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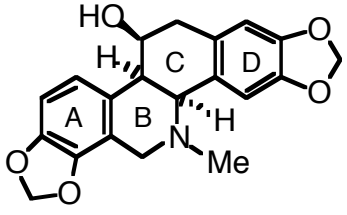
ALTERNATIVE SYNTHESIS OF B/C-*cis* HEXAHYDROBENZO[*c*]-PHENANTHRIDINE FROM 2-PHENYL-1-TETRALONE

Makoto Yoshida, Toshiko Watanabe, and Tsutomu Ishikawa*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage, Chiba 263-8522, Japan

Abstracts - A B/C-*cis* hexahydrobenzo[*c*]phenanthridine (**7**) was alternatively prepared by the hydride-reduction of a tetrahydrobenzo[*c*]phenanthridine derivative (**6**) under acidic condition, which was derived from 2-phenyl-1-tetralone oxime (**3**) through four steps (reductive amidation, methylation, Bischler-Napieralski cyclization, and hydride reduction).

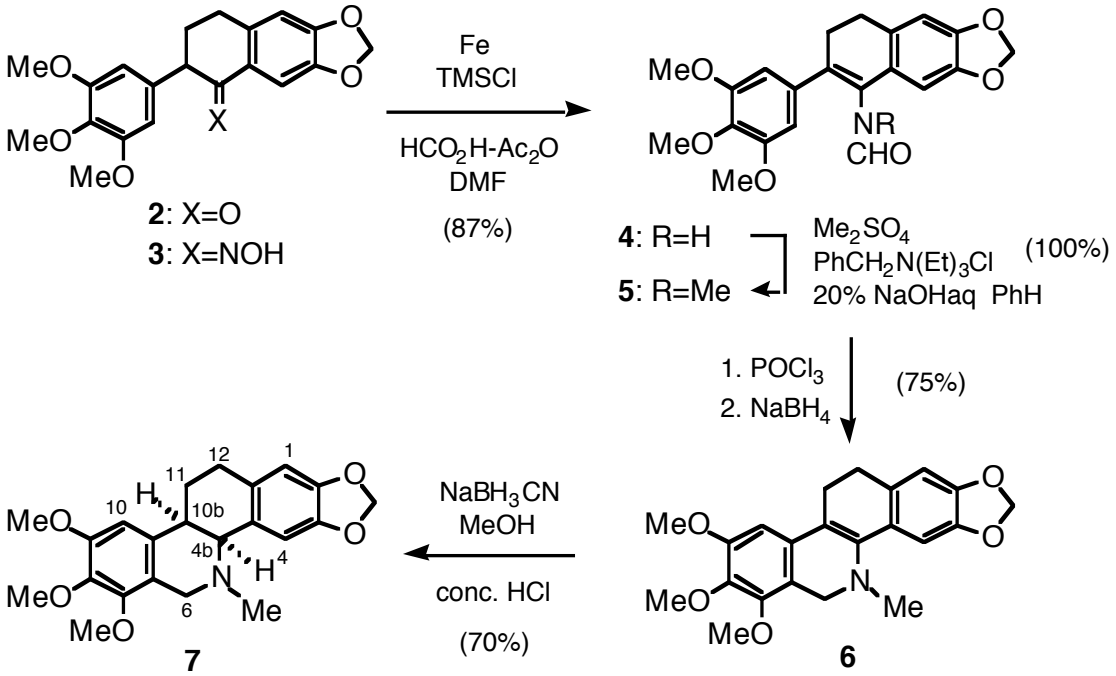
A B/C-*cis* hexahydrobenzo[*c*]phenanthridine system is a basic skeleton of well-known chelidonine (**1**)-type isoquinoline alkaloids showing various pharmacological activities.[1] Thus, several synthetic approaches have been developed for the construction of the system, for example cyclization of *cis*-2-phenyl-1-naphthylamine derivatives using Bischler-Napieralski[2] or Pictet-Spengler[2,3] reaction. However in some cases[2,4] a major reaction path is the elimination reaction of the nitrogen function, producing stilbene derivatives but not cyclized products. In this report we present alternative preparation method of a B/C-*cis* hexahydrobenzo[*c*]phenanthridine system from 6,7-methylenedioxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (**2**).



chelidonine (**1**)

It is known that acetoenamides are easily prepared from 1-tetralones by iron metal-participating reduction of the corresponding oximes in the presence of acetic anhydride. [5] We applied the reductive amidation reaction to prepare the corresponding formenamide of the 2-phenyl-1-tetralone (**2**). Treatment of the corresponding oxime[6] (**3**) with iron powder in dimethylformamide containing chlorotrimethylsilane in the presence of a mixed anhydride prepared from formic acid and acetic anhydride at room temperature for 20 min afforded a

desired product[7] (**4**) in 87% yield. After methylation Bischler-Napieralski reaction of the resulting methylformenamide[7] (**5**) with phosphorus oxychloride followed by reduction with sodium borohydride smoothly gave a 5,6,11,12-tetrahydrobenzo[*c*]phenanthridine (**6**).



Treatment of **6** in methanol with sodium cyanoborohydride in the presence of conc. hydrochloric acid at room temperature for 1 day afforded a 4*b*,5,6,10*b*,11,12-hexahydrobenzo[*c*]phenanthridine (**7**) in 70% yield. A small coupling (*J*=3.7 Hz) between 4*b*-H (δ 3.48) and 10*b*-H (δ 2.91) in the ^{1}H-NMR spectrum of **7** suggested the *cis* stereochemistry[8] of the B/C ring junction, which was supported by NOE experiments. Irradiation of the 4*b*-H caused 9.7% enhancement of the 10*b*-H, and 8.0% increment was observed in the reverse irradiation. This fact could be explained by hydride attack to an intermediacy iminium function produced by protonation to **6** from less hindered site, similar to exclusive formation of *cis* amines in the reductive amination[4] of 2-phenyl-1-tetralones through Schiff bases.

In conclusion a B/C-*cis* hexahydrobenzo[*c*]phenanthridine was alternatively prepared by the hydride-reduction of a tetrahydrobenzo[*c*]phenanthridine derivative under acidic condition, which was derived from a 2-phenyl-1-tetralone oxime through four steps (reductive amidation, methylation, Bischler-Napieralski cyclization, and hydride reduction).

EXPERIMENTAL

General

Mps were measured on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured with JASCO FT/IR 300E. ^{1}H-NMR spectra were recorded with JEOL JNM-GSX400A (400 MHz) spectrometers. The chemical shifts are relative to TMS in CDCl$_3$. MS spectra were measured with

JEOL JMS-HX110 spectrometer. Reactions were monitored by TLC on Kieselgel 60 F254 (Merck, 5715). Column chromatography was performed on silica gel (Fuji Silysia, FL100D).

1-Formamido-6,7-methylenedioxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalene (4): A mixture of acetic anhydride (0.60 mL, 6.36 mmol) and formic acid (0.30 mL, 7.95 mmol) was heated at 60 ℃ (bath temp) for 30 min under Ar and cooled. The mixed anhydride was added to a mixture of oxime (**3**) (298 mg, 0.801 mmol) and iron powder (447 mg, 8.00 mmol) in DMF (3.0 mL) under Ar. After addition of 1 drop of TMSCl the whole was stirred at rt for 20 min. After worked-up a crude product was recrystallized from $CHCl_3$-MeOH to give **4** as colorless prisms (267 mg, 87%), mp 250-253 ℃. IR (nujol) ν_{max} cm^{-1}: 3187 (NH), 3102 (NH), 1688 (CO). ^{1}H-NMR δ : 2.64-2.70 (2H, m, C_3-H), 2.80-2.89 (2H, m, C_4-H), 3.84 (3H, s, OMe), 3.85 (3H, s, OMe), 3.87 (3H, s, OMe), 5.93 (2Hx1/3, s, OCH_2O), 5.97 (2Hx2/3, s, OCH_2O), 6.51 (2Hx2/3, s, ArH), 6.52 (2Hx1/3, s, ArH), 6.56-6.61 (1H, br, NH), 6.69 (1Hx1/3, s, ArH), 6.72 (1Hx2/3, s, ArH), 6.73 (1Hx1/3, s, ArH), 6.88 (1Hx2/3, s, ArH), 8.08 (1Hx2/3, d, *J*=11.6 Hz, CHO), 8.29 (1Hx1/3, br, CHO). EIMS *m/z*: 383 (M^+, 100%).

6,7-Methylenedioxy-1-(*N*-methylformamido)-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalene (5): A mixture of **4** (102 mg, 0.27 mmol), benzytriethylammonium chloride (27 mg, 0.12 mmol), and Me_2SO_4 (0.08 mL, 0.85 mmol) in benzene (4 mL) and 20% NaOH (2 mL) was stirred at rt for 1.5 h. After addition of NH_4OH the mixture was stirred at rt for 0.5 h. After worked-up a crude product was purified by column chromatography on SiO_2 ($CHCl_3$-EtOAc=12 : 1) to give **5** as a pale yellow oil (113 mg, quant.). IR (nujol) ν_{max} cm^{-1}: 1685 (CO). ^{1}H-NMR δ 2.66-2.88 (4H, m, C_3-, C_4-H_2), 2.84 (3Hx1/9, s, NMe), 3.00 (3Hx8/9, s, NMe), 3.84 (3Hx8/9, s, OMe), 3.85 (3Hx1/9, s, OMe), 3.85 (6Hx8/9, s, OMex2), 3.87 (6Hx1/9, s, OMex2), 5.96 (2H, s, OCH_2O), 6.40 (2H, s, ArH), 6.56 (1Hx1/9, s, ArH), 6.58 (1Hx8/9, s, ArH), 6.70 (1Hx1/9, s, ArH), 6.73 (1Hx8/9, s, ArH), 7.87 (1Hx8/9, s, CHO), 8.18 (1Hx1/9, s, CHO). EIMS *m/z*: 397 (M^+, 100%).

5-Methyl-2,3-methylenedioxy-7,8,9-trimethoxy-5,6,11,12-tetrahydrobenzo[*c*]phenanthridine (6): A solution of **5** (140 mg, 0.35 mmol) in $POCl_3$ (1 mL, 10.7 mmol) was heated at 50 ℃ for 1 h under Ar. After evaporation of $POCl_3$ a residue was dissolved in MeOH (1 mL), $NaBH_4$ (154 mg, 4.08 mmol) was added, and the whole was stirred at rt for 2 h. After worked-up purification of the crude product by column chromatography on SiO_2 (hexane-EtOAc=12 : 1) gave **6** as pale yellow prisms (101 mg, 75%), mp 145-146 ℃ (from hexane-EtOAc). IR (nujol) ν_{max} cm^{-1}: no characteristic absorptions. ^{1}H-NMR δ: 2.43 (3H, s, NMe), 2.64-2.68 (2H, m, C_{11}-H), 2.78-2.82 (2H, m, C_{12}-H), 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 3.91 (3H, s, OMe), 4.13 (2H, s, C_6-H), 5.94 (2H, s, OCH_2O), 6.69 (2H, s, ArH), 7.20 (1H, s, ArH). EIMS *m/z*: 381 (M^+, 100%). *Anal.* Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.16; H, 6.07; N, 3.63.

***cis*-5-Methyl-2,3-methylenedioxy-7,8,9-trimethoxy-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (7)**: A mixture of **6** (21 mg, 0.05 mmol) and $NaBH_3CN$ (17 mg, 0.27 mmol) in

MeOH (1 mL) containing conc. HCl (1 drop) was stirred at rt for 1 day. After worked-up purification of the crude product by preparative TLC (benzene-EtOAc=4 : 1) gave **7** as a yellow oil (14 mg, 70%). IR (nujol) ν_{max} cm^{-1}: no characteristic absorptions. ^{1}H-NMR δ: 1.88-1.95 (1H, m, C_{11}-H), 2.35 (3H, s, NMe), 2.23-2.42 (1H, m, C_{11}-H), 2.68-2.85 (2H, m, C_{12}-H), 2.91 (1H, dt, *J*=10.4 Hz, 3.7 Hz, C_{10b}-H), 3.41 (1H, d, *J*=16.2 Hz, C_6-H), 3.48 (1H, d, *J*=3.7 Hz, C_{4b}-H), 3.850 (3H, s, OMe), 3.854 (3H, s, OMe), 3.87 (3H, s, OMe), 3.95 (1H, d, *J*=16.2 Hz, C_6-H), 5.90 and 5.91 (each 1H, d, *J*=1.2 Hz, OCH_2O), 6.52 (1H, s, ArH), 6.57 (1H, s, ArH), 6.84 (1H, s, ArH). EIMS *m/z*: 383 (M^+, 44%), 352 (100%). HRFABMS *m/z*: 384.1799 (Calcd for $C_{22}H_{26}NO_5$: 384.1811).

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7. A formenamide exsits as a mixture of the rotational isomers with respect to the *N*-formyl group.[4]
8. The coupling constant of $J_{4b,10b}$=5.1 Hz is reported in the *cis* derivative of related hexahydrobenzo-[*c*]phenanthridines, whereas that of $J_{4b,10b}$=11.2 Hz in the *trans* derivative.[3]