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Stereoselective Syntheses of (±)-Epibatidine Analogues

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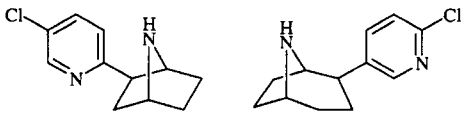
Stereoselective syntheses of (±)-epibatidine analogues **2**, which contain the 8-azabicyclo [3.2.1]octane ring system, were achieved by using palladium-catalyzed cross-coupling reaction from **4** and the analgesic activity was tested by Mouse writhing antinociceptive assay.

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

INTRODUCTION

Epibatidine(**1**), which was isolated 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 and nicotinic acetylcholine receptor agonist (Qian *et al.*, 1993; Fisher *et al.*, 1994). A number of its synthetic approaches have been reported (Bai *et al.*, 1996; Pandy *et al.*, 1998; Malpass *et al.*, 1999; Koren *et al.*, 1999; Helquist *et al.* 1999; Evans *et al.*, 2001) due to its unusual structure and its interesting biological activity. It has been found that this desirable activity is accompanied by high toxicity. This has generated interest in the preparation of analogues which may be selective nicotinic receptor analgesics with reduced toxicity.



1 **2**

3a Ar = 2-methoxyphenyl
3b Ar = 3-methoxyphenyl
3c Ar = 4-methoxyphenyl

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 stereoselective synthesis of (±)-epibatidine analogue, (±)-2β-(2-chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane (**2**) (Ham *et al.*, 1999). In this article, we wish to report a simple, efficient regio- and stereocontrolled syntheses of (±)-epibatidine analogues **3a-c** and the analgesic activity was tested by Mouse writhing antinociceptive assay.

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MATERIALS AND METHODS

8-Carboethoxy-3a-hydroxy-8-azabicyclo[3.2.1] octane (5)

To a stirred solution of **4** (1.0 mmol) in $CHCl_3$ (10 mL), was added ethylchloroformate (2.0 mmol), K_2CO_3 (3.0 mmol). The reaction mixture was reflux at 4 h. Evaporation of the solvent under reduced pressure and the residue was purified by flash chromatography.

Yield 98%; IR (neat); 3445, 2978, 1672 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.22 (t, 3H), 1.70 -1.98 (dd, 2H), 1.94-2.18 (m, 6H), 4.10 (m, 3H), 4.26 (br d, 2H).

8-Carboethoxy-8-azabicyclo[3.2.1]oct-2-ene (6)

To a stirred solution of **5** (1.0 mmol) in dry pyridine (5 mL) at 0°C, was added methanesulfonyl chloride (1.5 mmol). The reaction mixture was stirred at r.t. for 20 h, quenched with water (5 mL), organic layer was separated. The aqueous phase was extracted EtOAc (5 mL × 3). The combined organic layers were washed with 1 N-HCl, saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and rotary evaporated. The residue was purified by flash chromatography.

Mesylate

Yield 98%; IR (neat); 3495, 2980, 1694, 1349 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.22 (t, 3H), 1.95-2.16 (m, 8H), 2.98 (s, 3H), 4.10 (q, 2H), 4.26 (br s, 2H), 4.98 (m, 1H).

A solution of mesylate (1.0 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.1 mmol), dry s-collidine (5 mL) was reflux for 8 h, quenched with water (5 mL), organic layer was separated. The aqueous phase was extracted methylene chloride (5 mL × 3). The combined organic layers were washed with 0.5 N-HCl, saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and rotary evaporated. The residue was purified by flash chromatography.

Yield 82%; IR (neat); 3590, 2978, 1701 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.22 (t, 3H), 1.60-1.95 (m, 4H), 2.13 (br s, 1H), 2.71 (br s, 1H), 4.09 (br s, 2H), 4.32 (br s, 3H), 5.48 (m, 1H), 5.94 (br s, 1H).

General procedure for palldium-catalyzed cross-coupling reaction

To a stirred solution of **6** (1.0 mmol) in DMF (5 mL), was added 2-iodoanisole (1.5 mmol), $Pd(OAc)_2$ (0.15 mmol), PPh_3 (0.3 mmol). triethylamine (3.0 mmol). The reaction mixture was stirred at 80°C for 1.5 day, 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-Carboethoxy-2β-(2-methoxyphenyl)-8-azabicyclo [3.2.1]oct-2-ene (7a)

Yield 35%; IR (neat); 3495, 2975, 1699, 1600, 1431 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) rotamer δ 0.68 (t, 2H), 1.20 (br s, 1H), 1.70-1.90 (m, 3H), 2.23 (m, 1H), 3.43 (m, 0.77H), 3.60 (br s, 1H), 3.67 (m, 0.77H), 3.87 (s, 3H), 3.98 (br s, 0.46H), 4.39 (m, 0.77H), 4.52 (br s, 0.23H), 4.57 (br s, 1H), 5.57 (m, 1H), 6.19 (br s, 0.23H), 6.24 (m, 0.77H), 6.87 (m, 2H), 7.04 (d, 1H), 7.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 30.4, 34.6, 45.3, 53.4, 56.0, 57.3, 60.9, 110.4, 120.9, 126.3, 128.2, 130.9, 131.1, 133.9, 154.3, 157.3.

8-Carboethoxy-2β-(3-methoxyphenyl)-8-azabicyclo [3.2.1]oct-2-ene (7b)

Yield 36%; IR (neat); 3501, 2977, 1696, 1599, 1433 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) rotamer δ 0.78 (t, 2H), 1.20 (br s, 1H), 1.70-1.99 (m, 3H), 2.23 (m, 1H), 3.20 (d, 1H), 3.59 (m, 0.7H), 3.75 (m, 0.7H), 3.79 (s, 3H), 4.05 (br s, 0.6H), 4.38 (m, 0.7H), 4.57 (br s, 0.3H), 4.60 (m, 1H), 5.60 (m, 1H), 6.18 (br s, 0.3H), 6.23 (br s, 0.7H), 6.79 (m, 3H), 7.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.0, 31.2, 35.3, 46.1, 54.0, 56.0, 57.3, 61.1, 110.7, 121.1, 126.0, 128.5, 131.3, 131.6, 135.5, 154.5, 157.7.

8-Carboethoxy-2β-(4-dimethoxyphenyl)-8-azabicyclo [3.2.1]oct-2-ene (7c)

Yield 37%; IR (neat); 3499, 2970, 1689, 1587, 1433 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) rotamer δ 0.78 (t, 2H), 1.20 (br s, 1H), 1.70-1.95 (m, 2H), 2.20 (m, 1H), 3.20 (d, 1H), 3.60 (m, 0.77H), 3.75 (m, 0.77H), 3.79 (s, 3H), 4.05 (br s, 0.46H), 4.30 (m, 1H), 4.50 (br s, 0.23H), 4.59 (br s, 0.77H), 5.57 (m, 1H), 6.15 (br s, 0.23H), 6.25 (br s, 0.77H), 6.88 (m, 2H), 7.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.9, 21.3, 28.6, 29.6, 30.1, 45.4, 54.3, 56.0, 60.0, 61.1, 114.2, 129.5, 137.1, 154.7, 158.4.

General procedure for preparation of (±)-Epibatidine analogs 3a-c from 7a-c

To a stirred solution of **7a-c** (1.0 mmol) in absolute ethanol (5 mL), was added a catalytic amount of 10% Pd/C (7 mg). To this reaction mixture connected double balloon of H_2 gas and stirred at r.t. for 12 h. The reaction mixture filtered through a Celite pad, solvent was evaporated under reduced pressure. The crude product was immediately employed in the next step without further purification.

To a stirred solution of resulting product (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.

2β-(2-Methoxyphenyl)-8-azabicyclo[3.2.1]octane (3a)

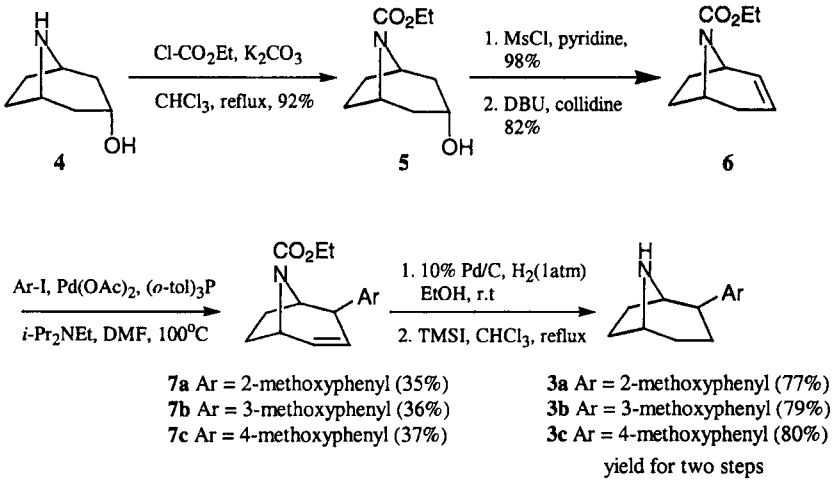
Yield 77%; IR (neat); 3440, 1590, 1430 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 1.50 (m, 1H), 1.70-2.20 (m, 8H), 3.09 (d, *J*=7.0Hz, 1H), 3.57 (m, 1H), 3.60 (m, 1H), 3.80 (s, 3H), 6.85 (dd, *J*=1.0, 8.0Hz, 1H), 6.98 (dt, *J*=1.0, 8.0Hz, 1H), 7.22 (dt, *J*=1.5, 7.5Hz, 1H), 7.45 (dd, *J*=1.5, 7.5Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 29.1, 30.8, 31.8, 39.0, 55.0, 55.9, 58.3, 110.8, 121.0, 127.7, 128.7, 133.9, 157.8.

2β-(3-Methoxyphenyl)-8-azabicyclo[3.2.1]octane (3b)

Yield 79%; IR (neat); 3450, 1597, 1433 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 1.45 (m, 1H), 1.70-2.20 (m, 8H), 2.75 (d, *J*=6.5Hz, 1H), 3.52 (m, 1H), 3.62 (d, 1H), 3.81 (s, 3H), 6.76 (dd, 1H), 6.94 (d, 1H), 6.98 (d, 1H), 7.27 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 24.3, 31.3, 32.1, 31.8, 39.0, 55.0, 55.9, 58.3, 110.8, 120.9, 128.0, 128.6, 133.9, 159.0.

2β-(4-Methoxyphenyl)-8-azabicyclo[3.2.1]octane (3c)

Yield 79%; IR (neat); 3445, 1587, 1432 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 1.45 (m, 1H), 1.60-2.20 (m, 8H), 2.75



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

(d, *J*=6.5Hz, 1H), 3.52 (m, 1H), 3.59 (m, 1H), 3.80 (s, 3H), 6.88 (m, 2H), 7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.5, 30.1, 31.5, 32.4, 41.5, 55.7, 57.6, 61.5, 111.2, 121.0, 127.8, 128.6, 140.0, 158.3.

RESULTS AND DISCUSSION

The syntheses of (±)-epibatidine analogues **3** were started from commercially available tropine (**4**). The conversion of **4** to **6** was accomplished by the efficient three step sequences. Ethoxycarbonylation, mesylation and then DBU treatment of **4** afforded **6** in 72% overall yield in three steps. The aryl group was then introduced into the 8-azabicyclo[3.2.1]octane ring system by a palladium catalyzed cross-coupling reaction under standard conditions (15 mol% palladium acetate, 3 equiv. triethylamine, and 30 mol% triphenylphophine) in dry DMF at 80°C to give **7a-c**.

Finally, hydrogenation of **7a-c** and deprotection of ethoxycarbonyl group with iodotrimethylsilane gave (±)-epibatidine analogues **3a-c** in 16-17.8 % overall yield from **6**. We were delighted to find that **3a-c** was found to be completely regio- and stereoselective as the only desired exo-isomer could be isolated. The exo-orientation of aryl group was determined on the basis of ^{1}H NMR (500 MHz) coupling constant (*J*=6.5-7.0Hz), which is in agreement with the reported value (Zhang *et al.*, 1997). And then, the analgesic activity of the synthesized (±)-epibatidine 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. **7a** and **3b** demonstrated analgesic effect at 100 mg/kg were similar to that of (±)-epibatidine at 10 mg/kg, whereas other compounds **7b**, **7c** showed low activity at 100 mg/kg. However, all tested compounds were more potent than (±)-homoepibatidine analogues in the assay.

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
7a	100	9.0 ± 2.1	57
7b	100	16.2 ± 3.0	23
7c	100	17.6 ± 4.1	16
3b	100	14.7 ± 2.3	30

[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.

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

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