[Chem. Pharm. Bull. 26(1) 166—170 (1978)] UDC 547.943.04 : 581.192

Studies on the Chemical Constituents of Rutaceous Plants. XXXV.[1] Structural Establishment and Synthesis of Bocconoline. Photochemical Reaction of a Benzo[*c*]phenanthridinium Salt with Methanol

Hisashi Ishii, Tsutomu Ishikawa, Katsuhiro Hosoya,[2a]
and Narao Takao[2b]

Faculty of Pharmaceutical Sciences, Chiba University[2a] *and*
Kobe Women's College of Pharmacy[2b]

(Received June 2, 1977)

The structure of bocconoline, mp 232—233°, which was isolated from *Macleaya cordata* (Willd.) R. Br. was established from its spectral data as the formula (**1**).

Bocconoline was photochemically synthesized from chelerythrine (**2**) and methanol in 59.3% yield using acetone as a sensitizer with a low pressure mercury lamp in nitrogen stream.

Keywords——structural establishment; bocconoline; benzo[*c*]phenanthridine alkaloid; synthesis; from chelerythrine; photochemistry of an immonium group; adduct of a hydroxymethyl group

Benzo[*c*]phenanthridine alkaloid is one of fairly common constituents of the Papaveraceous and the Rutaceous plants. In 1962, Tani and Takao[3] isolated a minor alkaloid, mp 223—224°, with several alkaloids from *Macleaya cordata* (Willd.) R. Br. [*Bocconia cordata* Willd.] (Papaveraceae: Japanese name "Takenigusa" or "Champa-giku") and tentatively called it as "Base C." In 1971, in the short communication,[4] we reported the structural establishment of this alkaloid and designated it as "bocconoline" (**1**). This alkaloid (**1**) was isolated from other plants, an Argentiniean *Fagara* species[5] (Rutaceae), and *Chelidonium japonicum* Thunb. (Papaveraceae)[6] afterwards. Recently, we succeeded in synthesizing bocconoline (**1**) by photochemical reaction of chelerythrine (**2**) or dihydrochelerythrine (**3**) with methanol. In this report, we wish to describe a full detail of the structural establishment and synthesis of bocconoline (**1**).

In the previous report, Tani and Takao[3] proposed the empirical formula $C_{21}H_{19}NO_4 \cdot H_2O$ to Base C according to the result of elemental analysis and showed the existence of two methoxy, one N-methyl, and one methylenedioxy groups in its molecule using Zeisel quantitative analysis and Gaebel colour test. However, when re-examined by thin-layer chromatography (TLC), Base C showed three spots, one main with two minor. Preparative TLC gave the pure compound, mp 232—233°, which, in the mass spectrum, does not show a peak at *m/e* 349 corresponding to the empirical formula $C_{21}H_{19}NO_4$, but at *m/e* 379, indicating that the proposed formula should be revised. Re-examination of elemental analysis supported the empirical formula $C_{22}H_{21}NO_5$ (M^+: *m/e* 379). Therefore, we[4] designated this pure compound as "bocconoline." The nuclear magnetic resonance (NMR) spectrum of bocconoline (**1**) shows the signals due to one N-methyl, two methoxy and one methylenedioxy groups. Further-

---

[1] Part XXXIV: H. Ishii, T. Ishikawa, Y.-I. Ichikawa, and M. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 3120 (1977).

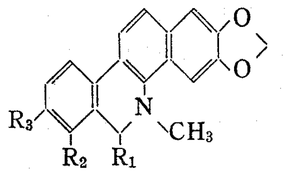
[2] Location: *a*) 1-33, *Yayoi-cho, Chiba*; *b*) *Motoyama-kitamachi, Higashinada, Kobe.*

[3] C. Tani and N. Takao, *Yakugaku Zasshi*, **82**, 755 (1962).

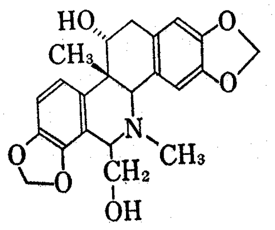
[4] H. Ishii, K. Hosoya, and N. Takao, *Tetrahedron Lett.*, **1971**, 2429.

[5] Private communication from Prof. S.M. Albnico, Facultad de Farmacia y Bioquimica (Jan. 19, 1976).

[6] Private communication from Prof. S. Itokawa, Tokyo College of Pharmacy (May 13, 1977).



1: $R_1=CH_2OH$, $R_2=R_3=OCH_3$
3: $R_1=H$, $R_2=R_3=OCH_3$
4: $R_1=H$, $R_2+R_3=OCH_2O$
5: $R_1=CH_2OCOCH_3$, $R_2=R_3=OCH_3$
6: $R_1=CH_2COCH_3$, $R_2=R_3=OCH_3$
7: $R_1=CN$, $R_2=R_3=OCH_3$



8

Chart 1

more, in the infrared (IR) spectrum, it has a hydroxy band at 3470 cm^{-1}. These evidences allowed us to expand the empirical formula to $C_{18}H_9(CH_2O_2)(OCH_3)_2(NCH_3)(OH)$.

The ultraviolet (UV) spectrum of bocconoline (**1**) is rigidly superimposable on that of dihydrochelerythrine (**3**) but slightly different from that of dihydrosanguinarine (**4**) as shown in Fig. 1. This fact strongly indicates that bocconoline (**1**) has the same chromophore including the positions of the methoxy and methylenedioxy groups as that of dihydrochelerythrine (**3**). Furthermore, since it is well known[7] in the mass spectrum of the C_6-substituted dihydrobenzo[*c*]phenanthridine alkaloid that the base peak due to an ion formed by a loss of a substituent at C_6 is characteristic, the appearance of the base peak at M^+-31 suggests that bocconoline (**1**) has a dihydrobenzo[*c*]phenanthridine skeleton bearing a substituent corresponding to the formula CH_3O at the C_6 position. This assumption was also supported by the fact that, in the NMR spectrum, each aromatic proton of bocconoline (**1**) has almost the same chemical shift as that of dihydrochelerythrine (**3**). Moreover, the NMR spectrum of bocconoline (**1**) has an ABX type signals due to the C_6 proton and the C_6-substituent at 3.09 δ (1H,

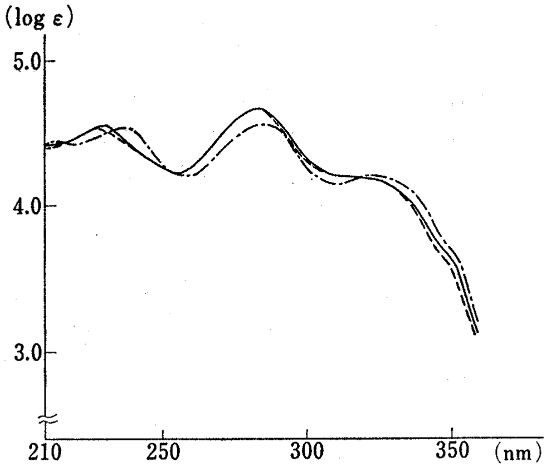


Fig. 1

———: bocconoline **1**.
- - - - -: dihydrochelerythrine **3**.
—·—·—: dihydrosanguinarine **4**.

Table I.[8] The Signals of Aromatic Protons ($CDCl_3$, δ)

	Bocconoline **1**	Acetyl bocconoline **5**	Dihydro-chelerythrine **3**
C_1–H	7.11 (s)	7.08 (s)	7.10 (s)
C_4–H	7.65 (s)	7.64 (s)	7.68 (s)
C_9–H	6.96 (d, $J=8.8$ Hz)	6.96 (d, $J=9.0$ Hz)	6.94 (d, $J=8.4$ Hz)
C_{10}–H	7.54 (d, $J=8.8$ Hz)	7.52 (d, $J=9.0$ Hz)	7.50 (d, $J=8.4$ Hz)
C_{11}–H	7.70 (d, $J=8.6$ Hz)	7.68 (d, $J=9.0$ Hz)	7.70 (d, $J=8.6$ Hz)
C_{12}–H	7.49 (d, $J=8.6$ Hz)	7.44 (d, $J=9.0$ Hz)	7.46 (d, $J=8.6$ Hz)

---

7) D.B. MacLean, D.E.F. Gracey, and J.K. Saunders, *Can. J. Chem.*, **47**, 1951 (1969); J. Slavík, L. Dolejš, V. Hanuš, and A.D. Cross, *Coll. Czech. Chem. Commun.*, **33**, 1619 (1968).

8) In the NMR spectrum of acetyl bocconoline (**5**), the figures of the chemical shift deviated from those in the preliminary report.[4] The previous data were obtained with JEOL JNM-4H-100.

t, J=10.5 Hz), 3.47 δ (1H, q, J_1=10.5 Hz and J_2=5.0 Hz), and 4.65 δ (1H, q, J_1=10.5 Hz and J_2=5.0 Hz), which were confirmed by spin decoupling experiments. These observations mentioned so far allowed us to depict the structure of bocconoline by the formula (**1**).

In order to confirm this formula, we prepared acetyl bocconoline (**5**), mp 188.5—189.5°. In the IR spectrum, this shows no hydroxy absorption but acetoxy bands at 1739 and 1249 cm^{-1}. In the NMR spectrum of it, a 2H multiplet between 3.76—4.14 δ and a 1H double doublet at 4.80 δ were observed. Down-field shift of a 2H signal in the NMR of acetyl bocconoline (**5**) indicates the presence of a primary hydroxy group in bocconoline (**1**). About the chiral center, bocconoline (**1**) naturally occurred as a racemate, because its optical rotatory dispersion curve shows a flat line along the base line.

Then, we attempted to synthesize bocconoline (**1**) from chelerythrine (**2**) or its derivatives. All trials to prepare it by chemical reaction such as Baeyer-Villiger oxidation of 6-acetonyldihydrochelerythrine (**6**), reduction of chelerythrine *ψ*-cyanide (**7**) with metal hydride, *etc*., were failed. But, irradiation[9] of a methanolic solution of the quaternary chelerythrine (**2**) chloride with a low pressure mercury lamp under the several conditions described in Table II afforded bocconoline (**1**) in fairly good yield. It should be noted here that simple irradiation of a methanolic solution of the base (**2**) did not absolutely produce the desired compound (**1**), but the condition using acetone as a sensitizer in nitrogen stream proved to be the best. Since,

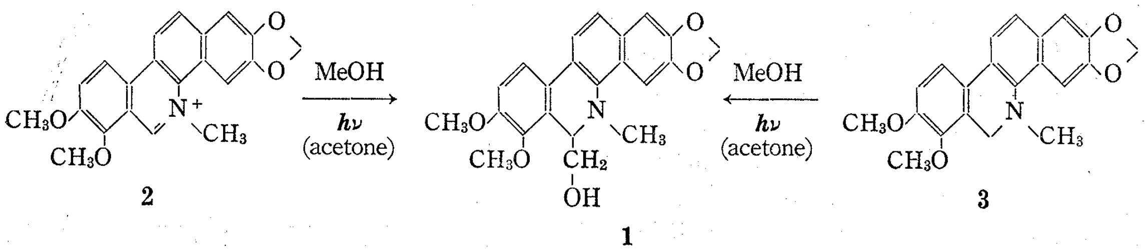


Chart 2

TABLE II. Photochemical Reactions[a] of Chelerythrine **2** Chloride and Dihydrochelerythrine **3** with Methanol

Starting material	Condition				Yield (%)
	Concentration (mM/1)	Solvent	Nitrogen stream	Reaction time	
Chelerythrine **2** chloride	2.5	MeOH	−	8.5 hr[b]	—
	2.5	MeOH 1 Acetone 1	−	3 hr	22.7
	2.5	MeOH	+	3 hr	31.5
	2.5	MeOH 1 Acetone 1	+	105 min	59.3
Dihydro-chelerythrine **3**	1.0	MeOH	−	2—2.5 hr[b]	—
	1.0	MeOH	+	8 hr[b]	—
	1.4	MeOH 1 Acetone 1	+	27 hr	8.2
	1.4	MeOH ($BF_3\cdot(C_2H_5)_2O$)	+	19.5 hr	7.6
	2.4	MeOH 1 Acetone 1 ($BF_3\cdot(C_2H_5)_2O$)	+	19.5 hr	5.7

a) Irradiation was performed with 120 W low pressure mercury lamp using external system.
b) The starting material could not be detected on TLC.

---

[9] Photochemical reaction of a derivative of indolenium salt with methanol under this condition was reported. [P. Cerutti and H. Schmid, *Helv. Chim. Acta*, **45**, 1992 (1962)].

recently, Onda, *et al.*[10] reported a success of insertion of a hydroxymethyl group into the C_6 position of 5,6-dihydrobenzo[*c*]phenanthridine derivative using methanol containing boron trifluoride etherate as a solvent, we also examined irradiation of a methanolic solution of dihydrochelerythrine (3) under various conditions and obtained bocconoline (1) in essentially poor yield.

The structure of bocconoline (1) was thoroughly established by the facts mentioned above, but is still fascinating. The presence of a hydroxymethyl group at C_6 allowed us easily to imagine that bocconoline (1) was formed by an attack of a C_1 precursor on chelerythrine (2) in plant body. However, this assumption would be denied from the chemical consideration that the bond formation should take place between electrophilic centers of both chelerythrine (2) and the general C_1 precursor, methionine or formic acid. Therefore, we could suppose the biogenetical pathway including attack of the C_2 or C_3 precursor to the C_6 position of chelerythrine (2) followed by oxidative cleavage such as Baeyer-Villiger oxidation. Independently, Takao, *et al.*[11] isolated corynolamine (8) from *Corydalis incisa* (Thunb.) Per., (Papaveraceous plant) and established the structure of it. As this alkaloid (8) has also a hydroxymethyl group at the C_6 position of hexahydrobenzo[*c*]phenanthridine nucleus, we believe that bocconoline (1) is a natural product but could not completely exclude the possibility of a photochemical artefact formed from chelerythrine (2) and methanol during extraction.

Experimental[12]

Bocconoline (1)——Preparative TLC of 96 mg of Base C,[3] mp 223—224°, using $CHCl_3$ as a solvent gave 43 mg of colourless pillars (*Rf*: 0.35), mp 232—233°, which were recrystallized from MeOH. *Anal.* Calcd. for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.72; H, 5.27; N, 3.74. IR ν_{max}^{KBr} cm^{-1}: 3460 (OH); ν_{max}^{Nujol} cm^{-1}: 3470 (OH). UV λ_{max}^{EtOH} nm (log ε): 229 (4.55), 283.5 (4.67), 321 (4.19) sh. NMR ($CDCl_3$) δ: 2.74 (3H, s, NCH_3), 2.88 (1H, s, OH, exchangeable), 3.09 (1H, t, $J=10.5$ Hz, $CH{-}C\underline{H}_AH_B{-}OH$), 3.47 (1H, d.d, $J=10.5$ Hz and 5.0 Hz, $CH{-}CH_A\underline{H}_B{-}OH$), 3.92 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.65 (1H, d.d, $J=10.5$ Hz and 5.0 Hz, $>C\underline{H}{-}CH_AH_B$), 6.03 (2H, s, OCH_2O), 6.96 (1H, d, $J=8.8$ Hz, $C_9{-}H$), 7.11 (1H, s, $C_1{-}H$), 7.49(1H, d, $J=8.6$ Hz, $C_{12}{-}H$), 7.54 (1H, d, $J=8.8$ Hz, $C_{10}{-}H$), 7.65 (1H, s, $C_4{-}H$), 7.70 (1H, d, $J=8.6$ Hz, $C_{11}{-}H$). MS *m/e*: 379 (M^+, 8.9%), 348 (base peak), 333 (11.2%), 310 (9.1%).

Acetyl Bocconoline (5)——A solution of 30 mg of bocconoline (1) in 1 ml of Ac_2O and 1 ml of pyridine was allowed to stand at room temperature overnight. The mixture was poured into ice-water, made alkaline with conc. NH_4OH aq. and extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on Al_2O_3 (500 mg, Woelm, neutral, grade II) using benzene as solvent to give 27 mg of colourless needles, mp 188.5—189.5°, which were recrystallized from $CHCl_3$–MeOH. *Anal.* Calcd. for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.33. Found: C, 68.35; H, 5.24; N, 3.29. NMR[8] ($CDCl_3$) δ: 1.38 (3H, s, $COCH_3$), 2.66 (3H, s, NCH_3), 3.92 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 3.76—4.14 (2H, m, $>CHC\underline{H}_2{-}OAc$), 4.80 (1H, d.d, $J=8.5$ Hz and 6.5 Hz, $>C\underline{H}{-}CH_2$), 6.01 (2H, s, OCH_2O), 6.96 (1H, d, $J=9.0$ Hz, $C_9{-}H$), 7.08 (1H, s, $C_1{-}H$), 7.44 (1H, d, $J=9.0$ Hz, $C_{12}{-}H$), 7.52 (1H, d, $J=9.0$ Hz, $C_{10}{-}H$), 7.64 (1H, s, $C_4{-}H$), 7.68 (1H, d, $J=9.0$ Hz, $C_{11}{-}H$). MS *m/e*: 421 (M^+, 11.0%), 348 (base peak), 333 (6.2%), 318 (6.9%), 304 (4.7%), 290 (10.2%), 275 (2.5%), 260 (1.3%), 232 (1.5%). $[\alpha]_D^{28}$ $0\pm0.5°$ ($c=1.90$, $CHCl_3$).

Synthesis of Bocconoline (1)——a) From Chelerythrine (2) Chloride: A solution of 67.4 mg of chelerythrine (2) chloride in 35 ml of abs. MeOH and 35 ml of acetone was irradiated at room temperature for 105 min in nitrogen[13] stream with monitoring by TLC and evaporated to dryness *in vacuo*. Trituration of the residue

---

10) Y. Harigaya, T. Suzuki, and M. Onda, Abstract papers, The 97th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1977, p. II-173.

11) N. Takao and K. Iwasa, Abstract papers, The 20th Annual Meeting of Kinki Branch, Pharmaceutical Society of Japan, Kobe, Nov., 1970.

12) All mp's were measured on a micro-melting hot-stage (Yanagimoto) and are uncorrected. IR and UV spectra were obtained with Hitachi EPI-G III and Hitachi EPI-3T spectrometers. NMR spectra were obtained with JEOL JNM-MH-100 using tetramethylsilane as internal standard, and the abbreviations of singlet, doublet, triplet and multiplet were represented as s, d, t and m, respectively. MS were measured with Hitachi RMU-6E at 70 eV of Chamber Voltage on direct inlet system. For TLC and preparative TLC, Kieselgel GF_{254} nach Stahl (Merck) were used. In the photochemical reactions, only the representative examples were described and irradiation was achieved with 120 W low pressure mercury lamp [external type, PIL-60 (Eiko-Ltd., Osaka, Japan)].

13) The nitrogen gas was purified through Fieser reagent [L.F. Fieser, *J. Am. Chem. Soc.*, **46**, 2639 (1924)].

with MeOH followed by filtration gave crystal mass. The filtrate was evaporated to dryness *in vacuo*. Preparative TLC of the residue with $CHCl_3$–AcOEt [10: 1 (v/v)] as solvent also afforded the same crystal (*Rf*: 0.51). Recrystallization of the gathered crystal from $CHCl_3$–MeOH gave 39.7 mg of colourless prisms, mp 231.5—233.5°. *Anal.* Calcd. for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.41; H, 5.60; N, 3.61. This compound was completely identified with an authentic sample of the naturally occurring bocconoline (1) by comparison of IR spectrum, the mixed melting point, and TLC.

b) From Dihydrochelerythrine (**3**): A solution of 34 mg of dihydrochelerythrine (**3**) in 70 ml of abs. MeOH containing 2 drops of $BF_3 \cdot (C_2H_5)_2O$ was irradiated at room temperature for 19.5 hr in nitrogen[13] stream and evaporated to dryness *in vacuo*. Purification of the residue by preparative TLC with a mixed solvent $(C_2H_5)_2O$–hexane [2: 1 (v/v)] gave 2.8 mg of colourless prisms (*Rf*: 0.40), mp 228—231°, which were recrystallized from $CHCl_3$–MeOH. This compound was identical with an authentic sample of bocconoline (**1**).

Acknowledgement We are grateful to Dr. M. Natsume and (the late) Dr. T. Onaka, Research Foundation ITSUU Laboratory, and Prof. T. Hino and Dr. M. Nakagawa, Chiba University for heartful discussion on the photochemical reaction of the N-methylisoquinolinium salt.