Arch Pharm Res Vol 25, No 1, 49-52, 2002

Archives of Pharmacal Research
http://apr.psk.or.kr

Syntheses of (±)-Homoepibatidine Analogues

Yong-Hyun Kim, Chang-Young Oh, Kee-Young Lee, Yiu-Suk Lee, Young-Hoon Jung, Hyun-Ju Park, and Won-Hun Ham

College of Pharmacy, SungKyunKwan University, Suwon 440-746, Korea

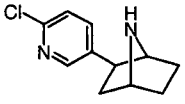
(Received December 10, 2001)

Syntheses of (±)-homoepibatidine analogues (**2**), which contain the 8-azabicyclo [3.2.1]octane ring system, were achieved by using palladium-catalyzed reductive-coupling reaction from **3** and the analgesic activity was tested by Mouse writhing antinociceptive assay

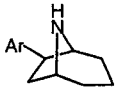
Key words : Alkaloids, Homoepibatidine, Analgesics, Palladium, Stereocontrol

INTRODUCTION

A new class of amphibian alkaloid epibatidine (**1**), which was isolated in a trace amount from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and co-workers (Spande *et al.*, 1992), has been reported to be a highly potent non-opioid analgesic. Subsequent studies showed that the analgesic activity of epibatidine is attributed to its distinctive property as an extremely potent agonist of the nicotinic acetylcholine receptor (Qian *et al.*, 1993; Fisher *et al.*, 1994). Due to its unique structure and remarkable pharmarcological activity, epibatidine has been the subject of many synthetic studies (Bai *et al.*, 1996; Pandy *et al.*, 1998; Malpass *et al.*, 1999; Koren *et al.*, 1999; Helquist *et al.*, 1999; Barros *et al.*, 1999; Evans *et al.*, 2001). It has been found that this desirable activity is accompanied by high toxicity. More recently, efforts have been directed toward finding more selective nicotinic analgesics that have fewer toxicity and adverse side effects associated with the natural alkaloid.



1



2a Ar = 2-methoxyphenyl
2b Ar = 3-methoxyphenyl
2c Ar = 2-chloro-5-pyridinyl
2d Ar = 2,4-methoxyphenyl

Correspondence to: Won-Hun Ham, College of Pharmacy, Sung KyunKwan University, Suwon 440-746, Korea
E-mail: whham@speed.ac.kr

Some of these efforts have resulted in the syntheses of biologically active epibatidine analogues (Bai *et al.*, 1996; Malpass *et al.*, 1996; Zhang *et al.*, 1997; Olivo *et al.*, 1999; Methfessel *et al.*, 2001; Che *et al.*, 2001; Ivy Carroll *et al.*, 2001). We have recently reported the total synthesis of (±)-homoepibatidine (Ham *et al.*, 1999). In this article, we wish to report a simple, efficient stereocontrolled syntheses of (±)-homoepibatidine analogues (**2**) and the analgesic activity was tested by Mouse writhing antinociceptive assay.

MATERIALS AND METHODS

General procedure for Palldium-catalyzed reductive coupling reaction

To a stirred solution of **3** (1.0 mmol) in DMF (5 mL), was added 2-chloro-5-iodopyridine (2.5 mmol), piperidine (3.5 mmol), $Pd(OAc)_2$ (0.08 mmol), PPh_3 (0.16 mmol). HCOOH (2.64 mmol). The reaction mixture was stirred at 80°C for 20 h, quenched with water (10 mL), organic layer was separated. The aqueous phase was extracted EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and rotary evaporated. The residue was purified by flash chromatography.

8-Carbomethoxy-6β-(2-methoxy phenyl)-8-azabicyclo[3.2.1]oct-3-one (4a)

Yield 76%; ^{1}H NMR (500MHz, $CDCl_3$) δ 2.04-2.23 (m, 2H), 2.43-2.80 (2br d, 2dd, 4H), 3.61 (m, 1H), 3.78 (m, 6H), 4.40-4.76 (4br s, 2H), 6.83 (m, 1H), 6.92 (m, 1H), 7.16 (m, 2H)

8-Carbomethoxy-6β-(3-methoxy phenyl)-8-azabicyclo[3.2.1]oct-3-one (4b)

Yield 75%; ^{1}H NMR (500MHz, $CDCl_3$) δ 2.17 (m, 1H), 2.27 (m, 1H), 2.42-2.57 (dd, 2H), 2.65-2.81 (2br d, 2H), 3.11 (m, 1H), 3.80 (m, 6H), 4.45-4.77 (4br s, 2H), 6.74 (m, 3H), 7.21 (m, 1H)

8-Carbomethoxy-6β-(2,4-dimethoxy phenyl)-8-azabicyclo[3.2.1]oct-3-one (4c)

Yield 73%; ^{1}H NMR (500MHz, $CDCl_3$) δ 2.02-2.20 (m, 2H), 2.42-2.79 (2br d, 2dd, 4H), 3.51 (m, 1H), 3.77 (m, 9H), 4.31-4.75 (4br s, 2H), 6.44 (m, 2H), 7.06 (m, 1H).

8-Carbomethoxy-6β-(2-chloro-5-pyridinyl)-8-azabicyclo[3.2.1]oct-3-one (4d)

Yield 74%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.28-1.34(br d, 3H), 2.12(m, 1H), 2.33(m, 1H), 2.46(dd, 1H), 2.57(dd, 1H), 2.70(br d, 1H), 2.83(br d, 1H), 3.18(br s, 1H), 4.25(br s, 2H), 4.42-4.52(br d, 1H), 4.71-4.79(br d, 1H), 7.29(m, 1H), 7.51(m, 1H), 8.21(m, 1H); ^{13}C NMR ($CDCl_3$) d 15.4, 40.0, 41.1, 45.0, 46.0, 54.6, 61.2, 62.6, 125.3, 137.2, 140.6, 148.7, 150.7, 154.5, 207.2; MS(*m/z*) 308/310(M^+), 169, 96.

General procedure for Reduction using L-Selectride

To a stirred solution of **4** (1.0 mmol) in THF (10 mL) at -78°C, was added L-selectride (1.22 mmol, 1 M in THF). The reaction mixture was stirred for 1h, quenched with 1 N-HCl, then organic layer was separated, washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and rotary evaporated. The residue was purified by flash chromatography.

8-Carbomethoxy-3α-hydroxy-6β-(2-methoxyphenyl)-8-azabicyclo[3.2.1]octane (5a)

Yield 85%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.80 (2s, 1H), 1.94 (m, 2H), 2.10 (m, 1H), 2.18 (m, 1H), 2.74 (m, 1H), 3.67-3.72 (2s, 3H), 3.82 (d, 3H), 4.15-4.50 (2br d, m, br s, 4H), 6.83 (m, 1H), 6.90 (m, 1H), 7.13 (m, 2H).

8-Carbomethoxy-3a-hydroxy-6β-(3-methoxyphenyl)-8-azabicyclo[3.2.1]octane (5b)

Yield 86%; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.70 (2s, 1H), 1.82-2.19 (m, 4H), 2.66 (m, 1H), 3.63-3.76 (m, 7H), 4.07-4.40 (3br s, m, br s, 3H), 6.70 (m, 3H), 7.11 (m, 1H)

8-Carbomethoxy-3α-hydroxy-6β-(2,4-dimethoxyphenyl)-8-azabicyclo[3.2.1]octane (5c)

Yield 86%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.79 (2s, 1H), 1.94 (m, 2H), 2.08 (m, 1H), 2.22 (m, 1H), 2.70 (m, 1H), 3.66-3.80 (m, 2s 9H), 4.32-4.47 (2br d, m, br s, 4H), 6.43 (m, 2H), 7.09 (m, 1H)

8-Carbomethoxy-3α-hydroxy-6β-(2-chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane (5d)

Yield 87%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.18-1.31(2t, 3H), 1.73-1.81(3br s, 2H), 1.88-1.96(m, 2H), 2.06-2.13(m, 1H), 2.20-2.26(m, 1H), 2.79-2.86(m, 1H), 3.88(m, 1H), 4.08-4.24(m, 4H), 4.40-4.50(2br d, 1H), 7.24(m, 1H), 7.52 (m, 1H), 8.22(m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.4, 39.7, 40.6, 43.8, 44.7, 54.2, 61.1, 61.9, 65.6, 125.1, 137.3, 142.8, 149.0, 150.0, 154.4; MS(*m/z*) 310/312(M^+), 171, 98.

General procedure for reductive deoxygenation using tributyltin hydride

To a stirred solution of **5** (1.0 mmol) in THF (10 mL) at r.t., was added sodium hydride (1.05 mmol), 1,1-thiocarbodiimi-dazole (1.15 mmol). The reaction mixture was stirred at r.t. for 5 h, quenched with 0.5 N-HCl, then organic layer was separated, washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and rotary evaporated. The crude xanthate was immediately employed in the next step without further purification.

A solution of the crude xanthate, tributyltin hydride (1.20 mmol) and azobisiso- butyronitrile (AIBN, 0.1 mmol) in benzene (10 mL) was heated under argon at 80°C for 12 h. benzene was evaporated and the residue purified by flash chromatography.

8-Carbomethoxy-6β-(2-methoxy phenyl)-8-azabicyclo[3.2.1]octane (6a)

Yield 42%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.50-1.98 (m, 8H), 2.23 (m, 1H), 3.67-3.73 (m, 4H), 3.82 (s, 3H), 4.11-4.31 (br d, 2br s, 2H), 6.83 (m, 1H), 6.91 (m, 1H), 7.18 (m, 2H)

8-Carbomethoxy-6β-(3-methoxy phenyl)-8-azabicyclo[3.2.1]octane (6b)

Yield 41%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.50 (m, 1H), 1.66-1.90 (m, 5H), 2.04 (m, 1H), 2.24 (m, 1H), 3.19 (m, 1H), 3.71-3.80 (s, 3H), 4.13-4.49 (2br d, 2br s, 2H), 6.76 (m, 3H), 7.19 (m, 1H).

8-Carbomethoxy-6β-(2,4-dimethoxy phenyl)-8-azabicyclo[3.2.1]octane (6c)

Yield 41%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.49 (m, 1H), 1.63-1.98 (m, 5H), 2.19 (m, 1H), 3.59 (m, 1H), 3.69-3.80 (m, d, 9H), 4.05-4.46 (2br d, 2br s, 2H), 6.43 (m, 2H), 7.08 (dd, 1H).

8-Carbomethoxy-6β-(2-chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane (6d)

Yield 45%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.51-1.98 (m, 7H), 2.31(m, 1H), 3.22 (m, 1H), 3.75 (2s, 3H), 4.05-4.206

(br s, 1H), 4.38-4.51 (2br d, 1H), 7.25 (m, 1H), 7.50 (m, 1H), 8.20 (m, 2H)

General procedure for preparation of (±)-Homoepibatidine analogues 2a-d from 6a-d

To a stirred solution of **6** (1.0 mmol) in $CHCl_3$ (5 mL), was added iodotrimethylsilane (5.0 mmol). The reaction mixture was reflux for 8 h, MeOH (1 mL) added. After rotary evaporated, quenched with 1N NaOH (5 mL), organic layer was separated. The aqueous phase was extracted $CHCl_3$ (10 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and rotary evaporated. The residue was purified by flash chromatography.

6β-(2-Methoxy phenyl)-8-azabicyclo[3.2.1]octane (2a)

Yield 59%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.52-2.02 (m, 7H), 2.24 (dd, *J*=13.0, 9.5 Hz, 1H), 3.20 (dd, *J*=9.5, 5.0 Hz,1H), 3.41 (br s, 1H), 3.71 (t, 1H), 3.85 (s, 3H), 6.74 (dd, 1H), 6.86 (m, 1H), 6.90 (m, 1H), 7.20 (m, 2H)

6β-(3-Methoxy phenyl)-8-azabicyclo[3.2.1]octane (2b)

Yield 59%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.52-2.02 (m, 7H), 2.24 (dd, *J*=13.0, 9.5 Hz, 1H), 3.20 (dd, *J*=9.5, 5.0 Hz,1H), 3.41 (br s, 1H), 3.71 (t, 1H), 3.81 (s, 3H), 6.73 (dd, 1H), 6.85 (m, 2H), 7.21 (m, 1H)

6β-(2,4-Dimethoxy phenyl)-8-azabicyclo[3.2.1] octane (2c)

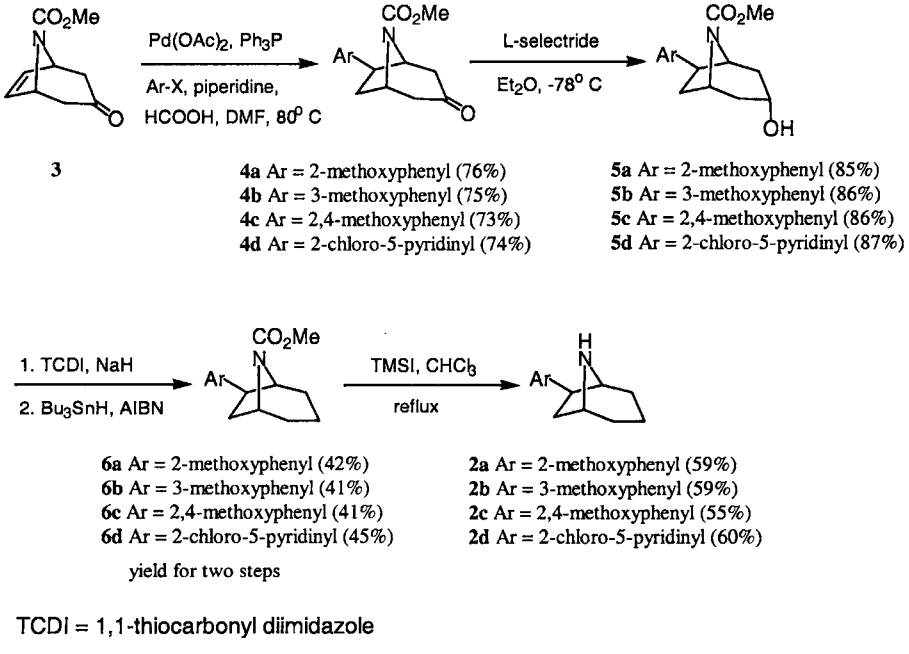
Yield 55%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.50-1.95 (m, 7H), 2.12 (dd, *J*=13.0, 9.5 Hz, 1H), 3.28 (br s, 1H), 3.48 (dd, *J*=9.5, 5.0 Hz, 1H), 3.69 (t, 1H), 3.80 (2s, 6H), 6.44 (m, 2H), 7.12 (dd, 1H),

6β-(2-Chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane (2d)

Yield 60%; ^{1}H NMR (500MHz, $CDCl_3$) δ 1.65-2.18 (m, 7H), 2.35 (dd, *J*=14.0, 9.5 Hz, 1H), 3.33 (dd, *J*=9.3, 6.0 Hz, 1H), 4.07 (t, 1H), 3.70 (brs, 1H), 7.33 (d, 1H), 8.06 (dd, 1H), 8.28 (d, 1H)

RESULTS AND DISCUSSION

The syntheses of (±)-homoepibatidine analogues (**2**) were started from 8-carbo- ethoxy-8-azabicyclo[3.2.1]oct-6-ene-3-one (**3**), which was early synthesized according to the efficient method developed by Barbosa et al(Mann *et al.*, 1992). **3** was heated at 80°C for 24 h in DMF containing piperidine (3.5 equiv.), formic acid (2.6 equiv.), palladium acetate (10 mol%) and triphenylphosphine (20 mol%)(Bai *et al.*, 1996). The desired reductively-coupled product (**4a-d**) was formed in a moderate yield (52 - 70%) after flash chromatography. **4a-d** was treated with L-selectride at -78°C to afford the corresponding alcohol (**5 a-d**). Deoxygenation was accomplished by way of the imidazolyl thionoester, followed by treatment with Bu_3SnH (Rasmussen *et al.*, 1998). Finally, cleavage of the methoxycarbonyl group in **6a-d** with iodotrimethylsilane gave (±)-homo- epibatidine analogues (**2a-d**) in 14 16 % overall



Scheme 1. Synthetic scheme of (±)-homoepibatidine analogues

Table I. Analgesic activity of the test compounds by Mouse writhing antinociceptive assay[a]

: mean ± S.E., No. of mouse : 10

Sample	Dose (μg/kg)	No. of writhing#	Inhibition rate (%)
Control	-	21 ± 4.1	0
(±)-Epibatidine	10	1.7 ± 0.3	92
2a	1000	16.2 ± 1.9	23
2b	1000	11.6 ± 3.5	45
2c	100	11.0 ± 3.1	43
2d	1000	14.3 ± 1.9	32

[a]ICR male mice (weight 25 g) were maintained in a controlled lighting environment (12 h on/12 h off). Animals received an intraperitoneal injection of 0.3 ml of the chemical irritant phenyl-*p*-quinone (4.5 mg/kg dissolved in saline containing 5% EtOH), and 6 min later the number of abdominal constrictions was counted in the subsequent 6 min period. Animals received drug or vehicle (10 animals/group) intraperitoneally 60 min prior to administration of phenyl-*p*-quinone. A reduction in the number of animals responding to phenyl-*p*-quinone relative to the number responding in the saline control group was considered as antinociceptive effect. (±) -epibatidine (10 g/kg, ip) was used as a positive control in all experiments.

yield from **3**.

And then, the analgesic activity of the synthesized (±)-homoepibatidine analogues was tested by Mouse writhing antinociceptive assay.

As shown in Table I, in comparison with (±)-epibatidine, all tested compounds failed to show significant antinociceptive effect in the assay. Homoepibatidine 2c showed modest analgesic activity at dose of 1000 mg/kg, whereas other compounds 2a, 2b, 2d showed very low activity.

In summary, syntheses of (±)-homoepibatidine analogues were accomplished by palladium-catalyzed coupling reaction and the analgesic activity was tested by Mouse writhing antinociceptive assay.

ACKNOWLEDGEMENTS

Financial support from Ministry of Health and Welfare(HWP-96-D-1-0006) is gratefully acknowledged.

RERERENCES

Bai, D., Xu, R., Chu, G., and Zhu, X. Synthesis of (±)-epibatidine and its analogues. *J. Org. Chem.*, 61, 4600-4606 (1996).

Barros, M. T., Maycock, C. D., and Ventura, M. R. The effect of DMSO on the borohydride reduction of a cyclohexanone: A formal enantioselective synthesis of (+)-epibatidine. *Tetrahedron Lett.*, 40, 557-560 (1999).

Che, D., Wegge, T., Stubbs, M. T., Seitz, G., Meier, H., and Methfessel, C. exo-2-(Pyridazin-4-yl)-7-azabicyclo[2.2.1]heptanes: Syntheses and nicotinic acetylation receptor agonist activity of potent pyridazine analogues of (±)-epibatidine. *J. Med. Chem.* 44, 47-57 (2001).

Evans, D. A., Scheidt, K. A., and Downey, C. W. Synthesis of (-) -epibatidine. *Organic Lett.*, 3, 3009-3012 (2001)

Fisher, M., Huang, D. F., Shen, T. Y., and Guyenet, P. G. *J. Pharmcol. Exp. Ther.*, 270, 702-707 (1994).

Ham, W. H., Kim, Y. H., Won, D. Y., Oh, C. Y., Lee, K. Y., Jeong, J. H., and Jung, Y. H. Total synthesis of (±)-homoepibatidine. *Arch. Pharm. Res.*, 22, 435-436 (1999).

Helquist, P., Palmgren, A., Larsson, A. L. E., and Backvall, J-E. Palladium(II)-Catalyzed 1,4-Oxidation of 2-Aryl-1,3-cyclohexadienes. Application to the Synthesis of (±)-Epibatidine and Analogues. *J. Org. Chem.*, 64, 836-842 (1999).

Ivy Carroll, F., Liang, F., Navaro, H. A., Brieaddy, L. E., Abraham, P., Damaj, M. I., and Martin, B. R. Synthesis, nicotinic acetylcholine receptor binding, and antinociceptive properties of 2-exo-2-(2'-substituted 5'-pyridinyl)-7-azabicyclo[2.2.1]heptanes. epibatidine analogues. *J. Med. Chem.* 44, 2229-2237 (2001).

Koren, A. O., Horti, A. G., Mukhin, A. G., Gundisch, D., Kimes, A. S., Dannals, R. F., London, E. D. 2-, 5-, and 6-halo-3-(2(S)-azetidinylmethoxy)pyridines: Synthesis, affinity for nicotinic acetylcholine receptors, and molecular modeling. *J. Med. Chem.*, 41, 3690-3698 (1999).

Malpass, J. R., Hemmings, D. A., and Wallis, A. L. Synthesis of epibatidine homoloues. *Tetrahedron Lett.*, 37, 3911-3914 (1996).

Malpass, J. R. and Cox, C. D. Synthesis of 5- and 6-chloropyridyl-substituted 2-azabicyclo[2.2.1]heptanes; novel epibatidine isomers. *Tetrahedron Lett.*, 40, 1419-1422 (1999).

Mann, J., Barbosa, L-C de A. An efficient route to the tropane alkaloids. *J. Chem. Soc. Perkin Trans. 1.*, 787-789 (1992).

Methfessel, C., Che, D., Wegge, T., Stubbs, M. T., Seitz, G., and Meier, H. exo-2-(Pyridazin-4-yl)-7-azabicyclo[2.2.1]heptanes: syntheses and nicotinic acetylcholine receptor agonist activity of potent pyridazine analogues of (±)-Epibatidine. *J. Med. Chem.*, 44, 47-57 (2001).

Pandey, G., Bagul, T. D., and Sahoo, A. K. [3+2] Cycloaddition of nonstabilized azomethine ylides. Stereoselective synthesis of epibatidine and analogues. *J. Org. Chem.*, 63, 760-768 (1998).

Qian, C., Li, T., Shen, T. Y., Libertine-Garaham, L., Eckman, J., and Biftu, T., Ip, S. *Eur. J. Pharmacol.*, 250, R13-R14 (1993).

Olivo, H. F., Colby, D. A., and Hemenway, M. S. Syntheses of new open-ring and *homo*-epibatidine analogues from tropinone *J. Org. Chem.*, 64, 4966-4968 (1999).

Rasmussen, J. R., Slinger, C. J., Kordish, R. J., and Newman-Evans, D. D. Synthesis of deoxy sugars. *J. Org. Chem.*, 46, 4843-4846 (1981).

Spande, T. F., Garraffo, H. M., Edwards, M. W., Yeh, H. J. C., Pannel, L., Daly, and J. W. Epibatidine: A novel (chloropyridyl) azabicycloheptane with potent analgesic activity from an ecuandoran poison fog. *J. Am. Chem. Soc.* 114, 3475-3478 (1992).

Zhang C., Gyermek, L., and Trudell, M. L. Synthesis of optically pure epibatidine analogs. *Tetrahedron Lett.*, 38, 5619-5622 (1997).