Chinese Chemical Letters Vol. 15, No. 3, pp 269-272, 2004
http://www.imm.ac.cn/journal/ccl.html

Synthesis of 7a-Aza-benzo[fg]naphthacen-7-one

Cheng Gang ZHANG[1, 2], Bo Gang LI[1], Xiang Ge ZHOU[1], Guo Lin ZHANG[1]*

[1]Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041
[2]Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041

Abstact: 2, 3, 11, 12-Tetramethoxy-3b, 4, 5, 6-tetrahydro-8H-7a-aza-benzo[fg]naphthacen-7-one **7** was synthesized *via* N-acyliminium ion cyclization of 6-hydroxy-1-(2, 3, 6, 7-tetramethoxy-phenanthren-9-yl-methyl)-piperidin-2-one **6** catalyzed by $BF_3{\cdot}OEt_2$. The stereostructure of the intermediate, 1-(2, 3, 6, 7-tetramethoxy-phenanthren-9-yl-methyl)-piperidine-2, 6-dione **5**, was confirmed by X-ray crystallographic analysis. Compound **7** showed no cytotoxicity.

Keywords: N-Acyliminium ion cyclization, cytotoxicity.

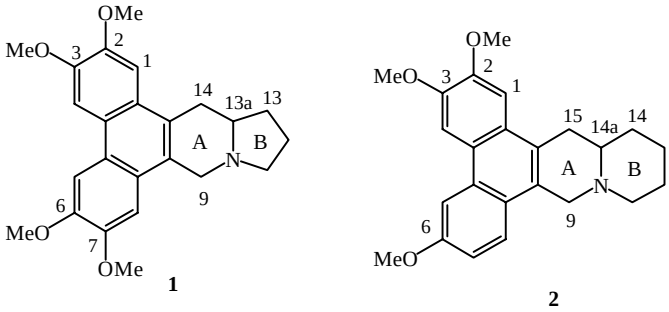
Phenanthroindolizidine and phenanthroquinolizidine are closely related groups of alkaloids. Since the first isolation of tylophorine **1** in 1935, these natural products have attracted much attention because of their interesting biological activities such as antitumor activity[1-3]. The obvious problems such as toxicity to nerve system, instability and uneconomical synthetical pathways restrict its application. Kozma reported that C-9, C-14 of tylophorine **1** and C-9, C-15 of cryptopleurine **2** were the possible attack sites to give complex oxidative products[4]. Synthesis of analogue of **1** or **2** has been widely studied[5] with long synthetic ways and low yields, but the synthesis of compounds with five-member ring A of **1** or **2** (**Figure 1**) was failed.

Considering above problems, compound **10** and their derivatives were designed in order to investigate their stabilities, bioactivities and structure-activity relationship. In the attempt to synthesize **10**, along the synthetic route (**Scheme 1**), surprisingly the cyclization of **6** gave exclusively 2, 3, 11, 12-tetramethoxy-3b, 4, 5, 6-tetrahydro-8H-7a-aza-benzo[fg]naphthacen-7-one **7**. To our best known, this kind of compound has not been reported. Compound **7** was reduced by $LiAlH_4$/THF at reflux to give compound **8** with $[M+1]^+$ 394 (ESIMS) (one spot on TLC, petroether:ethyl acetate= 1:1, R_f = 0.45). Unfortunately, compound **8** could not be isolated because of unstability, either in solid state or in solution of $CHCl_3$. When **8** was exposed to daylight for a few minutes or heated to 40°C by protection from light, it turned into quite complicated mixture.

Compound **7** showed no cytotoxicity against leukemia, lung cancer and breast cancer cell lines in *vitro* test. The intermediate **6** may be cyclized to C-10, if the aromatic ring C bears electron-withdrawing group. However, further study is needed.

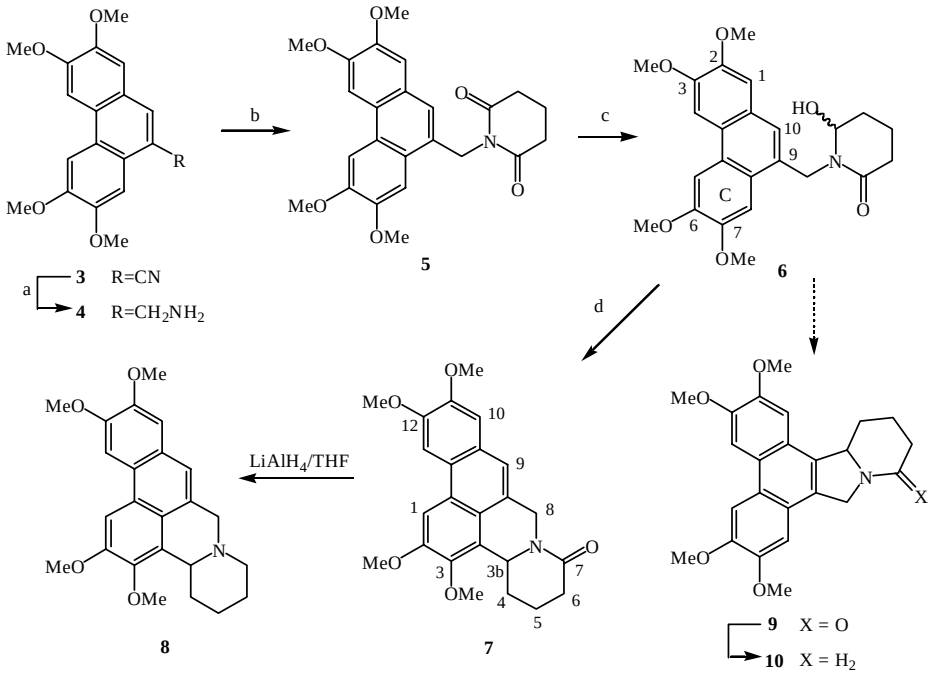
* E-mail: zhanggl@cib.ac.cn

Figure 1



1 **2**

Scheme 1



3 R=CN
4 R=CH_2NH_2
5 **6** **7** **8** **9** X = O
10 X = H_2

Reagents and conditions: (a) $LiAlH_4$/THF, rt.; (b) glutaric anhydride, then acetyl chloride; (c) $NaBH_4$/MeOH; (d) $BF_3.OEt_2/CH_2Cl_2$.

2, 3, 6, 7-Tetramethoxy-phenanthrene-9-carbonitrile 3[6] was reduced to give amine 4. 4, without further purification, was reacted with glutaric anhydride to afford 1-(2, 3, 6, 7-tetramethoxy-phenanthren-9-yl-methyl)-piperidine-2, 6-dione 5 (**Scheme 1**) with 52% yield[7], which was reduced to afford crude amide 6 as a white powder. 6, without further purification, was dissolved in dry CH_2Cl_2 and then reacted with $BF_3 \cdot OEt_2$ under N_2 at room temperature for 48 hr, to afford 7 as a light yellow powder with 85% yield[8, 9]. The structure of 7 was confirmed by NOESY experiment (**Figure 3**).

Figure 2 ORTEP drawing of compound **5** (EtOH was omitted)

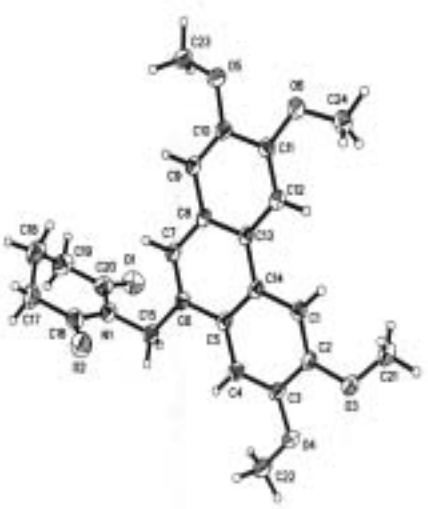
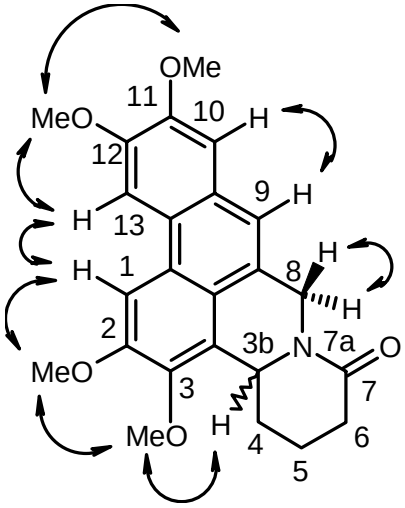


Figure 3 Major NOESY correlations in **7** (right)



Acknowledgments

The authors are grateful to Dr. Bin GUANG, Pharmaceutical Institute of Di-Ao Group, for valuable discussion and Prof. Zhongyuan ZHOU, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, for X-ray crystallographic analysis.

References and Notes

1. R. C. Bick, W. Sinchai, ed. by R. G. A. Rodrigo, Academic Press, New York, *The Alkaloids, Vol. 19*, **1981**, pp. 193-220.
2. E. Gellert, *J. Nat. Prod.*, **1982**, *45*, 50.
3. Z. G. Li, Z. Jin, R. Q. Huang, *Synthesis*, **2001**, *16*, 2365.
4. L. Kozma, S. Foldeak, M. Molnar, *et al.*, *Zh. Prikl. Spektrosk.*, **1979**, *30*, 281.
5. S. Lebrun, A. Couture, E. Deniau, *et al.*, *Tetrahedron*, **1999**, *55*, 2659; M. A. Cuifolini, F. Roschangar, *J. Am. Chem. Soc.*, **1996**, *118*, 12082, and references cited therein.
6. T. F. Buckley III, H. Rapoport, *J. Org. Chem.*, **1983**, *48*, 4222.
7. P. Chalard, R. Remuson, Y. Gelas-Mialhe, *et al.*, *Tetrahedron: Asymmetry*, **1998**, *9*, 4361.
8. S. P. Tanis, M. V. Deaton, L. A. Dixon, *et al.*, *J. Org. Chem.*, **1998**, *63*, 6914.
9. Y. S. Lee, S. S. Kang, J. H. Choi, *et al.*, *Tetrahedron*, **1997**, *53*, 3045.
10. Compound **5**: colorless crystal (EtOH). m.p. 201-203°C; IR (KBr, cm^{-1}) ν: 2922, 1670, 1512, 1251,1144; UVλ_{max}^{MeOH} nm: 213 (4.53), 257 (4.91), 287 (4.61); ^{1}H NMR ($CDCl_3$, 400 MHz): δppm 1.98 (q, 2H, J=6.4 Hz), 2.74 (t, 4H, J=6.4 Hz), 4.02 (s, 3H), 4.07 (s, 3H), 4.11 (s, 3H), 4.12 (s, 3H), 5.43 (s, 2H), 7.19 (s, 1H), 7.55 (s, 1H), 7.68 (s, 1H), 7.75 (s, 1H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δppm 172.6 (C=O), 149.1, 148.6 (3 carbons), 127.7, 125.6, 125.3, 124.7, 124.6, 124.1, 108.4, 104.7, 103.2, 102.6, 55.9 (3×OMe), 55.8, 41.0, 33.0 (2 carbons), 16.9; ESI-MS (*m/z*): 424 $[M+1]^+$, 446 $[M+Na]^+$; EI-HRMS: (M^+) calcd. 423.1682, found 423.1669. Crystal data: empirical formula, $C_{24}H_{25}NO_6 \cdot C_2H_5OH$; molecular weight, 469.52; crystal dimensions, 0.38 × 0.30 × 0.28 mm; crystal system, monoclinic; space group, $P2_1/c$; lattice parameters, a = 11.3534 (15) Å, b = 17.690 (3) Å, c = 13.0636

(18) Å; V = 2458.2 (6) $Å^3$; Z = 4; D_{calcd} = 1.269 g/cm^3; F (000) = 1000; μ(Mo-Ka) = 0.092 mm^{-1}.

11. Compound **7**: m.p. 202-203°C; IR (KBr, cm^{-1}) ν: 2942, 2829, 1627, 1470, 1415, 1249, 1166; UV λ_{max}^{MeOH} nm: 222 (4.42), 261 (4.77), 287 (4.55); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 1.59 (m, 1H, H-4a), 1.94 (m, 2H, H-5), 2.38 (m, 1H, H-4b), 2.62 (m, 1H, H-6a), 3.17 (m, 1H, H-6b), 3.89 (d, 1H, J=14.8 Hz, H-8a), 3.96 (s, 3H, 3-OMe), 4.03 (s, 3H, 11-OMe), 4.11 (s, 3H, 2-OMe), 4.12 (s, 3H, 12-OMe), 5.20 (dd, 1H, J=10.4, 4.0 Hz, H-3b), 5.94 (d, 1H, J=14.8 Hz, H-8b), 7.18 (s, 1H, H-10), 7.38 (s, 1H, H-9), 7.77 (s, 1H, H-13), 7.80 (s, 1H, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz): δppm 170.2 (C=O), 152.4, 149.5, 149.0, 145.4, 127.6, 127.1, 126.7, 126.6, 123.3, 121.6, 119.6, 108.1, 103.4, 103.1, 60.8, 56.8, 56.1, 55.9, 55.8, 43.1, 32.2, 29.6, 20.0; ESI-MS (*m/z*): 408 $[M+1]^+$, 837 $[2M+Na]^+$; Found: C, 70.85; H, 6.43; N, 3.55. $C_{24}H_{25}NO_5$ requires C, 70.74; H, 6.18; N, 3.44.

Received 3 March, 2003