem. Lett.* **1993**, 3, 2759.
3. Qian, C.; Li, T.; Shen, T.Y.; Libertine-Garaham, L.; Eckman, J.; Biftu, T.; Ip, S. *Eur. J. Pharmacol.* **1993**, 250, R13.
4. Badio, B.; Daly, J.W. *Mol. Pharmcol.* **1994**, 45, 563.
5. Fisher, M.; Huang, D.F.; Shen, T.Y.; Guyenet, P.G. *J. Pharmcol. Exp. Ther.* **1994**, 270, 702.
6. Damaj, M.I.; Creasy, K.R.; Grove, A.D.; Rosecrans, J.A.; Martin, B.R. *Brain Res.* **1994**, 664, 34.
7. Rupniak, N.M.J.; Patel, S.; Marwood, R.; Webb, J.; Traynor, J.R.; Elliott, J.; Freedman, S.B.; Fletcher S.R.; Hill, R.G. *Br. J. Pharmacol.* **1994**, 113, 1487.

8. Sullivan, J.P.; Decker, M.W.; Brioni, J.D.; Donnelly-Roberts, D.; Anderson, D.J.; Bannon, A.W.; Kang, C.H.; Adams, P.; Piattoni-Kaplan, M.; Buckley, M.J.; Gopalakrishnan, M.; Williams, M.; Arneric, S.P. *J. Pharmcol. Exp. Ther.* **1994**, 271, 624.
9. Bonhaus, D.W.; Bley, K.R.; Broka, C.A.; Fontana, D.J.; Leung, E.; Lewis, R.; Shieh, A.; Wong, E.H.F. *J. Pharmcol. Exp. Ther.* **1995**, 272, 1199.
10. Broka, C.A. *Tetrahedron Lett.* **1993**, 34, 3251.
11. Huang, D.F.; Shen, T.Y. *Tetrahedron Lett.* **1993**, 34, 4477.
12. Fletcher, S.R.; Baker, R.; Chambers, M.S.; Hobbs, S.C.; Mitchell, P.J. *J. Chem. Soc., Chem. Commun.*, **1993**, 1216.
13. Clayton, S.C.; Regan, A.C. *Tetrahedron Lett.* **1993**, 34, 7493.
14. Corey, E.J.; Loh, T.E.; AchyuthaRao, S.; Daley, D.C.; Sarshar, S. *J. Org. Chem.* **1993**, 58, 5600.
15. Senokuchi, K.; Nakai, H.; Kawamura, M.; Katsube, N.; Nonaka, S.; Sawaragi, H.; Hamanaka, N. *Synlett* **1994**, 343.
16. Okabe, K.; Natsume, M. *Chem. Pharm. Bull.* **1994**, 42, 1432.
17. Fletcher, S.R.; Baker, R.; Chambers, M.S.; Herbert, R.H.; Hobbs, S.C.; Thomas, S.R.; Verrier, H.M.; Watt, A.P.; Ball, R.G. *J. Org. Chem.* **1994**, 59, 1771.
18. Ko, S.Y.; Lerpiniere, J.; Linney, I.D.; Wrigglesworth, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1775.
19. Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay Jr., C.; Major-Temesváry, E.; Blaskó, G. *Ttrahedron Lett.* **1994**, 35, 3171.
20. Sestanj, K.; Melenski, E.; Jirkovsky, I. *Tetrahedron Lett.* **1994**, 35, 5417.
21. Albertini, E.; Barco, A.; Benetti, S.; Risi, C.D.; Pollini, G.P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, 35, 9297.
22. Kotian, P.L.; Carrol, F.I. *Synth. Commun.* **1995**, 25, 63.
23. Recently we accomplished the total synthesis of (±) epibatidine via a novel approach. The paper about this work has been submitted for publication.
24. Jones, J.B.; Pinder, A.R. *J. Chem. Soc.* **1959**, 615.
25. Montzka,T.A.; Matiskella, J.D.; Rartyka, R.A. *Tetrahedron Lett.* **1974**, 15, 1325.
26. Magidson, O.; Menschikoff, G. *Chem. Ber.* **1925**, 58, 113.
27. Arcadi, A.; Marinelli, F.; Bernocchi, E.; Cacchi, S.; Ortar, G.J. *J. Organometallic Chem.* **1989**, 368, 249.
28. ^{1}H NMR data for **2** (400MHz, $CDCl_3$): δ 8.20 (1H, d, J=2.2Hz, 6'-H), 7.66 (1H, dd, J=8.2, 2.2Hz, 4'-H), 7.15 (1H, d, J=8.2Hz, 3'-H), 3.61 (1H, m, 4-H), 3.24 (1H, brs, 1-H), 3.06 (1H, dd, J=9.2, 5.0Hz, 2-H), 2.15 (1H, dd, J=13.2, 9.2Hz, 3-H_{endo}), 1.50-1.90 (7H, m, 5,6,7-H, 3-H_{exo}).
29. Kawaguchi, M.; Hayashi, O.; Kanamoto, M.; Hamada, M.; Yamamoto, Y.; Oda, J. *Agric. Biol. Chem.* **1987**, 51, 435.
30. Larock, R.C.; Baker, B.E. *Tetrahedron Lett.* **1988**, 29, 905.
31. ^{1}H NMR data for **3** (400MHz, $CDCl_3$): δ 8.22 (1H, d, J=2.4Hz, 6'-H), 7.52 (1H, dd, J=8.4, 2.4Hz, 4'-H), 7.23 (1H, d, J=8.4Hz, 3'-H), 3.39-2.83 (5H, m, 2,3,5-H), 2.25,1.80 (2H, 2m, 4-H).

(*Received in Japan* 23 *October* 1995; *accepted* 25 *December* 1995)