Chinese Chemical Letters Vol. 13, No. 9, pp 814 – 817, 2002
http://www.imm.ac.cn/journal/ccl/html

Synthesis and Their Endothelium Vascular Relaxation of Arecoline Derivatives Containing Oxadiazoline

Guo Qiang HU[1], Wen Long HUANG[1]*, Hui Bin ZHANG[1], Hai WANG[2]

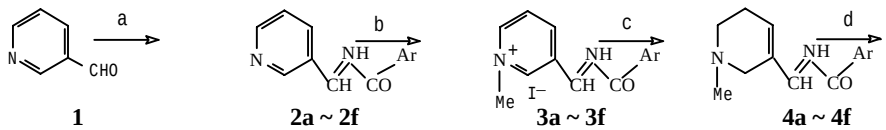
[1]China pharmaceutical University, Nanjing 210009
[2]Academy of Military Medical Sciences, Beijing 100850

Abstract: Ten novel 1, 1-dimethyl-3-(2-or 5-aryl-4-acetyl-2, 3-dihydro-1, 3, 4-oxadiazoline-5-or-2-yl)-1, 2, 5, 6- tetrahydropyridinium iodides were synthesized from starting material nicotinaldehyde or nicotinic acid by two different synthetic methods respectively. The preliminary bioactive tests indicate som compounds exhibit potent relaxing effect on endothelial cells, comparable to Ach or arecoline.

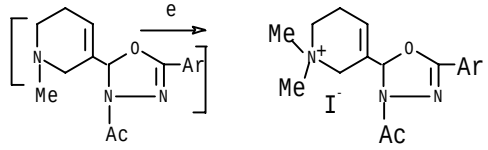
Keywords: Arecoline derivatives, oxadiazoline, muscarinic agonist, EPA, relaxing effect.

Arecoline derivatives as muscarinic agonist not only had useful profiles in treatment of Alzheimer's disease (AD) on basis of cholinergic hypothesis[1-5] but might act on endothelial protein-activated by acetylcholine(EPA)[6, 7] receptor. On the other hand, both oxadiazolines and tetrahydropyridines are also important structural units found in a variety of natural products with interesting biological activities[8, 9]. In cojunction with our urgent needs for EPA research , we wish herein describe the two different synthetic methods (**Scheme 1** and **Scheme 2**) to introduce of oxadiazoline ring in place of the ester moiety of arecoline for the preparation of its novel derivatives that might be useful for selective muscarinic agonists acting on EPA.

Scheme 1



1 **2a ~ 2f** **3a ~ 3f** **4a ~ 4f**



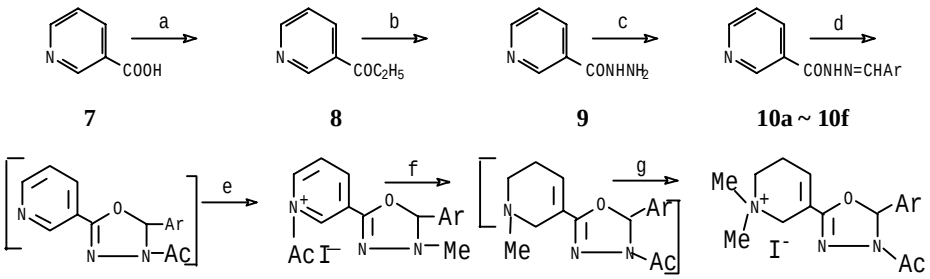
5a ~ 5f

6a ~ 6f

2a~6a Ar = C_6H_5, **2b ~ 6b** Ar = 4-FC_6H_4, **2c ~ 6c** Ar = 4-ClC_6H_4, **2d ~ 6d** Ar = 4-$CH_3C_6H_4$, **2e~6e** Ar =4-$CH_3OC_6H_4$, **2f ~ 6f** Ar = 3, 4-$(OCH_2O)C_6H_3$

Reagents and contions: a, $ArCONHNH_2$, 3% HAc, 0°C ~ 50°C; b, MeI, DMF, r.t.;
c, $NaBH_4$, *iso*proanol, H_2O, 80°C; d, Ac_2O, xylene, reflux; e, MeI, acetone, reflux.

Scheme 2



10a ~14a Ar = C_6H_5 , **10b ~14b** Ar = 4-FC_6H_4 , **10c ~ 14c** Ar =4- ClC_6H_4 , **10d ~14d** Ar = 4-$CH_3C_6H_4$,
10e ~ 14e Ar = 4-$CH_3OC_6H_4$, **10f ~ 14f** Ar = 3, 4- $(OCH_2O)C_6H_3$

Reagents and contions: a, C_2H_5OH , H_2SO_4, reflux; b, 85% $NH_2NH_2.H_2O$; c, ArCHO, C_2H_5OH , reflux ;
d, Ac_2O, reflux; e, MeI, acetone, reflux; f, $NaBH_4$, methanol, H_2O, 0°C; g, ether, MeI, reflux.

Nicotinaldehyde **1** was condensated with various aroylhydrazines to give corresponding hydrazones **2a ~ 2f** at 0°C in aqueous HAc solution, which were quaternized with MeI at room temperature in DMF for 24 h to give quaternary salts **3a ~3f**, the reduction of **3a ~ 3f** with $NaBH_4$ at 80°C in *iso*propanol-H_2O to afford tetrahydronicotinaldehyde aroylhydrazones **4a ~ 4f.** Next treatment of **4a ~ 4f** with Ac_2O in xylene gave the compounds **5a ~ 5f**, without isolation, **5a ~ 5f** were requaternized to give the expected compounds **6a ~ 6f (Scheme 1)**.

10a ~10f was obtained according to the knowed procedure[10]**,** which were cyclized with Ac_2O to give 5-pyridyl-4, 5-dihydro-1, 3, 4-oxadiazol **11a ~ 11f**, and sequently quaternized with MeI at reflux in acetone for 24 h to form corresponding pyridiniums **12a ~ 12f.** Ttreatment of **12a ~ 12f** with $NaBH_4$ at 0°C in methanol-H_2O to give 5-tetrahydropyridinoxadiazolines 1**3a ~13f**, which were requaternized to give the desired compounds **14a-14f** (**Scheme 2**).

Attempted synthesis of the title compounds **6a ~ 6f** according to **Scheme 2** was unsuccessful , but **14a ~ 14f** could be synthesized with method **1** as well.

The preliminary biological tests demonstrated that the relaxation effects of isolated endothelial cells are 19, 17, 15, 11, 9, 8% for the compounds **6a**, **6e**, **6f, 13a**, **13e** and **13f** respectively, which is comparable to that of classical muscarinic agonists[11,12]. Further studies on the structure activity relationships (SAR) and structural modifications of arecoline are underway.

The structure of the target compound **6a ~6f**, **14a ~ 14f** were confirmed by ^1H NMR, IR, MS and elemental analysis[13] .

Acknowledgment

Fianncial support of this work by the State Key Basic Research and Development Project (No. G 1998051112)

References and Notes

1. E .K. Moltzen, B. Bjornholm, *Drugs Fut.*, **1995 ,** *20* (1) **,** 37.
2. E. Meier, K . Frederiksen, *Drug Dev Res.*, **1997** , 40 , 1.
3. C . F . Christian, P . B . Frank, W . John, *J Med. Chem.* , **2000** , *43*, 4335.
4. M . F. Siddiqui, A . I . Levey, *Drugs Fut.*, **1999,** *24* (4**) ,** 417.
5. P . Sauerberg, P.. H . Olesen, *J Med. Chem.*, **1998**, *41*, 109.
6. L . L. Wang, H. Wang , *Chin Pharmaco Bull* (in Chinese), **2001**, *17* (1), 1.
7. L . L. Jung, H. Wang, *Life Sci.*, **2001** (in press).
8. M . H . Jung, J.. G.. Park, *Heterocyclic Chem.*, **1999**, *36* , 429.
9. F . M . Liu, J. X . Yu , Y*ouji Huaxue* (in Chinese), **1999**, *36* , 429.
10. T . S . Gardner, F. A. Smith, *J . Org . Chem.*, **1956**, *21*, 530.
11. T . M . Cocks, J. A . Angus, *J Cell Physiol.*, **1985,** *123***,** 310.
12. L . L . Wang, H. Wang, *Chin Pharmaco. Bull.* (in Chinese), **2001**, *17* (3), 275.
13. **6a:** Ar=C_6H_5, mp 218-220°C. EA.Calcd for $C_{17}H_{22}IN_3O_2$: C, 47.79, H, 5.19, N, 9.83; Found: C, 47.79, H, 5.11, N, 10.11. IR (KBr, cm^{-1}): 3025, 2932, 1667, 1634, 943. ^1H NMR (500MHz, D_2O, δ ppm, J Hz) : 8.09- 7.3 (m, 5H), 6.86 (s,1H), 6.68 (br s, 1H), 4.12 (dd, 2H, J=15.6, 16) , 3.70 (t, 2H, J=6), 3.34, 3.28 (2s, 6H), 2.54 (s, 3H). EIS-MS(*m/z*): 300(M^+-127). **6b:** Ar=4-FC_6H_4, mp 222-224°C. EA.Calcd for $C_{17}H_{21}FIN_3O_2$: C, 45.86, H, 4.75, N, 9.44; Found: C, 45.65, H, 4.55, N, 9.70. IR (KBr, cm^{-1}): 3015, 2946, 1668, 1633, 943. ^1H NMR (500MHz, D_2O, δ ppm, J Hz): 7.88- 7.22 (m, 4H), 6.64 (s, 1H), 6.44 (br s, 1H), 3.92 (dd, 2H, J=11.5, 10.5), 3.46 (t, 2H, J=6.6, 6), 3.10, 3.04 (2s, 6H), 2.62 (br s, 2H), 2.30 (s, 1H). EIS-MS (*m/z*): 318(M^+-127). **6c**: Ar=4-ClC_6H_4, mp 214-216°C**.** EA.Calcd for $C_{17}H_{21}ClIN_3O_2$: C, 44.23, H, 4.6, N, 9.10; Found**:** C, 44.03, H, 4.58, N, 9.32. IR (KBr, cm^{-1})**:** 3035, 3007, 1662, 1633, 941. ^1H NMR (500MHz, D_2O, δ ppm, J Hz)**:** 7.88- 7.44 (m, 4H), 6.65 (s, 1H), 6.45 (br s**,** 1H), 3.88 (dd, 2H, J=16.5), 3.46 (t, 2H, J=6.6, 6), 3.12, 3.05 (2s, 6H), 2.63 (m, 2H), 2.30 (s, 3H). EIS-MS (*m/z*): 334(M^+-127). **6d:** Ar=4-$CH_3C_6H_4$, mp 211-213°C**.** EA.Calcd $C_{18}H_{24}IN_3O_2$: C, 49.00, H, 5.48, N, 9.52; Found **:** C, 48.76, H, 5.32, N, 9.75. IR (KBr, cm^{-1})**:** 3033, 2937, 1676, 1633, 945**.** ^1H NMR (500MHz, D_2O, δ ppm, J Hz)**:** 7.72- 7.31 (m, 4H), 6.60 (s, 1H), 6.42 (br s, 1H), 3.86 (dd, 2H, J=16), 3.46 (t, 2H, J=6.6, 6)**,** 3.09, 3.03 (2s, 6H), 2.63 (br s, 2H), 2.30 (s, 3H), 2.14 (s, 1H). EIS-MS (*m/z*): 314(M^+-127). **6e :** Ar=4-$CH_3OC_6H_4$, mp 217-219°C**.** EA.Calcd for $C_{18}H_{24}IN_3O_3$: C,47.32, H, 5..31, N, 9.22; Found**:** C, 47.15, H, 5.12, N, 9.43. IR (KBr, cm^{-1}): 3015, 2934, 1663, 1633, 954. ^1H NMR (500MHz, D_2O, δ ppm, J Hz)**:** 7.88- 7.12 (m, 4H), 6.67 (s, 1H), 6.49 (br s, 1H), 3.94 (dd, 2H, J=10.5) , 3.90 (s, 3H), 3.52 (br s, 2H), 3.17, 3.11 (2s, 6H), 2.69 (br s, 2H), 2.36 (s, 3H). EIS-MS (*m/z*): 330(M^+-127). **6f :** Ar=3,4-$(OCH_2O)C_6H_3$, mp 232-234°C**.** EA.Calcd $C_{18}H_{21}IN_3O_4$: C, 45.87, H, 4.71, N, 8.92; Found**:** C, 45.67, H, 4.94, N, 9.02. IR (KBr, cm^{-1}) **:** 3203, 2935, 1667, 1628, 931**.** ^1H NMR (500MHz, D_2O, δ ppm, J Hz) **:** 7.50- 7.02 (m, 3H), 6.63 (s, 1H), 6.43 (br s, 1H), 6.06 (s, 2H), 3.85 (dd, 2H, J=16), 3.46 (t, 2H, J=6), 3.11, 3.05 (2s, 6H), 2.61 (br s, 2H), 2.30 (s, 3H). EIS-MS (*m/z*): 344(M^+-127). **14a:** Ar=C_6H_5 , mp 208-210°C. EA.Calcd for $C_{17}H_{22}IN_3O_2$ 1/3H_2O: C, 47.12, H, 5.27, N, 9.70; Found: C, 47.32, H, 5..35, N, 9.86. IR (KBr, cm^{-1}): 3022, 2979, 1664, 1634, 1042. ^1H NMR (500MHz, D_2O, δ ppm): 7.16- 6.85 (m, 7H), 4.17 (br s, 2H), 3.48 (br s, 2H), 3.17 (s, 6H), 2.70 (br s, 2H), 2.33 (s, 3H). **14b:** Ar=4-FC_6H_4 , mp 222-223℃. EA.Calcd for $C_{17}H_{21}FIN_3O_2$ 1/3H_2O: C, 45.24, H, 4.84, N, 9.31; Found: C, 45.13, H, 5.12, N, 9.46. IR(KBr, cm^{-1}): 3076, 2996, 1658, 1624, 1072: ^1H NMR (500MHz, D_2O, δ ppm): 7.16- 6.82 (m, 6H), 4.21 (br s, 2H), 3.54 (br s, 2H), 3.17, 3.22 (s, 6H), 2.76 (m, 2H), 2.23 (s, 3H). **14c**: Ar=4-ClC_6H_4 , mp 214-216℃. EA.Calcd: C, 44.23, H, 4.58, N, 9.67; Found: C, 44.21, H, 4.65, N, 9.82. IR (KBr, cm^{-1}): 3056, 3047, 1654, 1627, 1087. ^1H NMR (500MHz, D_2O, δ ppm): 7.23- 6.85 (m, 4H), 6.64 (s, 1H), 6.48 (br s,.1H), 4.17 (br s, 2H), 3.56 (m, 2H), 3.27, 3.21 (s, 6H), 2.67 (br s, 2H),.2.21 (s, 3H). **14d:** Ar=4-$CH_3C_6H_4$, mp 211-212°C. EA.Calcd: C, 48.99, H, 5.48, N, 9.52; Found: C,

49.21, H, 5.65, N, 9.76. IR (KBr, cm^{-1}): 3053, 2994, 1658, 1645, 1089. ^1H NMR (500MHz, D_2O, δ ppm): 7.32- 7.02 (m, 4H), 6.67(s, 1H), 6.58 (s,1H), 4.23(br s,.2H), 3.56 (br s, 2H), 3.42, 3.47 (s, 6H), 2.72 (s, 2H), 2.43 (s, 3H). **14e:** Ar=4-$CH_3OC_6H_4$, mp 217-218°C: EA.Calcd for $C_{18}H_{24}IN_3O_32/3H_2O$: C, 46.07, H, 5.44, N, 8.95; Found: C, 46.17, H, 5.60, N, 8.95. IR (KBr, cm^{-1}): 3062, 2997, 1657, 1642, 1077. ^1H NMR (500MHz, D_2O, δ ppm): 7.35- 7.02 (m, 4H), 6.85 (s, 1H), 6.70 (s.1H), 4.21-3.96(m, 5H), 3.47 (br s, 2H), 3.42, 3.47 (2s, 6H), 2.57 (br s, 2H), 2.23 (s, 3H). **4f:** Ar=3,4-$(OCH_2O)C_6H_3$, mp 228-230℃. EA.Calcd for $C_{18}H_{22}IN_3O_4$ $2/3H_2O$: C, 44.73, H, 4.87, N, 4.87; Found: C, 44.86, H, 5.02, N, 8.72. IR (KBr, cm^{-1}): 3072, 2997, 1663, 1643,1057. ^1H NMR (500MHz, D_2O, δ ppm): 7.05-6.77(m, 5H), 5.94 (s, 2H), 4.23 (br s, 2H), 3.51(br s, 2H), 3.17 (s, 6H) , 2.70 (s, 2H), 2.23 (s, 3H).

Received 24 September, 2001