

## Transformation of Sanguinarine into Bocconine

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Nitration of ethoxysanguinarine with equimolar potassium nitrate and sulfuric acid, followed by treatment with sodium hydroxide and methanol, gives 10-nitromethoxysanguinarine. Successive hydrogenation, diazotization and methanolysis convert 10-nitromethoxysanguinarine into bocconine.

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Bocconine (**1**), sanguinarine (**2**) and chelerythrine (**3**) are the nematocidal and antimicrobial alkaloids isolated from *Bocconia Cordata* by Onda *et al.* [2]. Among them, **1** was a new compound, whose structure was assigned as 2,3,9,10-bis(methylenedioxy)-7-methoxy-5-methylbenzo[*c*]phenanthridine [3]. Later, this structure was revised to be 2,3,7,8-bis(methylenedioxy)-10-methoxy-5-methylbenzo[*c*]phenanthridine by means of nmr analysis ( $^1\text{H}$ - $^{13}\text{C}$  COSY, gated decoupling, nOe) [1]. We now report a chemical support for the revised structure based upon the transformation of **2** into **1**.

It is well known that benzo[*c*]phenanthridines exist in I- and II-forms under acidic or basic conditions and that the II-form is easily transformed into the III-form upon alcoholysis. Thus, as shown in Scheme 1, the I-, II- and III-forms are mutually convertible depending upon the employed conditions.

Nitration of ethoxysanguinarine (**4**) [2] with equimolar potassium nitrate and sulfuric acid, followed by treatment with sodium hydroxide and methanol gave compound **5**. Protons and carbons in **5** were straightly assigned by  $^1\text{H}$ - $^{13}\text{C}$  COSY experiments as well as comparison with those in related compounds [1-3] (Table 1). Ring A possessed one singlet proton ( $\delta$  7.25) correlated to C-7 and -10a (three bond coupling), showing unambiguously nitration to occur at C(10). Interestingly, an up-field shift of H-11 ( $\Delta \delta_{4.5} = 0.55$  ppm [2]) was observed. This would be ascribed to the shielding effect of the nitro group deviated out of the ring A plane (dihedral angle, *ca.* 90°) by a steric interaction between 10-NO<sub>2</sub> and ring C.

Hydrogenation of **5** over Raney nickel afforded compound **6**, whose structure was supported by ir (NH<sub>2</sub>, 3450, 3370 cm<sup>-1</sup>) and  $^1\text{H}$  nmr (H<sub>2</sub>-6,  $\delta$  4.05) spectroscopy.

Successive treatments with isopentyl nitrite, methanol and sodium hydroxide converted **6** into compound **8** which furnished compound **9** on methanolysis of the 6-O-function. Compounds **8** and **9** were identified with each au-

thentic sample [3] by direct comparison. Thus, it is clear that oxidation occurred at N(5) and C(6) to give an intermediate **7** during diazotization of **6**. Reduction of **8** with sodium borohydride afforded compound **10** identical with an authentic sample [2].

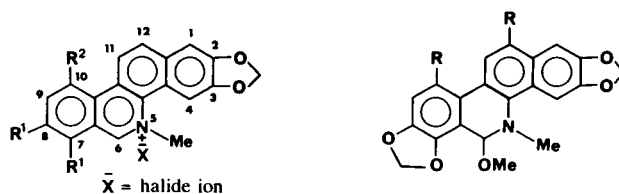
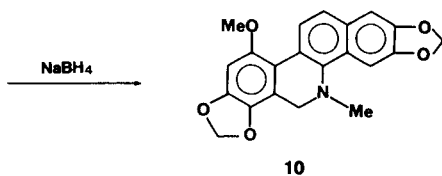
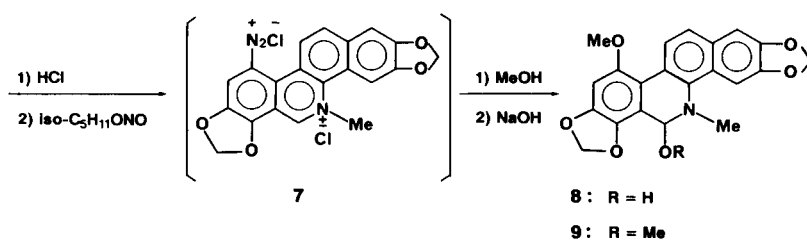
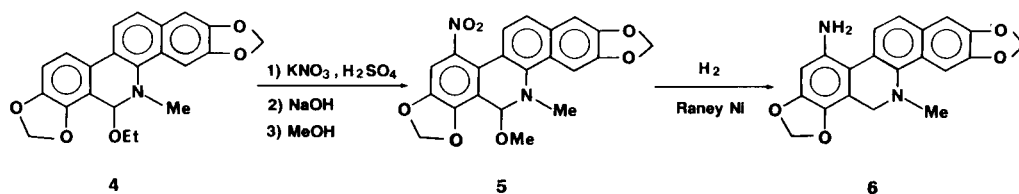
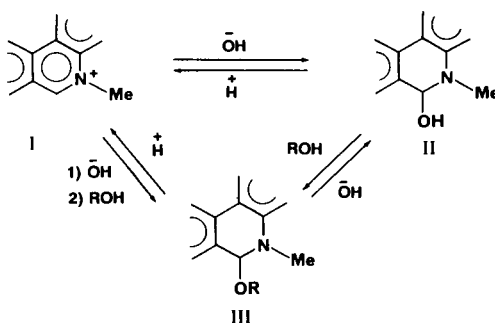
Nitration of **4** with excess nitric acid yielded compounds

Table 1  
NMR Data for Compound **5** [a]

No.	Carbon $\delta_{\text{C}}$	Correlated Proton [b] $\delta_{\text{H}}$	Proton coupled with Carbon [c]
1	104.7 d	7.12 s	H-12
2 [d]	148.2 s		H-1, H-4
3 [d]	147.9 s		
4	100.4 d	7.69 s	
4a	127.1 s		H-1, H-12
4b	139.6 s		H-6, H-11, 5-Me
6	85.3 d	5.31 s	5-Me
6a	116.3 s		
7	148.1 s		H-6, H-9
8	146.3 s		H-9
9	105.9 d	7.25 s	
10	142.1 s		H-9
10a	121.4 s		H-6, H-9
10b	119.2 s		H-12
11	122.0 d	7.23 d (9.0)	
12	123.8 d	7.41 d (9.0)	H-1
12a	131.7 s		H-4, H-11
5-Me	40.6 q	2.86 s	
6-OMe	54.5 q	3.39 s	H-6
OCH <sub>2</sub> O	103.3 t	6.21 d	
		6.19 d (1.5)	
OCH <sub>2</sub> O	101.2 t	6.08 d	
		6.07 d (1.2)	

[a] Spectra were taken on a Varian XL-400 in deuteriochloroform. [b]  $^1\text{H}$ - $^{13}\text{C}$  (one-bond) COSY. Figures in parentheses are coupling constants (Hz). [c]  $^1\text{H}$ - $^{13}\text{C}$  (long-range) COSY. [d] These are exchangeable.

Scheme 1

1 :  $R^1 + R^1 = \text{OCH}_2\text{O}$ ,  $R^2 = \text{OMe}$ 11 :  $R = \text{NO}_2$ 2 :  $R^1 + R^1 = \text{OCH}_2\text{O}$ ,  $R^2 = \text{H}$ 12 :  $R = \text{OMe}$ 3 :  $R^1 = \text{OMe}$ ,  $R^2 = \text{H}$ 

**5** and **11**. Rings A and C in **11** contained one singlet proton ( $\delta$  7.34, 8.11), respectively, which were established as H-9 and -11 by the correlation to C-7, -10a and C-4b, -10a, -12a (Table 2). A down-field shift of H-1 ( $\Delta \delta_{45-11} = -0.93$

ppm) observed also supported 12-NO<sub>2</sub>.

Macarpine (**12**) would be expected to prepare from **11** in the same manner as above.

Table 2  
NMR Data for Compound 11 [a]

No.	Carbon $\delta_C$	Correlated Proton [b] $\delta_H$	Proton coupled with Carbon [c]
1	101.4 d	8.06 s	
2 [d]	151.2 s		H-4
3 [d]	149.1 s		H-1, H-4
4	101.0 d	7.78 s	
4a	128.6 s		H-1
4b	144.9 s		H-6, 5-Me
6	85.2 d	5.37 s	5-Me, 6-OMe
6a	116.4 s		H-6
7	148.2 s		H-6, H-9
8	147.4 s		H-9, 7,8-OCH <sub>2</sub> O
9	106.5 d	7.34 s	
10	142.2 s		H-9
10a	119.8 s		H-6, H-9, H-11
10b	118.6 s		
11	121.6 d	8.11 s	
12	142.6 s		H-1, H-11
12a	124.0 s		H-4, H-11
2,3- OCH <sub>2</sub> O		6.18 d 6.17 d (1.0)	
5-Me	40.8 q	2.95 s	
6-OMe	54.8 q	3.38 s	
7,8- OCH <sub>2</sub> O		6.26 d 6.24 d (1.3)	

[a] Spectra were taken on a Varian XL-400 in deuteriochloroform. [b] <sup>1</sup>H-<sup>13</sup>C (one-bond) COSY. Figures in parentheses are coupling constants (Hz). [c] <sup>1</sup>H-<sup>13</sup>C (long-range) COSY. [d] These are exchangeable.

## EXPERIMENTAL

Melting points (uncorrected) were determined on a micro hot-stage apparatus. Spectra were recorded on the following spectrometers: ir, Hitachi 260-30; <sup>1</sup>H nmr, Varian XL-400 (400 MHz) or EM-390 (90 MHz) (reference, tetramethylsilane); <sup>13</sup>C nmr, Varian XL-400 (100.6 MHz) (reference, tetramethylsilane); hrms, fabms, JEOL JMS DX-300; elemental analysis, Perkin-Elmer 240 B.

The <sup>1</sup>H-<sup>13</sup>C COSY experiments were performed using Varian's standard pulse sequences [1,4].

### 10-Nitromethoxysanguinarine (5).

To a solution of **4** (60 mg, 0.16 mmole) in acetic acid (0.1 ml) was added a mixture of potassium nitrate (14 mg, 0.16 mmole), concentrated sulfuric acid (0.1 ml) and acetic acid (0.1 ml). After stirring at room temperature for 5 minutes, the reaction mixture was made alkaline with 10% aqueous sodium hydroxide and extracted with ethyl acetate. Workup of the organic layer, followed by preparative tlc (alumina, benzene-ethyl acetate = 3:1) and recrystallization from methanol, gave **5** (36 mg), Rf 0.40, as orange needles, mp 251-253°; hrms: m/z M<sup>+</sup>, 408.0972 (M, 408.0958 for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O<sub>7</sub>).

Anal. Calcd. for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O<sub>7</sub>: C, 61.76; H, 3.95; N, 6.86. Found: C, 61.67; H, 4.07; N, 7.02.

### 10-Aminodihydrosanguinarine (6).

A solution of **5** (57 mg, 0.14 mmole) in methanol (200 ml) was

hydrogenated over Raney nickel W-2 (ca. 100 mg) at room temperature for 4 hours. Workup of the reaction mixture, followed by preparative tlc (alumina, benzene), afforded **6** (28 mg), Rf 0.31, as colorless granules, mp 176-177° (methanol); ir (chloroform):  $\nu$  cm<sup>-1</sup> 3450, 3370 (NH<sub>2</sub>); <sup>1</sup>H nmr (90 MHz) (deuteriochloroform):  $\delta$  8.07 (1H, d, J = 9.0 Hz, H-11), 7.72 (1H, s, H-4), 7.55 (1H, d, J = 9.0 Hz, H-12), 7.12 (1H, s, H-1), 6.32 (1H, s, H-9), 6.04, 5.93 (each 2H, s, OCH<sub>2</sub>O x 2), 4.05 (2H, s, H-6), 2.60 (3H, s, 5-Me); hrms: m/z M<sup>+</sup>, 348.1108 (M, 348.1109 for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>).

Bocconines **8** (II-form) and **9** (III-form).

A solution of **6** (10 mg, 0.029 mmole) in 5% methanolic hydrochloric acid (1 ml) was concentrated *in vacuo*, and the residue was dissolved in methanol (0.5 ml). To the methanol solution was added a solution of isopentyl nitrite (10 mg, 0.075 mole) in acetic acid (0.5 ml), and the whole was stirred at -5° for 20 minutes. The reaction mixture was diluted with ether (30 ml) to yield the precipitate which was stirred with methanol (2 ml) at room temperature for 24 hours. After it was made alkaline with 10% aqueous sodium hydroxide, workup of the reaction mixture, followed by preparative tlc (silica gel, chloroform-methanol = 50:1), gave **8** (1.3 mg), Rf 0.19, as colorless amorphous, mp 140-151°; <sup>1</sup>H nmr (400 MHz) (deuteriochloroform):  $\delta$  8.44 (1H, d, J = 8.8 Hz, H-11), 7.67 (1H, s, H-4), 7.48 (1H, d, J = 8.8 Hz, H-12), 7.11 (1H, s, H-1), 6.69 (1H, s, H-9), 6.07, 6.05 (each 2H, m, OCH<sub>2</sub>O x 2), 5.55 (1H, d, J = 1.5 Hz, H-6), 3.90 (3H, s, 10-OMe), 2.69 (3H, s, 5-Me); fabms: m/z M<sup>+</sup>+1-H<sub>2</sub>O, 362 (M, 379 for C<sub>21</sub>H<sub>17</sub>NO<sub>6</sub>).

Treatment of **8** with methanol quantitatively furnished **9** [3] as colorless needles, mp 197-200° (chloroform-methanol); hrms: m/z M<sup>+</sup>, 393.1219 (M, 393.1213 for C<sub>22</sub>H<sub>19</sub>NO<sub>6</sub>).

### Dihydrobocconine (10).

Reduction of **8**, derived from **6** (13 mg, 0.037 mmole), with sodium borohydride (10 mg, 0.26 mmole) in methanol (2 ml) was carried out at room temperature for 15 minutes. Workup of the reaction mixture, followed by preparative tlc (silica gel, chloroform-methanol = 50:1), afforded **10** [2] (1.5 mg), Rf 0.36, as colorless needles, mp 206-207° (methanol); hrms: m/z M<sup>+</sup>, 363.1106 (M, 363.1106 for C<sub>21</sub>H<sub>17</sub>NO<sub>5</sub>).

### 10,12-Dinitromethoxysanguinarine (11).

To a solution of **4** (35 mg, 0.093 mmole) in acetic acid (0.15 ml), were added concentrated nitric acid (0.05 ml, 0.83 mmole), and the whole was stirred at room temperature for 20 minutes. The reaction mixture was made alkaline with 5% aqueous sodium hydroxide and extracted with ethyl acetate. Workup of the organic layer, followed by preparative tlc (alumina, benzene) and recrystallization from methanol, afforded **5** (10 mg) and **11** (10 mg).

Compound **11** was orange needles, mp 251-253° (methanol); hrms m/z M<sup>+</sup>, 453.0800 (M, 453.0807).

Anal. Calcd. for C<sub>21</sub>H<sub>15</sub>N<sub>3</sub>O<sub>9</sub>: C, 55.63; H, 3.33; N, 9.27. Found: C, 55.89; H, 3.53; N, 9.01.

## REFERENCES AND NOTES

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