Tetrahedron 67 (2011) 1076–1082

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Novel reactions of lycoctonine analogs: unusual pyrolysis of C4–COOH and hydrogenolysis of *N*–C6 bond

Pei Tang, Ling Wang, Qiao-Hong Chen, Feng-Peng Wang *

*Department of Chemistry of Medicinal Natural Products, West China College of Pharmacy, Sichuan University, No. 17, Duan 3, Renmin Nan Road, Chengdu 610041, PR China*

ARTICLE INFO

*Article history:*
Received 28 October 2010
Received in revised form 2 December 2010
Accepted 14 December 2010
Available online 17 December 2010

*Keywords:*
$C_{19}$-Diterpenoid alkaloids
Lycoctonine
Pyrolysis
Hydrogenolysis

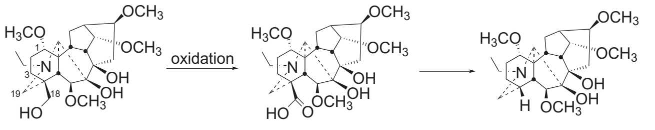
ABSTRACT

Pyrolysis of carboxylic acid group at C-4 of **2**, an oxidation product from the $C_{19}$-diterpenoid alkaloid lycoctonine **1**, generated an unexpected but novel rearranged product **13** (37%). The structure of **13** was confirmed by its 2D NMR data and its single crystal X-ray crystallographic analysis. In addition, hydrogenolysis of **13** in the presence of acetic acid yielded the *N*–C6 bond fission products **16** and **17**, which represents the first hydrogenolysis involving the breakage of the *N*–C6 bond of the diterpenoid alkaloids. Some new observations on the oxidation of lycoctonine **1** were described as well.

## 1. Introduction

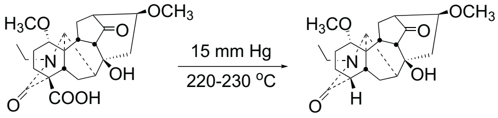
Lycoctonine (**1**) was firstly isolated from *Aconitum lycoctonum* L in 1886.[1] As a diterpenoid alkaloid with the widest distribution, it extensively exists in around 80 plants of the genera, *Delphinium Aconitum* and *Consolida*.[2] The chemical reactions, especially the oxidation, of lycoctonine have made great contributions to the skeletal structure establishment of the diterpenoid alkaloids before the 1970's.[3–14] For example, investigation on its oxidative products by Edwards and Marion indicated that lycoctonine possesses a methylene group adjacent to the nitrogen and a primary hydroxyl group, and a vicinal glycol moiety.[3] The first successful skeleton establishment of the $C_{19}$-diterpenoid alkaloids was based on the X-ray crystallographic analysis of the derivative of lycoctonine.[8] However, the oxidation products of lycoctonine from the earlier investigations were poorly characterized due to the unavailable techniques of separations and spectroscopy at that time. Recently, Benn et al. revisited the structures of some oxidation products of lycoctonine and provided the insightful summarization on the relationship between the oxidation products of lycoctonine and specific oxidants.[1]

As part of our ongoing research project, we attempted to semi-synthesize the $C_{18}$-diterpenoid alkaloid **3** from the $C_{19}$-diterpenoid alkaloid lycoctonine **1** through the oxidation of its primary hydroxyl group followed by decarboxylation (Scheme 1). It has been reported that decarboxylation of the diterpenoid alkaloid **4** could be completed under vacuum to generate decarboxylated product **5** in 98% yield (Scheme 2).[15] However, in our present study, heating the carboxylic acid **2** under vacuum gave us an unexpected rearranged product instead. In this paper, we wish to report this novel rearranged product and its unusual hydrogenolysis, as well as some new observations on the oxidation of lycoctonine.



1 2 3

**Scheme 1.** Attempt to convert the $C_{19}$-diterpenoid alkaloid lycoctonine to the $C_{18}$-diterpenoid alkaloids.



4 5

**Scheme 2.** Decarboxylation of **4**.

## 2. Results and discussion

As summarized by Benn et al.,[1] the oxidation products of lycoctonine are greatly dependent on the specific oxidants. For example, oxidation of lycoctonine with chromic acid yields preferably lycoctonal (**6**), a primary hydroxyl oxidation product. In

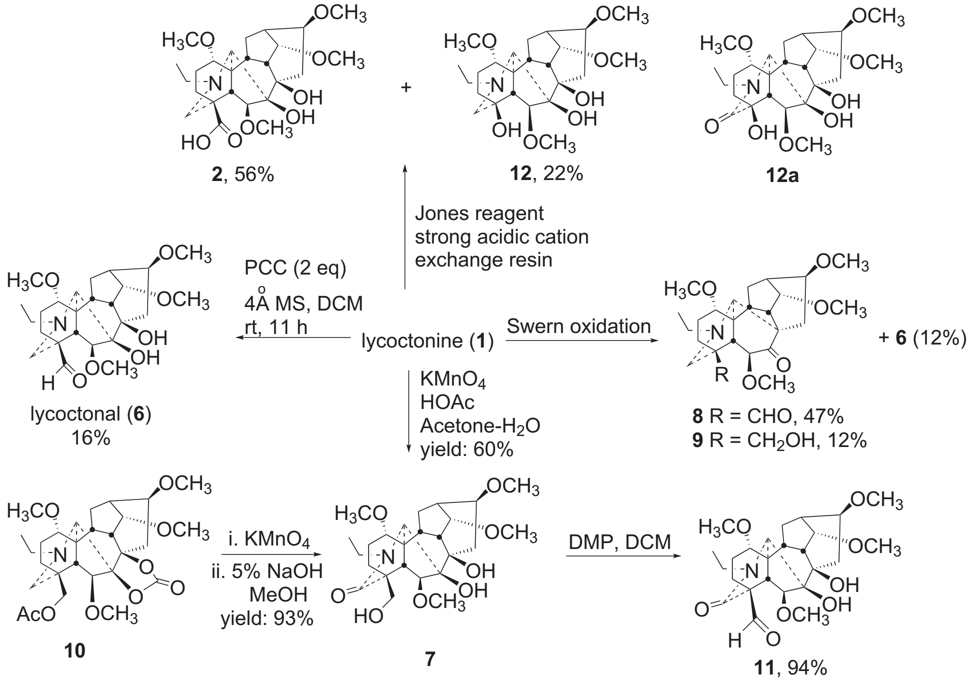
---

* Corresponding author. Tel./fax: +86 28 85501368; e-mail address: wfp@scu.edu.cn (F.-P. Wang).

doi:10.1016/j.tet.2010.12.042

contrast to its behavior with chromic acid, oxidation of lycoctonine with permanganate in neutral, weakly acidic, or alkaline solution affords lactam **7**, a C-19 methylene oxidation product. Intriguingly, further oxidation of lactam with chromic acid gives a product (**12a**) of C4–C18 bond fission. This kind of bond fission could be avoided in the presence of oxalic acid.

In order to make carboxylic acid **2** from lycoctonine (**1**), we have tried different oxidants. As shown in Scheme 3, treatment of lycoctonine with PCC only yielded lycoctonal (**6**) in poor yield (16%); while oxidation with $KMnO_4$ could generate lactam **7** in 60% yield. These results are consistent with those described in the literature.[1] In addition, we have observed the following new oxidation of lycoctonine: (1). alkaloid **10**, with all hydroxyl groups in lycoctonine protected, was oxidized with $KMnO_4$ followed by deprotection to generate lactam **7** in an excellent yield (93%); (2) Swern oxidation of lycoctonine gave us Pinacol rearrangement products **8** (47%) and **9** (12%), together with minor lycoctonal (**6**); (3) the oxidative status of *N*-atom has significant influence on the oxidation with Dess–Martin Periodinance (DMP): oxidation of lycoctonine with DMP provided us with complicated products, while oxidation of lactam **7** with DMP yielded **11** in an excellent yield (94%); (4) the normal Jones oxidation of lycoctonine could generate the expected carboxylic acid **2**, but in a poor yield (8%); and (5) inspired by the solid phase synthesis, we found that the strong acidic cation resin loaded with lycoctonine could smoothly react with Jones reagent to generate carboxylic acid **2** in 56% yield, as well as a C4–C18 fission product **12** in 22% yield.



**Scheme 3.** Oxidation of lycoctonine.

With carboxylic acid **2** in hand, we attempted to make the $C_{18}$-diterpenoid alkaloid **3** employing the similar procedure as described in the literature.[15] Very intriguingly, heating **2** under vacuum (15 mm Hg) at 220 °C for 25 min generated an unexpected but novel rearranged product **13** (37%) instead of **3**. The structure of this novel product was elucidated using the 1D and 2D NMR experiment, as well as by X-ray crystallographic analysis. Its ESIMS showed a quasimolecular ion peak at *m*/*z* 388 $[M+1]^+$ and its NMR spectroscopic patterns are quite different from those of its starting material **2**. The NMR ($^1H$, $^{13}C$, and HMQC) data feature an *N*-ethyl group ($\delta_C$ 13.9 q, $\delta_H$ 1.07, 3H, t, $J$=7.2 Hz; $\delta_C$ 43.1t, $\delta_H$ 2.45, 2.69, each 1H, m), three methoxyl groups ($\delta_H$ 3.32, 3.36, 3.37, each 3H, s; $\delta_C$ 57.3 q, 57.1 q, 56.7 q), an exocyclic double bond ($\delta_C$ 146.3s; $\delta_C$ 111.8t; $\delta_H$ 4.73, 2H, t, $J$=2.8 Hz), and a ketone carbonyl group ($\delta_C$ 213.2s). The $^{13}C$ NMR of **13** showed the absence of the C-18 carboxyl group, as compared with **2**. The ketone carbonyl group could be assigned at C-7 due to the correlations from $H_2$-15 ($\delta_H$ 1.65, 2.44) and H-9 ($\delta_H$ 2.32, m) to C-7 ($\delta_C$ 213.2s) in the HMBC spectrum (Fig. 1), which indicated that the vicinal glycol moiety in **2** had undergone Pinacol rearrangement. The exocyclic double bond was located at C-4 and C-19 on the basis of the HMBC correlations from $H_2$-3 ($\delta_H$ 2.21, 2.60) and H-5 ($\delta_H$ 2.62) to C-19, from $H_2$-19 to C-3 ($\delta_C$ 28.3) and C-5 ($\delta_C$ 48.6), and from H-6 to C-4. This suggested that the bond between *N*-atom and C-19 was broken. Similarly, three methoxyl groups could be readily assigned at C-1, C-14, and C-16 on the basis of the related correlations in the HMBC spectrum (Fig. 1), implying the disappearance of the methoxyl group at C-6 in **2**. In addition, the newly formed *N*–C6 bond was evident from the critical HMBC correlations between H-17 ($\delta_H$ 3.82) and C-6 ($\delta_C$ 73.3), and between H-6 and C-17 ($\delta_C$ 70.7), as well as from the W-type coupling (1.6 Hz) between H-6 and H-17. Finally, our proposed structure of **13** was confirmed by its X-ray crystallographic analysis (Fig. 2). The formation of **13** might be explained by the mechanism depicted in Scheme 4. Firstly,

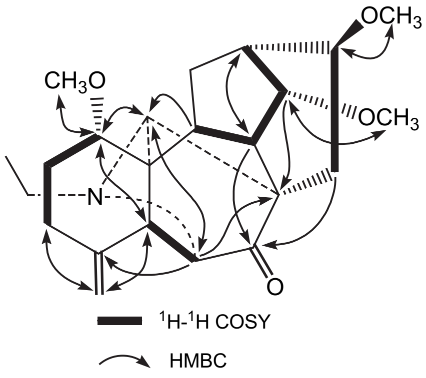


**Fig. 1.** Key $^1H$–$^1H$ COSY and HMBC correlations of **13**.