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$NaIO_4$-Catalyzed Bromination of the Aromatic Ring of Lappaconitine

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Abstract: Treatment of lappaconitine **1** with $NaIO_4$ and Br_2-HOAc at room temperature for 7 h afforded smoothly the bromine-containing derivative **4** in 71% yield.

Keywords: Bisnorditerpenoid alkaloid, lappaconitine, bromination.

Lappaconitine **1**, a bisnorditerpenoid alkaloid, was isolated from many plants of Aconitum species such as *A. barbatum* var. *pulerulum* and *A. sinomontanum* (*Ranunculaceae*)[1-3], and used clinically for treatment of analgic disease as a nonaddicted drug in China[4], and as an antiarrythmic in Uzbekistan[5]. In order to search for high activity, low toxicity compounds, we have carried out the structure modifications of lappaconitine. In this case, an attempt to induce the oxygenated group at C-10 in **1** by cleavage of the 8, 9-glycol with $NaIO_4$ leads to the unexpected compound **2** instead of **3**[6]. But, one-pot treatment of **1** with $NaIO_4$ and Br_2-HOAc afforded a bromine-containing derivative **4** in good yield instead of the desired compound **5**, and we found that $NaIO_4$ was necessary for the bromination. In this communication, we wish to report the $NaIO_4$-catalyzed bromination of the aromatic ring of lappaconitine **1**.

To a mixture of lappaconitine **1** (300 mg, 0.51 mmol) and $NaIO_4$ (610 mg), Br_2 (0.026 mL, 0.51 mmol) and HOAc (10 mL) were added and the solution was allowed to stand at room temperature for 7 h. After removal of the solvent the compound **4**[7] (245 mg, 71%), $C_{30}H_{39}N_2O_8Br$ (FABMS + ^{13}CNMR), was afforded as a white amorphous powder. The ^{1}H (^{13}C) NMR spectra of **4** showed the disappearance of the *N*-ethyl group and the appearance of a tri-substituted aromatic moiety (δ_H, 7.51, 1H, dd, J = 10.0, 2.4 Hz; 7.91, 1H, d, J = 2.4 Hz; 8.55, 1H, d, J = 10.0 Hz; δ_C114.5 s, 117.3 d, 121.8 s, 133.1 d,137.0 d, 140.6 s). Its FABMS indicated the typical molecular ions at *m/z* 637 (M_1^+ + 1, 100) and 635 (M_2^+ + 1, 96) corresponding to the substitution by one bromine. Comparison of the ^{13}C NMR spectra of both compounds **1** and **4** in **Table 1** showed a series of the changes (**Figure 1**) caused by bromination, and the structure of **4** can thus be determined. It is to be emphasized that, in this case, the bromination can be carried out smoothly only in the presence of $NaIO_4$ as a catalyst otherwise none of the bromo-compounds such as **4** was produced even after extended time (24 h) of treatments

conditions. Thus, the role of $NaIO_4$ in this bromination is worthy of further study.

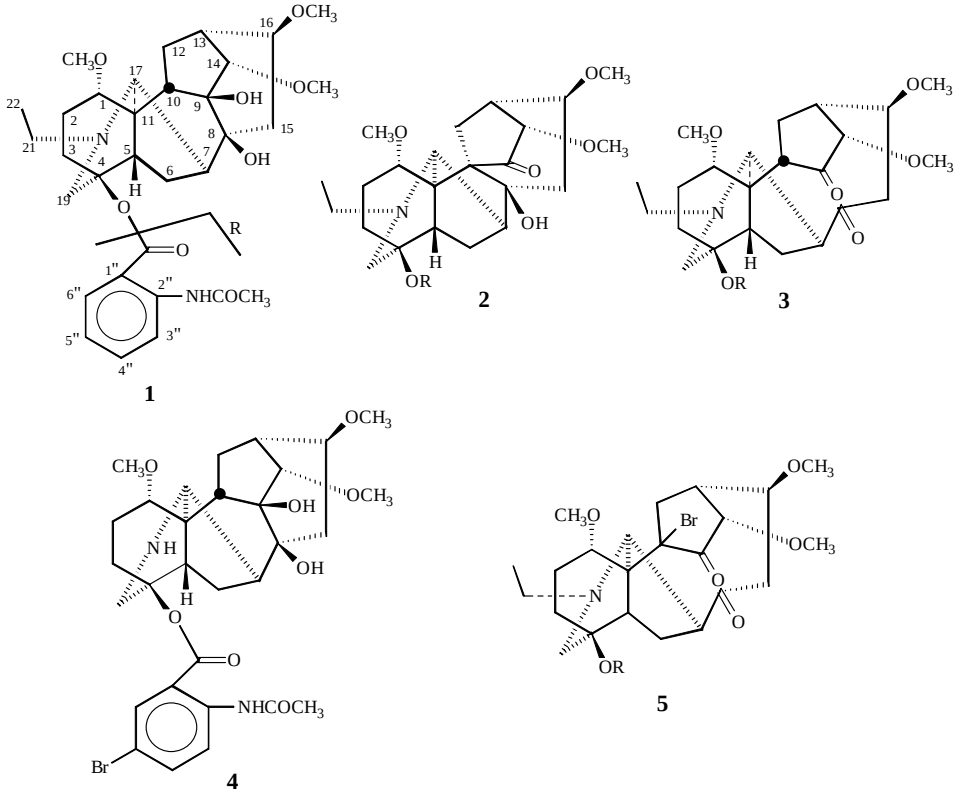
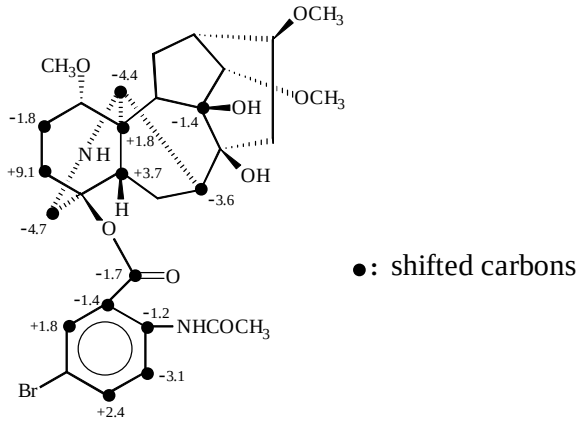


Figure 1 Shift changes from **1** to **4**



In addition, it is of interest to note that treatment of lappaconitine **1** with $NaIO_4/Br_2$-HOAc gave the *N*-deethyl derivative **4** with a bromination of the aromatic ring. This is a novel *N*-deethylation in addition to the reported methods[8] and worth to further investigate.

Table 1 ^{13}C NMR data for lappaconitine **1** and **4** (50 MHz, $CDCl_3$)

No.	**1**	**4**	No.	**1**	**4**
1	84.2	82.4 (d)	17	61.5	57.1 (d)
2	26.2	24.4 (t)	19	55.5	50.8 (t)
3	31.9	41.0 (t)	21	49.9	—
4	84.7	84.4 (s)	22	13.5	—
5	48.6	52.3 (d)	1’	56.5	56.0 (q)
6	26.8	26.2 (t)	14’	57.9	57.8 (q)
7	47.6	44.0 (d)	16’	56.1	55.8 (q)
8	75.6	75.8 (s)	COO	167.7	166.0 (s)
9	78.6	77.2 (s)	1	115.9	141.6 (s)
10	36.4	36.8 (d)	2”	141.8	115.9 (s)
11	51.0	52.8 (s)	3”	120.4 [a]	117.3 (d)
12	24.2	23.6 (t)	4”	134.6 [b]	137.0 (d)
13	49.0	49.2 (d)	5”	122.6 [a]	121.8 (s)
14	90.2	89.9 (d)	6”	131.3 [b]	133.1 (d)
15	44.9	44.0 (t)	NH*CO*	169.5	168.9 (s)
16	82.9	82.2 (d)	$NHCOCH_3$	25.6	25.4 (q)

a, b: exchangeable.

Acknowledgments

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References and Notes

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7. **4**: ^1H NMR (200 MHz, $CDCl_3$, δ ppm): 2.16 (s, 3H, $NHCOCH_3$), 3.23, 3.23, 3.34 (s, each 3H, OCH_3 × 3), 7.51 (dd, 1H, *J* = 10.0, 2.4 Hz, H-4"), 7.92 (d, 1H, *J* = 2.4 Hz, H-6"), 8.55 (d, 1H, *J* = 10.0 Hz, H-3"), 10.9 (s, 1H, *NH*CO).
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