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## SYNTHESIS OF 2,3,9,10-TETRAOXYGENATED BENZO[*c*]PHENANTHRIDINE DERIVATIVES VIA PALLADIUM- MEDIATED ARYL-ARYL COUPLING REACTION

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**Abstract** – Two 2,3,9,10-tetraoxygenated benzo[*c*]phenanthridine alkaloids, **1** and **2**, originally reported as zanthoxyline and broussonpapyrine, respectively, were synthesized using the Pd-mediated intramolecular aryl-aryl coupling reaction as the key step.

### INTRODUCTION

The palladium-mediated aryl-aryl coupling reaction is a powerful method to construct biaryl compounds, and many syntheses of biaryl-type natural products have been accomplished using this technique.<sup>1</sup> Especially, intramolecular coupling is useful for the formation of polyfunctionalized heterocyclic systems.<sup>2</sup> Among such heterocyclic compounds, the benzo[*c*]phenanthridine alkaloids are recognized as an important class of natural products because of their interesting biological activities such as antitumor and antiviral activities, inhibition of DNA topoisomerase I, etc.<sup>3</sup> In this context, we have reported several syntheses of the benzo[*c*]phenanthridine natural products via the intramolecular aryl-aryl coupling reaction of the benzonaphthamide derivatives.<sup>4</sup>

Recently, two unique natural benzo[*c*]phenanthridine alkaloids, zanthoxyline (**1**)<sup>5</sup> and broussonpapyrine (**2**),<sup>6</sup> were independently isolated, which possess an unusual substituent pattern (Figure).<sup>7</sup> Namely, they contain four oxygen functional groups at positions 2, 3, 9, and 10 on the benzo[*c*]phenanthridine skeleton. Thereafter, the originally reported structures of both **1** and **2** were revealed to be incorrect based on synthetic studies.<sup>8</sup> From the viewpoint of a structure-bioactivity relationship, even if these compounds are

not natural products, we considered that the establishment of a synthetic method of such unusual benzo[*c*]phenanthridine derivatives is a meaningful challenge. Thus, in this report, we demonstrate the synthesis of **1** and **2** using the palladium-mediated intramolecular aryl-aryl coupling reaction as the key step.<sup>9</sup>

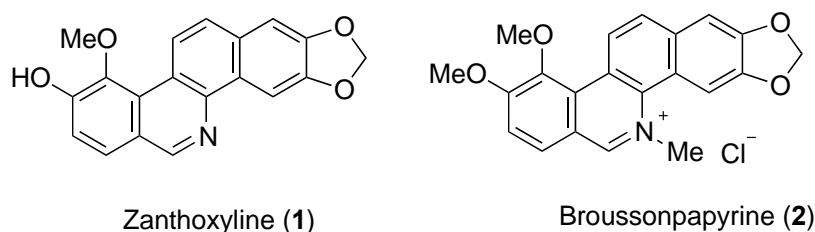
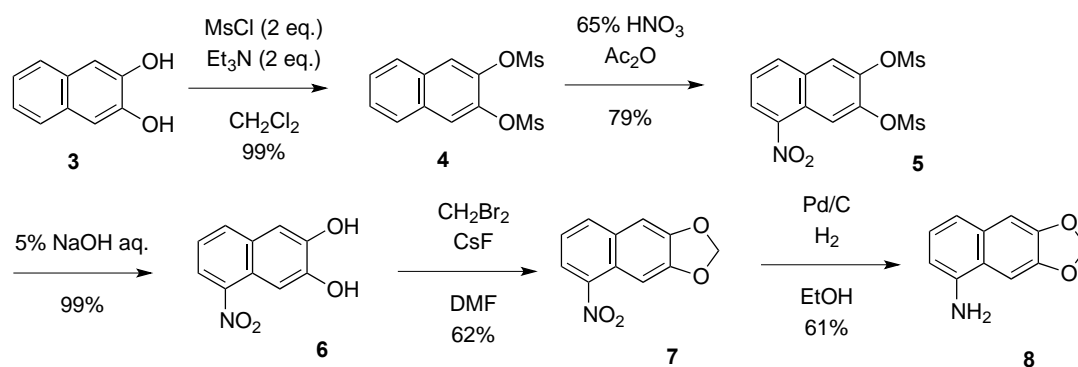


Figure. Originally Reported Structures of Zanthoxyline (**1**) and Broussonpapyrine (**2**)

## RESULTS AND DISCUSSION

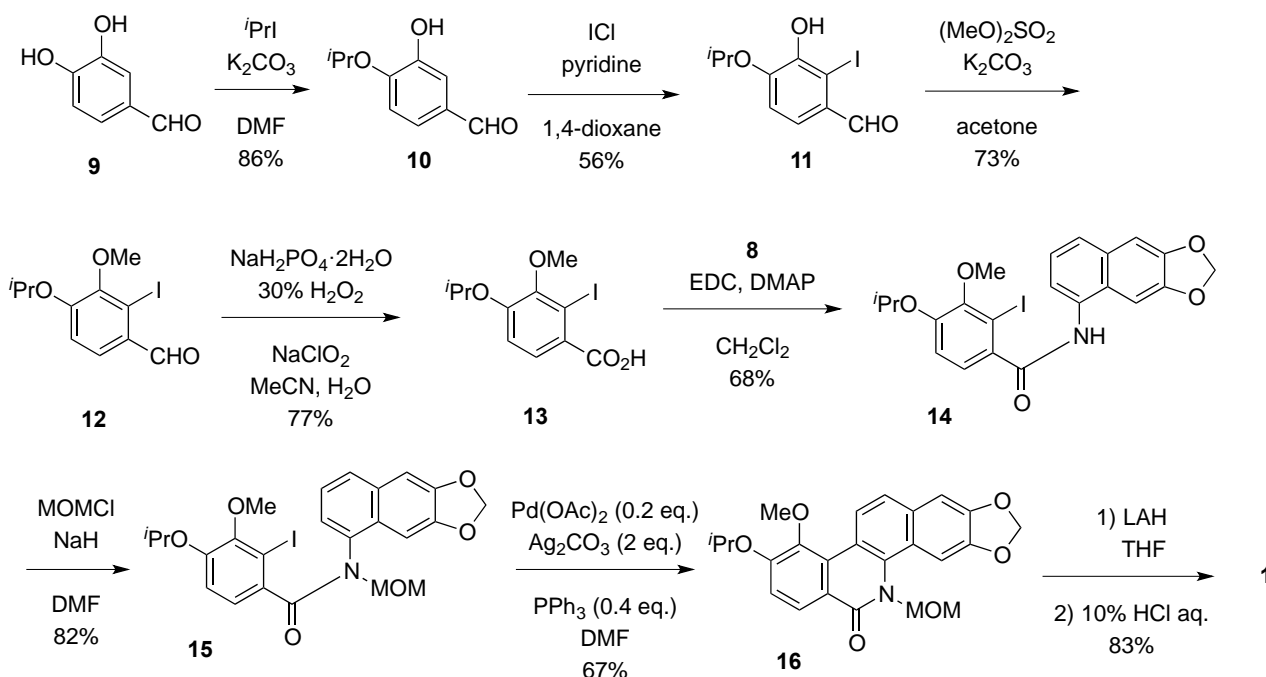
For the total synthesis of **1**, we commenced the preparation of 6,7-methylenedioxy-1-naphthylamine (**8**) by the reported method (Scheme 1).<sup>10</sup> First, 2,3-dihydroxynaphthalene (**3**) was mesylated to afford **4**<sup>11</sup> followed by regioselective nitration for producing **5**.<sup>11</sup> Alkaline hydrolysis of **5** and successive methylenation of the generated catechol moiety produced the tricyclic compound **7**, which was reduced to **8**<sup>12</sup> using the conventional catalytic hydrogenation technique.



Scheme 1. Preparation of 1-Naphtylamine

Next, we employed 3,4-dihydroxybenzaldehyde (**9**) as a starting material to prepare the key coupling precursor **15** (Scheme 2). Selective protection of the 4-hydroxy group of **9** with the isopropyl unit and successive iodination afforded **11**. The leaving hydroxy group was methylated to form **13** which was further transformed into the benzoic acid **13**. Condensation between **8** and **13** for the amide bond formation using the EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) - DMAP system produced **14**, leading to the *N*-protected compound **15** with the MOM group. The intramolecular aryl-aryl coupling reaction (Pd(OAc)<sub>2</sub>-Ag<sub>2</sub>CO<sub>3</sub>-PPh<sub>3</sub>)<sup>4a,13</sup> of **15** smoothly proceeded to construct the lactam compound **16**. Finally, the synthesis of the target compound **1** was completed by the hydride reduction with LiAlH<sub>4</sub> and successive acid treatment involving removal of both the MOM and isopropyl

groups.



Scheme 2. Synthesis of **1** via Pd-mediated Aryl-Aryl Coupling Reaction

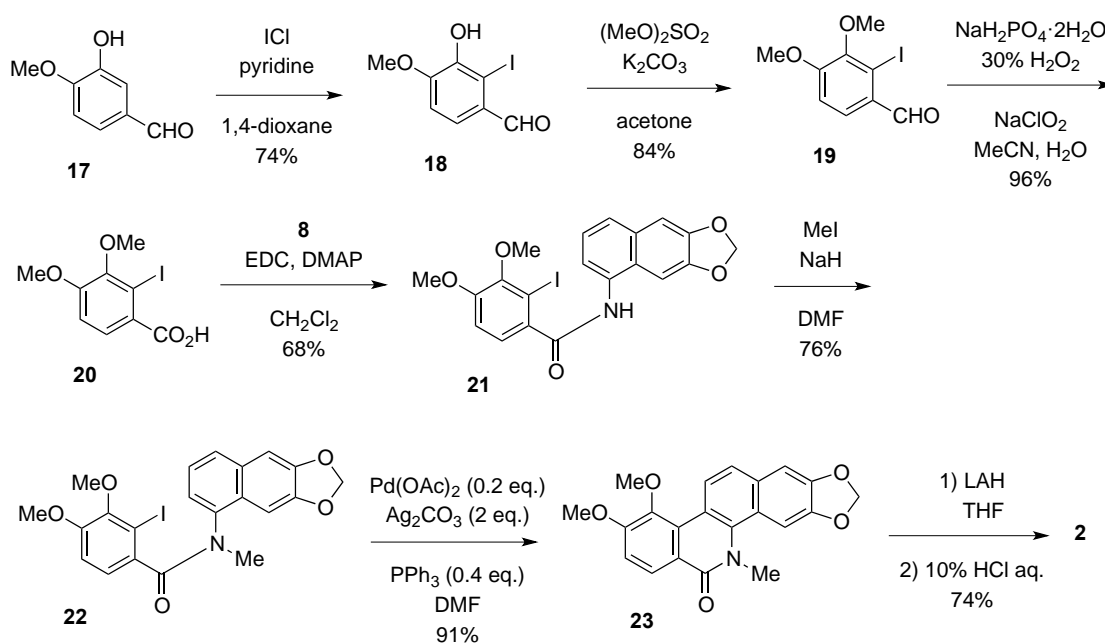
On the other hand, the second target **2** was synthesized as illustrated in Scheme 3. Isovanillin **17** was regioselectively iodinated to prepare **18**<sup>14</sup> which was converted into the dimethoxy compound **19**<sup>15</sup> using dimethyl sulfate. The formyl group of **19** was oxidized to a carboxylic acid for the formation of **20**,<sup>16</sup> which was subjected to the condensation reaction with **8** using EDC-DMAP. Methylation of the amide nitrogen of **21** was also successful to afford the coupling precursor **22**. Conditions similar to Scheme 2 were employed for the intramolecular coupling reaction to produce **23**. The final reduction using LiAlH<sub>4</sub> followed by the treatment with hydrochloric acid succeeded in the synthesis of **2**.

## CONCLUSION

We demonstrated the synthesis of two benzo[*c*]phenanthridine alkaloids which possess an unusual substituent pattern, i.e., the 2,3,9,10-tetraoxygenated compounds. The Pd-mediated aryl-aryl coupling reaction was efficiently used as the key step for the construction of the benzo[*c*]phenanthridine skeleton. Further application of this method for the synthesis of other heterocyclic compounds is currently in progress in our laboratory.

## EXPERIMENTAL

**General:** Melting points were measured using a Yanagimoto micro-melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 or Shimadzu FTIR-8400 spectrophotometer. The NMR spectra were obtained using a Varian MERCURY-300, JEOL  $\alpha$ -400, or JNX-ECX500 instrument with the chemical shifts being reported as  $\delta$  ppm and the couplings expressed in

Scheme 3. Synthesis of **2** via Pd-mediated Aryl-Aryl Coupling Reaction

Hertz. The elemental analysis was performed using a Yanaco MT-5 or Thermo Scientific FlashEA1112 analyzer. Electron ionization mass spectra (EI-MS) was obtained using a JEOL JMS-700 instrument. Silica gel column chromatography was carried out using Merck 9385 Kieselgel 60 or Wako-gel C-200.

### 2,3-Bis(methylsulfonyloxy)naphthalene (**4**)

MsCl (39.3 g, 26.5 mL, 0.343 mol) was added to a solution of 2,3-dihydroxynaphthalene (**3**) (25 g, 0.156 mol), Et<sub>3</sub>N (34.7 g, 47.9 mL, 0.343 mol) in CHCl<sub>3</sub> (500 mL) at 0 °C, then the mixture was allowed to stand at rt. After the resulting precipitates were removed by filtration, water was added to the mother liquid which was extracted with CHCl<sub>3</sub>. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a crude residue. Recrystallization from CHCl<sub>3</sub> gave **4** (48.8 g, 99%) in almost a pure form. Colorless needles, mp 153.9–157.2 °C (CHCl<sub>3</sub>) [lit.<sup>11</sup> 159–160 °C]. IR (KBr) cm<sup>-1</sup>: 1360, 1180. <sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>) δ: 3.29 (6H, s, CH<sub>3</sub>), 7.58–7.95 (6H, m, Ar-H).

### 6,7-Bis(methylsulfonyloxy)-1-nitronaphthalene (**5**)

To a solution of **4** (18 g, 0.057 mol) in acetic anhydride (180 mL), conc. HNO<sub>3</sub> (42.5 mL) was dropwise added while maintaining the reaction mixture at 35–40 °C. The mixture was then cooled to 5 °C, and stirred for 1 day. After the reaction mixture was poured into ice-water, the resulting precipitates were collected and recrystallized from MeCN to give **5** (16.2 g, 79%). Yellow needles, 198.8–199.8 °C [lit.<sup>11</sup> 200–201 °C]. IR (KBr) cm<sup>-1</sup>: 1520, 1350, 1170. <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) δ: 3.37 (6H, s, CH<sub>3</sub>), 7.65 (1H, t, *J* = 8.0 Hz, C<sub>7</sub>-H), 8.11 (1H, s, C<sub>1</sub>-H), 8.17 (1H, d, *J* = 8.5 Hz, C<sub>8</sub>-H), 8.43 (1H, d, *J* = 8.5 Hz, C<sub>6</sub>-H),

8.78 (1H, s, C<sub>4</sub>-H).

### 6,7-Dihydroxy-1-nitronaphthalene (6)

The mixture of **5** (18.7 g, 0.033 mol) and a 5% NaOH aqueous solution (165 mL) was heated overnight at 100 °C. After acidification with a 10% HCl aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give **6** (10.5 g, 99%). Yellow needles, 206.2-207.0 °C [lit.<sup>10</sup> 207-209 °C]. IR (KBr) cm<sup>-1</sup>: 3360 (OH). <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) δ: 5.99 (1H, s, ArOH), 6.31 (1H, s, ArOH), 7.35 (1H, s, C<sub>1</sub>-H), 7.36 (1H, t, *J* = 8.0 Hz, C<sub>7</sub>-H), 7.92 (1H, d, *J* = 8.0 Hz, C<sub>8</sub>-H), 8.15 (1H, s, C<sub>4</sub>-H), 8.17 (1H, d, *J* = 8.0 Hz C<sub>6</sub>-H).

### 6,7-Methylenedioxy-1-nitronaphthalene (7)

CsF (8.51 g, 0.056 mol) was added to a solution of **6** (2.3 g, 0.0112 mol) in DMF (23 mL), then the mixture was stirred at rt for 1.5 h. To the mixture, CH<sub>2</sub>Br<sub>2</sub> (2.92 g, 1.18 mL, 0.0168 mol) was added, which was heated at 115 °C for 2.5 h. After the mixture was diluted with AcOEt and the insoluble material was removed by filtration, the mixture was washed with a 5% NaOH aqueous solution and brine, dried over MgSO<sub>4</sub>, and concentrated. The resulting solid was recrystallized from AcOEt to give **7** (1.5 g, 62%). Yellow needles, mp 159.3-163.0 °C. IR (KBr) cm<sup>-1</sup>: 1470, 1320. <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) δ: 6.13 (2H, s, O-CH<sub>2</sub>-O), 7.20 (1H, s, C<sub>1</sub>-H), 7.38 (1H, t, *J* = 8.0 Hz, C<sub>7</sub>-H), 7.91 (1H, d, *J* = 7.5 Hz, C<sub>8</sub>-H), 7.98 (1H, s, C<sub>4</sub>-H), 8.17 (1H, d, *J* = 7.5 Hz C<sub>6</sub>-H).

### 1-Amino-6,7-methylenedioxy-naphthalene (8)

Under an H<sub>2</sub> atmosphere, the mixture of **7** (2.0 g, 0.0092 mol), EtOH (100 mL), and 10% Pd/C (250 mg) was vigorously stirred at rt for 1.5 h. After filtration, the solvent was evaporated to give a crude residue, and then recrystallization from EtOH gave **8** (1.06 g, 61%). Yellow needles, mp 151.5-154.0 °C [lit.<sup>12a</sup> 154-155 °C (Et<sub>2</sub>O-hexane); lit.<sup>12b</sup> 152-154 °C (EtOH-H<sub>2</sub>O)]. IR (KBr) cm<sup>-1</sup>: 3210 (NH). <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) δ: 6.03 (2H, s, O-CH<sub>2</sub>-O), 6.29-7.21 (5H, m, Ar-H).

### 3-Hydroxy-4-isopropoxybenzaldehyde (10)

To a suspension of K<sub>2</sub>CO<sub>3</sub> (12.5 g, 0.090 mol) in DMF (50 mL), 3,4-dihydroxybenzaldehyde (**9**, 25 g, 0.28 mol) and 2-iodopropane (18 mL, 0.18 mol) were successively added, then the mixture was stirred at 50 °C for 1 day. The mixture was acidified with a 10% HCl aqueous solution and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:6). The title compound **10** (28.2 g, 86 %) was obtained. Yellow needles, mp 63.7-65.2 °C (AcOEt). IR (KBr) cm<sup>-1</sup>: 3300 (OH), 1680

(C=O), 1280.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.41 (3H, s, ArOCHCH<sub>3</sub>), 1.42 (3H, s, ArOCHCH<sub>3</sub>), 4.72 (1H, heptet,  $J = 6.3$  Hz, ArOCH(CH<sub>3</sub>)<sub>2</sub>), 5.89 (1H, s, ArOH), 6.95 (1H, d,  $J = 8.0$  Hz, C<sub>5</sub>-H), 7.39 (1H, dd,  $J = 8.0, 2.5$  Hz, C<sub>6</sub>-H), 7.43 (1H, d,  $J = 2.5$  Hz, C<sub>2</sub>-H), 9.82 (1H, s, ArCHO). *Anal.* Calcd for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>: C, 66.65; H, 6.71. Found: C, 66.61; H, 6.52.

### 3-Hydroxy-2-iodo-4-isopropoxybenzaldehyde (11)

To a solution of **10** (12 g, 0.13 mol) in pyridine (80 mL), a solution of ICl (21.9 g, 0.135 mol) in 1,4-dioxane (160 mL) was dropwise added under cooling at 0 °C. The mixture was warmed to rt and allowed to stand for 15 h. After the volatile materials were removed in vacuo, water was added to the mixture. The resulting precipitates were collected, then recrystallization from AcOEt gave **11** (14.27 g, 56%). Pale yellow needles, mp 152.5-156.7 °C (AcOEt). IR (KBr)  $\text{cm}^{-1}$ : 3400 (OH), 1670 (CO), 1280.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.41 (3H, s, ArOCHCH<sub>3</sub>), 1.43 (3H, s, ArOCHCH<sub>3</sub>), 4.75 (1H, heptet,  $J = 6.3$  Hz, ArOCH(CH<sub>3</sub>)<sub>2</sub>), 6.36 (1H, s, ArOH), 6.89 (1H, d,  $J = 8.7$  Hz, C<sub>5</sub>-H), 7.53 (1H, d,  $J = 8.7$  Hz, C<sub>6</sub>-H), 10.03 (1H, s, ArCHO).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 194.9, 149.0, 146.4, 128.4, 123.6, 111.6, 88.2, 72.7, 22.1. *Anal.* Calcd for C<sub>10</sub>H<sub>11</sub>IO<sub>3</sub>: C, 39.24; H, 3.62. Found: C, 39.23; H, 3.64.

### 2-Iodo-4-isopropoxy-3-methoxybenzaldehyde (12)

A mixture of **11** (14 g, 0.045 mol), K<sub>2</sub>CO<sub>3</sub> (12.7 g, 0.092 mol), (MeO)<sub>2</sub>SO<sub>2</sub> (8.66 mL, 0.092 mol), and acetone (50 mL) was heated under reflux for 1 h. The solvent was removed under reduced pressure, then water was added to the mixture which was extracted with Et<sub>2</sub>O. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a crude solid. Recrystallization from Et<sub>2</sub>O gave **12** (10.6 g, 73%). Pale yellow prisms, mp 48.1-51.9 °C (Et<sub>2</sub>O).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.41 (3H, s, ArOCHCH<sub>3</sub>), 1.42 (3H, s, ArOCHCH<sub>3</sub>), 3.86 (3H, s, ArOCH<sub>3</sub>), 4.70 (1H, heptet,  $J = 6.0$  Hz, ArOCH), 6.94 (1H, d,  $J = 8.5$  Hz, C<sub>5</sub>-H), 7.68 (1H, d,  $J = 8.5$  Hz, C<sub>6</sub>-H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 195.1, 156.2, 149.4, 128.6, 127.2, 113.8, 100.9, 71.7, 60.3, 22.0. *Anal.* Calcd for C<sub>11</sub>H<sub>13</sub>IO<sub>3</sub>: C, 41.27; H, 4.09. Found: C, 41.50; H, 4.07.

### 2-Iodo-4-isopropoxy-3-methoxybenzoic acid (13)

To a solution of **12** (150 mg, 0.467 mmol), NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O (18.3 mg, 0.12 mmol), and 30% H<sub>2</sub>O<sub>2</sub> (79.7 mg, 2.34 mmol) in MeCN (15 mL), an 80% aqueous solution of NaClO<sub>2</sub> (0.5 mL, 79.5 mg, 0.879 mmol) was added at 0 °C. The mixture was stirred at the same temperature for 5.5 h, then poured into a sat. NaHSO<sub>3</sub> aqueous solution. After acidification with 10% HCl aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a residue. Recrystallization from AcOEt gave **13** (120 mg, 77%). Colorless needles, mp 152-153 °C

(AcOEt). IR (KBr)  $\text{cm}^{-1}$ : 3000 (OH), 1700 (CO), 1280.  $^1\text{H-NMR}$  (300MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.40 (3H, s, ArOCHCH<sub>3</sub>), 1.42 (3H, s, ArOCHCH<sub>3</sub>), 3.84 (3H, s, ArOCH<sub>3</sub>), 4.67 (1H, heptet,  $J = 6.3$  Hz, ArOCH(CH<sub>3</sub>)<sub>2</sub>), 6.90 (1H, d,  $J = 8.7$  Hz, C<sub>5</sub>-H), 7.82 (1H, d,  $J = 8.7$  Hz, C<sub>6</sub>-H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.5, 154.5, 150.8, 129.4, 125.7, 113.7, 95.9, 71.7, 60.3, 22.1. *Anal.* Calcd for C<sub>11</sub>H<sub>13</sub>IO<sub>4</sub>: C, 39.31; H, 3.90. Found: C, 39.27; H, 3.86.

#### **2-Iodo-4-isopropoxy-3-methoxy-N-(6,7-methylenedioxy-1-naphthyl)benzamide (14)**

A mixture of **13** (100 mg, 0.31 mmol), **8** (67 mg, 0.37 mmol), EDC (98 mg, 0.53 mmol), DMAP (7.9 mg, 0.068 mmol), and  $\text{CH}_2\text{Cl}_2$  (10 mL) was heated at 30 °C for 4.5 h. After being poured into water, the mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt/hexane (1:4). Recrystallization from  $\text{CH}_2\text{Cl}_2$  gave **14** (103 mg, 68%). Colorless needles, mp 226-229 °C ( $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H-NMR}$  (300MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.40 (3H, s, ArOCHCH<sub>3</sub>), 1.42 (3H, s, ArOCHCH<sub>3</sub>), 3.89 (3H, s, ArOCH<sub>3</sub>), 4.65 (1H, heptet,  $J = 6.3$  Hz, ArOCH(CH<sub>3</sub>)<sub>2</sub>), 6.05 (2H, s, OCH<sub>2</sub>O), 6.98 (1H, d,  $J = 8.1$  Hz, C<sub>5</sub>-H), 7.33-7.61 (5H, m, Ar-H), 7.83 (1H, d,  $J = 8.1$  Hz, C<sub>6</sub>-H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 167.9, 152.2, 150.3, 148.5, 147.8, 135.5, 135.4, 131.6, 125.9, 125.3, 124.9, 124.4, 121.1, 115.5, 104.7, 101.4, 98.5, 92.5, 71.7, 60.4, 22.1. *Anal.* Calcd for C<sub>22</sub>H<sub>20</sub>INO<sub>5</sub>: C, 52.29; H, 3.99; N, 2.77. Found: C, 52.38; H, 4.10; N, 2.69.

#### **2-Iodo-4-isopropoxy-3-methoxy-N-(methoxymethyl)-N-(6,7-methylenedioxy-1-naphthyl)benzamide (15)**

NaH (50% in mineral oil, 28 mg, 0.59 mmol) was washed with hexane before use. To a mixture of the prepared base and DMF (10 mL), **14** (100 mg, 0.198 mmol) was added and stirred at rt for 30 min. MOMCl (24 mg, 0.023 mL, 0.30 mmol) was added to the mixture, then stirred at rt for 5 h. The mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , and concentrated to give a residue. Silica gel column chromatography with AcOEt/hexane (1:3) gave **15** (88.7 mg, 82%) as an amorphous solid.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.17-1.42 (6H, m, ArOCH(CH<sub>3</sub>)<sub>2</sub>), 3.69-3.89 (6H, m, N-CH<sub>2</sub>OCH<sub>3</sub>, ArOCH<sub>3</sub>), 4.29-4.68 (1H, m, ArOCH(CH<sub>3</sub>)<sub>2</sub>), 4.86, 5.75 (2H, d,  $J = 9.9$ , NCH<sub>2</sub>OCH<sub>3</sub>), 6.32-6.37 (1H, m, C<sub>5</sub>-H), 6.56-6.64 (1H, m, C<sub>6</sub>-H), 7.06-7.50 (5H, m, Ar-H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ ) (selected peaks)  $\delta$ : 171.6, 150.5, 150.1, 148.9, 147.9, 136.7, 131.6, 127.7, 126.2, 124.1, 114.4, 104.6, 101.5, 99.3, 93.4, 78.7, 71.3, 60.2, 57.9, 22.1, 21.7. *Anal.* Calcd for C<sub>24</sub>H<sub>24</sub>INO<sub>6</sub>: C, 52.47; H, 4.40; N, 2.55. Found: C, 52.71; H, 4.51; N, 2.37.

#### **9-Isopropoxy-10-methoxy-N-methoxymethyl-2,3-methylenedioxybenzo[c]phenanthridin-6(5H)-**

**one (16)**

A mixture of **15** (100 mg, 0.18 mmol), PPh<sub>3</sub> (19.2 mg, 0.072 mmol), Ag<sub>2</sub>CO<sub>3</sub> (101 mg, 0.36 mmol) Pd(OAc)<sub>2</sub> (8.2 mg, 0.036 mmol), and DMF (2 mL) was heated under reflux for 1 h. After the mixture was diluted with AcOEt, any undissolved materials were filtered off. The mother liquid was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:4). The title compound **16** (52 mg, 67%) was obtained, which was recrystallized from AcOEt for use as an analytical sample. Yellow needles, mp 175.7-177.7 °C (AcOEt). IR (KBr) cm<sup>-1</sup>: 1660 (CO). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 1.46 (3H, s, ArOCHCH<sub>3</sub>), 1.48 (3H, s, ArOCHCH<sub>3</sub>), 3.72 (3H, s, NCH<sub>2</sub>OCH<sub>3</sub>), 3.87 (3H, s, ArOCH<sub>3</sub>), 4.77 (1H, heptet, *J* = 6.3 Hz, ArOCH(CH<sub>3</sub>)<sub>2</sub>), 5.37 (2H, s, NCH<sub>2</sub>OCH<sub>3</sub>), 6.09 (2H, s, OCH<sub>2</sub>O), 7.15-7.56 (4H, m, Ar-H), 8.35 (1H, d, *J* = 9.0, C<sub>7</sub>-H), 9.12 (1H, d, *J* = 9.0, C<sub>8</sub>-H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 165.1, 155.6, 147.8, 147.6, 146.3, 136.3, 132.0, 128.7, 125.8, 123.2, 122.9, 121.2, 119.5, 116.7, 114.6, 104.0, 102.7, 101.3, 82.1, 71.1, 60.0, 57.1, 22.1. *Anal.* Calcd for C<sub>24</sub>H<sub>23</sub>NO<sub>6</sub>·0.5 H<sub>2</sub>O: C, 66.97; H, 5.62; N, 3.25. Found C, 66.93, H, 5.56; N, 3.34.

**9-Hydroxy-10-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (1)**

To a solution of **16** (120 mg, 0.285 mmol) in THF (5 mL), LiAlH<sub>4</sub> (32 mg, 0.855 mmol) was added at 0 °C, then the mixture was vigorously stirred for 1 h. After quenching with ice water, a NaOH aqueous solution was added as the mixture was adjusted to pH 12-13. After extraction with Et<sub>2</sub>O, the organic layer was washed with brine, dried over K<sub>2</sub>CO<sub>3</sub>, and concentrated. To the resulting solid, a conc. HCl aqueous solution (10 mL) was added, then the mixture was stirred for 24 h. After adjusting to pH 9 by adding a sat. NH<sub>4</sub>Cl aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:2). The title compound **1** (63 mg, 83 %) was obtained, which was recrystallized from CHCl<sub>3</sub> for use as an analytical sample. Brown needles, mp 226-228 °C (CHCl<sub>3</sub>) [lit.<sup>5</sup> 220-222 °C (originally reported zanthoxyline); lit.<sup>8b</sup> 226-227 °C (synthesized by Hibino)]. IR (KBr) cm<sup>-1</sup>: 3400 (OH), 1480. <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 3.88 (3H, s, ArOCH<sub>3</sub>), 6.21 (2H, s, OCH<sub>2</sub>O), 7.43 (1H, d, *J* = 9.0 Hz, C<sub>8</sub>-H), 7.48 (1H, s, C<sub>1</sub>-H), 7.94 (2H, d, *J* = 9.0 Hz, C<sub>7,12</sub>-H), 8.58 (1H, s, C<sub>4</sub>-H), 9.21 (1H, d, *J* = 9.0 Hz, C<sub>11</sub>-H), 9.27 (1H, s, C<sub>6</sub>-H), 10.46 (1H, br, OH). <sup>13</sup>C-NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 153.43, 151.88, 148.52, 148.10, 143.05, 129.86, 127.03, 126.57, 126.36, 122.12, 119.27, 119.14, 104.16, 101.72, 101.66, 59.65. *Anal.* Calcd for C<sub>19</sub>H<sub>13</sub>NO<sub>4</sub>·0.5 H<sub>2</sub>O: C, 69.51; H, 4.30; N, 4.27. Found: C, 69.70; H, 4.26; N, 4.26. FAB-MS *m/z*: 320 (M+1)<sup>+</sup>.

**3-Hydroxy-2-iodo-4-methoxybenzaldehyde (18)**

To a solution of isovanillin (**17**) (10.0 g, 65.7 mmol) in pyridine (40 mL), a solution of ICl (12.1 g, 74.5 mmol) in 1,4-dioxane (80 mL) was dropwise added under cooling at 0 °C. The mixture was warmed to rt and allowed to stand for 3 h. After water was added to the mixture, the resulting precipitates were collected, then recrystallization from AcOEt gave **18** (13.4 g, 74%). Yellow needles, mp 162.3-163.6 °C (AcOEt) [lit.<sup>14</sup> 169-171.5 °C]. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ: 10.03 (1H, s, ArCHO), 7.56 (1H, d, *J* = 8.3 Hz, C<sub>5</sub>-H), 6.93 (1H, d, *J* = 8.3 Hz, C<sub>6</sub>-H), 6.31 (1H, s, ArOH), 4.00 (3H, s, ArOCH<sub>3</sub>).

### 2-Iodo-3,4-dimethoxybenzaldehyde (**19**)

A mixture of **11** (10.0 g, 36.0 mmol), K<sub>2</sub>CO<sub>3</sub> (9.40 g, 68.0 mmol), (MeO)<sub>2</sub>SO<sub>2</sub> (6.80 mL, 70.1 mmol), and acetone (50 mL) was heated under reflux for 1 h. The solvent was removed under reduced pressure, and then water was added to the mixture which was extracted with ET<sub>2</sub>O. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a crude solid. Recrystallization from ET<sub>2</sub>O gave **19** (8.78 g, 84%). Colorless needles, mp 80.5-82.0 °C (AcOEt) [lit.<sup>15a</sup> 82 °C]. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ: 9.93 (1H, s, ArCHO), 7.63 (1H, d, *J* = 8.5 Hz, C<sub>6</sub>-H), 6.92 (1H, d, *J* = 8.5 Hz, C<sub>5</sub>-H), 3.91 (3H, s, ArOCH<sub>3</sub>), 3.80 (3H, s, ArOCH<sub>3</sub>).

### 2-Iodo-3,4-dimethoxybenzoic acid (**20**)

To a solution of **19** (1.00 g, 3.42 mmol), NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O (137 mg, 0.878 mmol), and 30% H<sub>2</sub>O<sub>2</sub> (600 mg, 5.29 mmol) in MeCN (15 mL), an 80% aqueous solution of NaClO<sub>2</sub> (1.5 mL, 385 mg, 5.34 mmol) was added at 0 °C. The mixture was stirred at the same temperature for 4 h, then poured into a 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution. After acidification with a 10% HCl aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a residue. Recrystallization from AcOEt gave **20** (1.01 g, 96%). Colorless needles, mp 203.8-204.5 °C (AcOEt) [lit.<sup>16</sup> 204.5-205 °C]. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.85 (1H, d, *J* = 8.5 Hz, C<sub>6</sub>-H), 6.93 (1H, d, *J* = 8.5 Hz, C<sub>5</sub>-H), 3.94 (3H, s, ArOCH<sub>3</sub>), 3.85 (3H, s, ArOCH<sub>3</sub>).

### 2-Iodo-3,4-dimethoxy-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**21**)

A mixture of **20** (197 mg, 0.641 mmol), **8** (100 mg, 0.534 mmol), EDC (246 mg, 1.28 mmol), DMAP (7.3 mg, 0.059 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was stirred at rt overnight. After being poured into water, the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt/hexane (1:4). Recrystallization from CHCl<sub>3</sub>-MeOH gave **21** (173 mg, 68%). Colorless needles, mp 124.6-125.8 °C (CHCl<sub>3</sub>-MeOH). IR (KBr) cm<sup>-1</sup>: 1654 (CO), 1468 (C-N), 1289, 1250 (COC). <sup>1</sup>H-NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ: 10.18 (1H, s), 7.65 (1H, d, *J* = 8.3 Hz, C<sub>6</sub>-H), 7.54 (1H, d, *J* = 7.5 Hz,

naphC<sub>2</sub>-H), 7.49 (1H, s, naphC<sub>5</sub>-H), 7.31 (3H, m, naphC<sub>2</sub>, C<sub>4</sub>, C<sub>8</sub>-H), 7.19 (1H, d,  $J = 8.3\text{Hz}$ , C<sub>5</sub>-H), 6.14 (2H, s, OCH<sub>2</sub>O), 3.88 (3H, s, OCH<sub>3</sub>), 3.76 (1H, s, OCH<sub>3</sub>). <sup>13</sup>C-NMR (125 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 168.3, 153.0, 148.4, 147.7, 147.5, 136.7, 133.0, 131.3, 125.8, 125.3, 124.4, 124.0, 121.7, 112.9, 104.0, 101.5, 99.9, 93.0, 60.0, 56.4. *Anal.* Calcd for C<sub>20</sub>H<sub>16</sub>INO<sub>4</sub>·0.1H<sub>2</sub>O: C, 50.14; H, 3.41; N, 2.92. Found: C, 49.84; H, 3.11; N, 2.97.

### 2-Iodo-3,4-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (22)

To a mixture of NaH (60% in mineral oil, 76 mg, 1.89 mmol) and DMF (10 mL), **21** (300 mg, 0.629 mmol) was added and stirred at rt for 30 min. MeI (1.57 mL, 0.30 mmol) was added to the mixture, then stirred at 70 °C overnight. The mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a residue. Silica gel column chromatography with AcOEt/hexane (1:4) gave **22** (235 mg, 76%). Colorless prisms, mp 189.9-190.4 °C (AcOEt-hexane). IR (KBr) cm<sup>-1</sup>: 1654 (CO), 1463(C-N), 1246 (COC). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.68 (0.15H, d,  $J = 8.5\text{ Hz}$ , C<sub>6</sub>-H), 7.47 (1H, d,  $J = 7.7\text{ Hz}$ , naphC<sub>6</sub>-H) 7.35 (1H, d,  $J = 7.7\text{ Hz}$ , naphC<sub>8</sub>-H), 7.29 (1H, s, naphC<sub>1</sub>-H) 7.10 (1H, t,  $J = 7.7\text{ Hz}$ , naphC<sub>7</sub>-H), 7.19, 7.08 (0.15, 0.8H, s, naphC<sub>4</sub>-H), 7.03 (0.15H, d,  $J = 8\text{ Hz}$ , C<sub>5</sub>-H), 6.61 (0.85H, d,  $J = 8.5\text{ Hz}$ , C<sub>6</sub>-H), 6.36 (0.85H, d,  $J = 8.5\text{ Hz}$ , C<sub>5</sub>-H), 6.11, 6.09 (1.7H, d,  $J = 1.5\text{ Hz}$ , OCH<sub>2</sub>O), 6.08, 6.05 (0.3H, d,  $J = 1.5\text{ Hz}$ , OCH<sub>2</sub>O) 3.93, 3.90 (0.45H, s, OCH<sub>3</sub>), 3.73, 3.64 (2.55H, s, OCH<sub>3</sub>), 3.51 (2.55H, s, NCH<sub>3</sub>), 3.21 (0.45H, s, NCH<sub>3</sub>). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 170.8, 152.1, 148.94, 148.91, 148.0, 139.4, 135.2, 131.6, 127.3, 127.1, 124.4, 124.2, 122.4, 111.3, 104.5, 101.5, 99.3, 93.3, 60.3, 55.7, 37.3. *Anal.* Calcd for C<sub>21</sub>H<sub>18</sub>INO<sub>5</sub>: C, 51.34; H, 3.69; N, 2.85. Found: C, 51.58; H, 3.66; N, 2.92.

### 9,10-Dimethoxy-*N*-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (23)

A mixture of **22** (500 mg, 1.02 mmol), PPh<sub>3</sub> (107.4 mg, 0.408 mmol), Ag<sub>2</sub>CO<sub>3</sub> (563 mg, 2.04 mmol) Pd(OAc)<sub>2</sub> (45.8 mg, 0.036 mmol), and DMF (5 mL) was heated under reflux for 1 h. After the mixture was diluted with AcOEt, any undissolved materials were filtered off. The mother liquid was washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:3). The title compound **23** (337 mg, 91%) was obtained, which was recrystallized from AcOEt for use as an analytical sample. Colorless needles, mp 261.6-262.4 °C (AcOEt). IR (KBr) cm<sup>-1</sup>: 1644 (CO), 1464 (CN), 1321, 1040 (COC). <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>)  $\delta$ : 9.10 (1H, d,  $J = 8.8\text{ Hz}$ , C<sub>11</sub>-H), 8.38 (1H, d,  $J = 8.8\text{ Hz}$ , C<sub>7</sub>-H), 7.538 (1H, d,  $J = 8.8\text{ Hz}$ , C<sub>12</sub>-H), 7.535 (1H, s, C<sub>4</sub>-H), 7.20 (1H, d,  $J = 8.8\text{ Hz}$ , C<sub>8</sub>-H), 7.15 (1H, s, C<sub>1</sub>-H), 6.08 (2H, s, OCH<sub>2</sub>O), 4.02 (3H, s, NCH<sub>3</sub>), 3.89 (6H, s, OCH<sub>3</sub>). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 164.7, 156.8, 147.9, 146.7, 145.6, 136.9, 132.1, 128.0, 125.8, 123.1, 122.8, 120.8, 120.1, 117.1, 112.2, 104.3, 102.8, 101.5, 60.3, 56.2, 41.7. HRMS (EI)  $m/z$ : calcd for 363.1107, found: 363.1109.

**9,10-Dimethoxy-N-methyl-2,3-methylenedioxybenzo[c]phenanthridinium chloride (2)**

To a solution of **23** (100 mg, 0.275 mmol) in THF (5 mL), LiAlH<sub>4</sub> (31.3 mg, 0.825 mmol) was added at 0 °C, then the mixture was vigorously stirred for 30 min. After quenching with ice water, any undissolved materials were filtered off. To the mother liquid, a 10% HCl aqueous solution was added to leave yellow precipitates which were recrystallized from MeOH. The title compound **2** (78 mg, 74%) was obtained as yellow needles, mp 195.6-196.1 °C (MeOH) [lit<sup>8b</sup> 152-153 °C (CHCl<sub>3</sub>-MeOH)]. IR (KBr) cm<sup>-1</sup>: 1619 (C=N), 1495 (CN), 1285, 1259 (COC). <sup>1</sup>H-NMR (500 MHz, CD<sub>3</sub>OD) δ: 9.77 (1H, s, C<sub>6</sub>-H), 9.16 (1H, d, *J* = 9.3 Hz, C<sub>11</sub>-H), 8.33 (1H, d, *J* = 9.3 Hz, C<sub>7</sub>-H), 8.00 (1H, s, C<sub>4</sub>-H), 7.95 (1H, d, *J* = 9.3 Hz, C<sub>12</sub>-H), 7.88 (1H, d, *J* = 9.3 Hz, C<sub>8</sub>-H), 7.36 (1H, s, C<sub>1</sub>-H), 6.24 (2H, s, OCH<sub>2</sub>O), 4.81 (3H, s, NCH<sub>3</sub>), 4.18 (3H, s, OCH<sub>3</sub>), 3.93 (3H, s, OCH<sub>3</sub>). <sup>13</sup>C-NMR (125 MHz, CD<sub>3</sub>OD) δ: 162.2, 155.7, 151.0, 150.1, 145.9, 134.4, 134.1, 132.1, 130.9, 129.1, 125.4, 122.9, 121.2, 120.5, 118.1, 106.1, 105.0, 104.2, 60.9, 57.8, 52.1. *Anal.* Calcd for C<sub>21</sub>H<sub>18</sub>ClNO<sub>4</sub>·0.8 H<sub>2</sub>O: C, 63.34; H, 4.96; N, 3.52. Found: C, 63.38; H, 5.10; N, 3.59.

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