Pergamon

Tetrahedron Letters, Vol. 36, No. 9, pp. 1531-1532, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00077-1

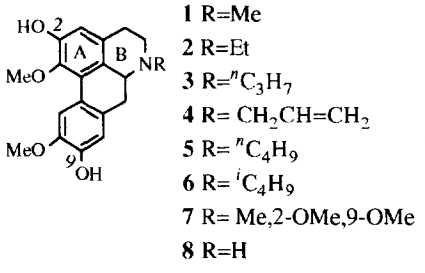
PREPARATION OF PHENANTHRENE ALKALOIDS VIA SOLVOLYSIS OF 2-HYDROXYAPORPHINES

Shoei-Sheng Lee,* Chi-Ming Chiou, Huey-Yi Lin and Chung-Hsiung Chen

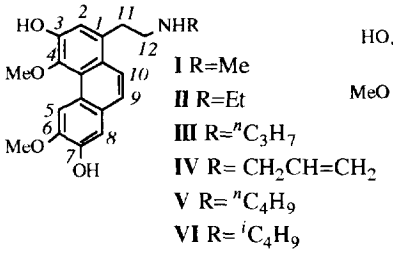
School of Pharmacy, College of Medicine, National Taiwan University, Taipei 100, Taiwan, R.O.C.

Summary: Phenanthrene alkaloids was semisynthesized from *N*-alkyllaurolitsines such as boldine directly from solvolysis with 1M ammonium acetate under reflux overnight. This one step reaction is easily workup and the yield is high (> 80%).

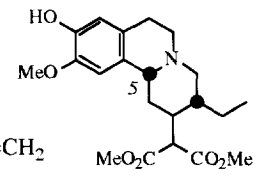
Phenanthrene alkaloids, generally believed derived from aporphines biogenetically, have recently demonstrated to possess interesting biological activities including vasorelaxation of the rat aorta and antiarrhythmia.[1-3] We reported modified methods to prepare the phenanthrene alkaloid secoboldine (**I**), a direct intermediate for synthesizing litebamine, from boldine (**1**) recently via two reaction steps, exhaustive *N*-benzylation (give *N*-benzylsecoboldine) and catalytic hydrogenation.[4] This method gave **I** in about 60% yield at a gram scale. For a large-scale reaction (>10 g), we found that the purification of *N*-benzylsecoboldine and **I** become tedious. To obtain a good amount of phenanthrene alkaloids for pharmacological study, other facile approaches needed to be investigated. We report herein the outcome for this purpose.



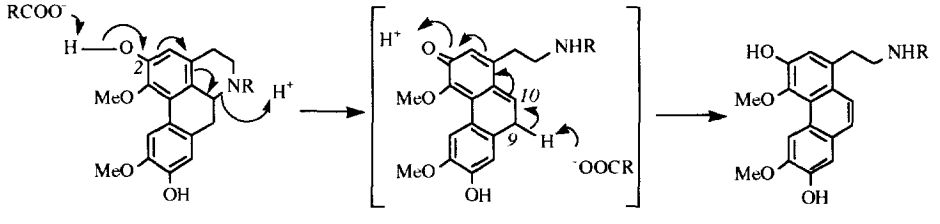
1 R=Me
2 R=Et
3 R=$^{n}C_3H_7$
4 R= $CH_2CH{=}CH_2$
5 R= $^{n}C_4H_9$
6 R= $^{i}C_4H_9$
7 R= Me,2-OMe,9-OMe
8 R=H



I R=Me
II R=Et
III R=$^{n}C_3H_7$
IV R= $CH_2CH{=}CH_2$
V R= $^{n}C_4H_9$
VI R= $^{i}C_4H_9$



A



During the preparation of the monoterpenoid isoquinoline alkaloid protoemetine, C-5 epimerization occurred for an intermediate **A** possessing a phenolic group *para* to the *N*-methine (C-5) in refluxing propionic acid.[5] The participation of the phenolic group is essential since the reaction could not take place for the *O*-methylated product. Based on this, we considered that **1** possessing a phenolic OH *para* to *N*-methine might undergo a similar reaction. This is the case. While **1** was refluxed with propionic acid for 6 h, **I** (25%) and *N*-propionylsecoboldine (50%) were isolated. If a diluted propionic acid (80% in water) was used, only **I** (65%) was

obtained. If propionic acid was replaced by acetic acid or butyric acid, the reaction was either incomplete despite of longer reaction time (> 2 d, HOAc) or suffering workup problem (removal of butyric acid). In addition, glaucine (**7**) possessing 2-OMe did not form secoglaucine under this reaction condition. Hence, the dissociated carboxylic acid serves as push and pull roles to 2-OH and *N*-Me to take apart the B ring of the aporphines as shown in the scheme. Apparently, deprotonation at C-9 of the intermediate rather than the nucleophilic attack of the nitrogen to C-10 dominates the reaction and yielded exclusively the stable phenanthrene product.

Although solvolysis of **1** with 80% propionic acid gave **I** as the sole product, the workup is interfered by the removal of propionic acid. Based on the proposed reaction mechanism, we thought that ammonium acetate could possess such push and pull property. Indeed, reaction of **1** (5.0 g) with 1M NH_4OAc_{aq}- EtOH (1:1, 75 ml) under reflux for 1 d gave **I** (4.5 g, 90% yield) as crystalline product after cooling the reaction mixture. Glaucine did not react under this reaction condition, either. Under such conditions, *N*-alkylsecolaurolitsines **II-VI** [6] were synthesized from *N*-alkyllaurolitsines **2-6**, prepared from laurolitsine (**8**), isolated from *Phoebe formosana* [7], by *N*-alkylation (DMF, RCH_2X, $NaHCO_3$)[8] in a yield of over 80% at 100 mg level.

This study simplifies the preparation of 3-hydroxyphenanthrene alkaloids derived from 2-hydroxy-*N*-methylaporphines and the method is practical for a large-scale preparation. The cardiovascular effects of the prepared compounds are currently investigated.

Acknowledgment. This research was supported by NSC, R.O.C., under Grant NSC 82-0420-B002-450-M13 and NSC 83-0425-B-002-001.

References

1. C.M. Teng, S.M. Yu, C. P. Pan, and S.S. Lee, *J. Biomed. Sci.*, **1994**, *1*, 54.
2. S.M. Yu, S.S. Lee, Y.S. Hou, and C.M. Teng, *Naunyn Schmiedebergs Arch Pharmacol.*, **1994**, *349*, 637.
3. M.H. Wu, M.J. Su, S.S. Lee, and M. L. Young, *Br. J. Pharmacol.*, **1994**, *113*, 221.
4. S.S. Lee, Y.J. Lin, M.Z. Chen, Y.C. Wu, and C.H. Chen, *Tetrahedron Lett*, **1992**, *33*, 6309.
5. R.T. Brown and M.F. Jones, *Tetrahedron Lett*, **1984**, *25*, 3127.
6. ^{1}H Nmr and eims data of **II-VI**: **II-VI** show similar ^{1}H nmr data (MeOH-d_4, 400.13 MHz) for the signals in phenanthrene moiety. As a example, the signals in **II** are as follows δ 7.13 (s, H-2), 9.12 (s, H-5), 7.20 (s, H-8), 7.48 (d, *J*= 9.1 Hz, H-9), 7.70 (d, *J*= 9.1 Hz, H-10), 3.84 (s, 4-OMe), 4.04 (s, 6-OMe); the signals for the side chain are as follows: **II** δ 3.36 (m, H-11), 3.25 (m, H-12), 3.06 (q, *J*= 7.2 Hz, $NC\underline{H}_2CH_3$), 1.30 (t, *J*= 7.2 Hz, $NCH_2C\underline{H}_3$); **III** δ 3.20 (t, *J*= 7.6 Hz, H-11), 2.90 (t, *J*= 7.6 Hz, H-12), 2.60 (t, *J*= 7.4 Hz, $NC\underline{H}_2C_2H_5$), 1.53 (m, $NCH_2C\underline{H}_2CH_3$), 0.91 (t, *J*= 7.3 Hz, $NCH_2CH_2C\underline{H}_3$); **IV** δ 3.21 (m, H-11), 2.96 (m, H-12), 3.33 (d, *J*= 6.6 Hz, $NC\underline{H}_2CH{=}CH_2$), 5.89 (ddt, *J*= 17.2, 10.2, 6.6 Hz, $NCH_2C\underline{H}{=}CH_2$), 5.18 (dd, *J*= 10.2, 1.3 Hz, $NCH_2CH{=}C\underline{H}_EH_Z$), 5.25 (dd, *J*= 17.2, 1.3 Hz, $NCH_2CH{=}CH_E\underline{H}_Z$); **V** δ 3.20 (t, *J*= 7.3 Hz, H-11), 2.92 (t, *J*= 7.3 Hz, H-12), 2.65 (t, *J*= 7.3 Hz, $NC\underline{H}_2C_3H_7$), 1.50 and 1.32 (m, $NCH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.90 (t, *J*= 7.3 Hz, $NC_3H_7C\underline{H}_3$); **VI** δ 3.37 (m, H-11), 3.22 (m, H-12), 2.83 (d, *J*= 7.5 Hz, $NC\underline{H}_2{}^iC_3H_7$), 1.99 [m, $NCH_2C\underline{H}(CH_3)_2$], 1.03 (d, *J*= 6.7 Hz, $NCH_2CH(C\underline{H}_3)_2$); eims (20 eV): **II**. *m/z* [M]$^+$ 341 (15), 284 (100), 269 (22), 58 (23); **III**. *m/z* [M]$^+$ 355 (18), 284 (100), 269 (18), 72 (77); **IV**. *m/z* [M]$^+$ 353 (12), 284 (100), 269 (26), 70 (44); **V**. *m/z* [M]$^+$ 369 (10), 284 (100), 269 (19), 86 (44); **VI**. *m/z* [M]$^+$ 369 (10), 284 (100), 269 (15), 86 (54).
7. S.S. Lee, F.Y. Tsai, I.S. Chen, and K.C.S. Liu, *J. Chin. Chem. Soc.* , **1992**, *40*, 209.
8. J.L. Neumeyer, S. J. Law, B. Meldrum, G. Anlezark, and K. J. Watling, *J. Med. Chem.*, **1981**, *24*, 898.

(*Received in Japan* 14 *November* 1994; *revised* 17 *December* 1994; *accepted* 26 *December* 1994)