Re-examination of the Synthesis of 7,8-Dimethoxy-2-methyl-3-(4′,5′-methylenedioxy-2′-vinylphenyl)isocarbostyril[1)]

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Oxidation of the enamine (6) to the isocarbostyril (7) was re-examined. Simply stirring a dimethylformamide (DMF) solution of 6 provided 7 with good reproducibility, in the presence of KCN under an oxygen atmosphere. The structure of the chloroform adduct (8) was determined by an X-ray analysis.

Keywords chelerythrine; protoberberine; Hofmann degradation; X-ray analysis; biomimetic synthesis; oxy functionality

Fully aromatized (quaternary) benzo[*c*]phenanthridine alkaloids (A) have attracted much attention because of their potent biological activities[2)] against leukemia L1210 and P-388 in mice. Considerable effects have, therefore, been directed towards the development of general and convenient methods for syntheses of these alkaloids.[3)] One of the authors (H.I.) has reported a versatile method for synthesis of fully aromatized benzo[*c*]phenanthridine alkaloids (A) from the appropriately substituted chalcones (B) *via* 2-aryl-1-tetralone derivatives (C),[4)] and another author (M.H.) has reported an efficient method for synthesis of A from protoberberine alkaloids (D) through a biomimetic route[5)] (see Chart 1).

Recently, 2,3,7,8-tetraoxygenated dihydrobenzo[*c*]-phenanthridine alkaloids (**1**) with a substituent group at C_6 have been isolated from *Xanthoxylum*,[6)] *Corydalis*,[7)] and *Hypecoum*[8)] plants and their structures elucidated (Chart 2). In this connection, we needed a relatively large amount of chelerythrine (**2**) in order to synthesize ailanthoidine (**1a**).[6b)] We planned to prepare **2** using the biomimetic method[5a)]; *e.g.* the transformation of berberine chloride (**3**) to chelerythrine (**2**) *via* the enamine (**6**) and the isocarbostyril (**7**) reported by Onda *et al.*,[9)] because **3** is commercially available and few synthetic steps are required. The details of these results are the subject of this paper.

Berberine chloride (**3**) was reduced with lithium aluminum hydride (LAH)[10)] in dry tetrahydrofuran (THF) at room temperature to afford the dihydro derivative (**4**), which was immediately methylated with dimethyl sulfate in refluxing benzene, providing the methomethylsulfate (**5**) in 73% yield from **3**. Hofmann degradation of **5** in 25% methanolic potassium hydroxide yielded the labile enamine (**6**), which was subsequently oxidized overnight with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in chloroform ($CHCl_3$) at room temperature according to the literature.[9)] However, in our hands we obtained the desired isocarbostyril (**7**) in a variable and low yield (5—25%) in contrast to Onda's report (44% yield). Attempts were made to improve the yield of **7** under various reaction conditions; DDQ oxidation in various solvents (benzene, carbon tetrachloride, methanol, and dioxane) and DDQ oxidation in $CHCl_3$ followed by potassium ferricyanide in the presence of 25% aqueous potassium hydroxide in refluxing methanol,[4d)] but they were not fruitful. Interestingly, on oxidizing **6** with DDQ in $CHCl_3$, a new compound, mp 161—163 °C, was always

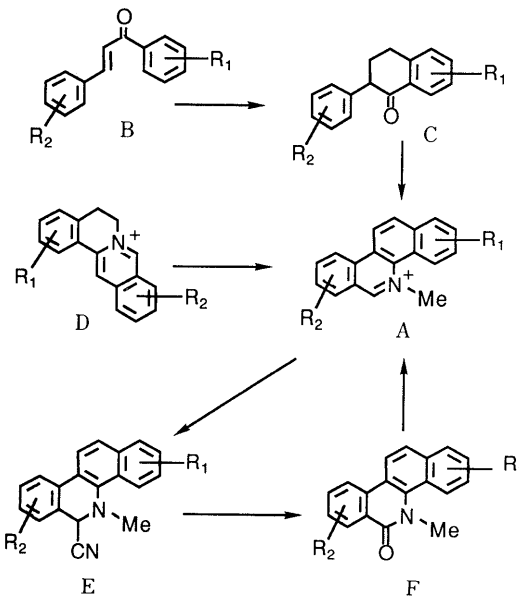

Chart 1

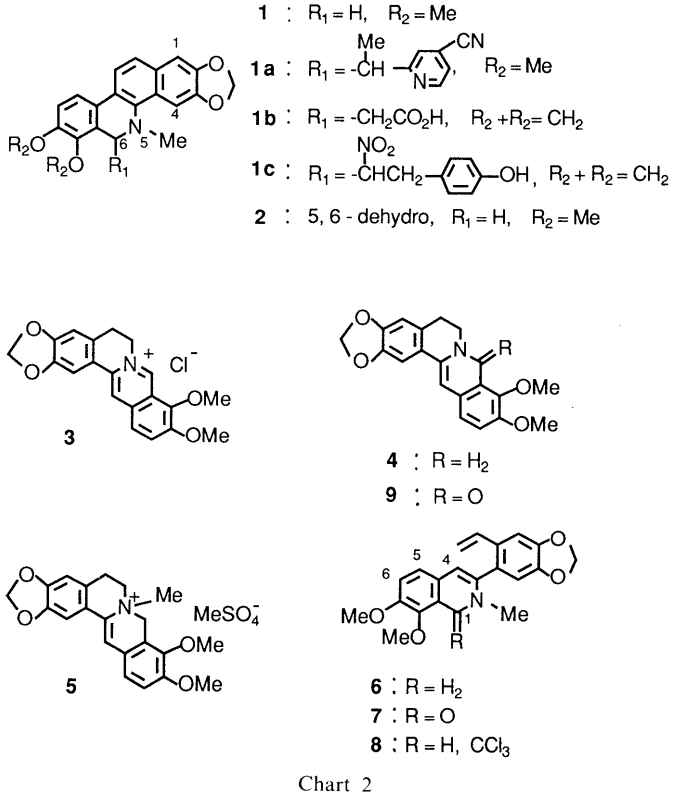

Chart 2

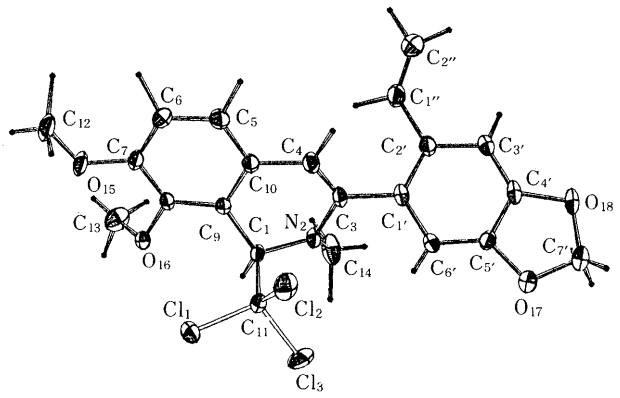

Fig. 1. Molecular Structure of the Chloroform Adduct (**8**)

TABLE I. Atomic Parameters for Non-hydrogen Atoms in the Chloroform Adduct (**8**)

	X	*Y* (×10000)	*Z*	*B*
Cl1	9722 (1)	8799 (2)	3407 (1)	4.7
Cl2	10029 (1)	8798 (2)	1783 (1)	4.7
Cl3	11278 (1)	8971 (3)	3054 (1)	6.0
O15	7888 (2)	3857 (7)	3282 (2)	4.0
O16	9334 (2)	4956 (5)	3851 (2)	2.9
O17′	12989 (2)	7818 (7)	384 (2)	4.6
O18′	13251 (2)	5331 (7)	−358 (2)	4.5
N2	11044 (2)	5315 (7)	2336 (2)	2.6
C1	10437 (3)	5891 (8)	2789 (3)	2.4
C1′	11517 (3)	4811 (9)	1040 (3)	2.8
C1″	11227 (4)	1569 (9)	626 (4)	4.0
C2′	11668 (3)	3253 (8)	591 (3)	2.9
C2″	11127 (4)	300 (11)	89 (5)	5.1
C3	10864 (3)	4838 (8)	1528 (3)	2.8
C3′	12269 (3)	3333 (9)	100 (3)	3.3
C4	10129 (3)	4547 (9)	1203 (3)	3.2
C4′	12658 (3)	4922 (9)	84 (3)	3.0
C5	8800 (3)	3705 (9)	1423 (3)	3.4
C5′	12507 (3)	6411 (8)	530 (3)	2.9
C6	8247 (3)	3482 (9)	1932 (4)	3.5
C6′	11950 (3)	6395 (8)	1021 (3)	2.9
C7	8414 (3)	3939 (9)	2749 (4)	2.9
C7′	13497 (3)	7104 (8)	−124 (3)	5.7
C8	9143 (3)	4579 (8)	3040 (3)	2.3
C9	9678 (4)	4962 (13)	2523 (5)	2.3
C10	9518 (3)	4453 (8)	1703 (3)	2.9
C11	10363 (3)	7943 (7)	2751 (3)	3.2
C12	7108 (3)	3532 (9)	2965 (3)	5.1
C13	9313 (3)	3417 (9)	4385 (3)	4.7
C14	11741 (4)	4593 (12)	2791 (4)	4.9

Estimated standard deviations are given in parentheses.

obtained, although in a very low yield, along with **7**. In its infrared (IR) spectrum no characteristic absorption band is observed and in its ^{1}H-nuclear magnetic resonance (NMR) spectrum a singlet signal assignable to C_1-H at δ 5.64 is seen. These findings indicate that the structure of the new compound can be represented by formula **8** in view of its elemental analysis ($C_{22}H_{20}Cl_3NO_4$). This assumption was supported by an X-ray analysis of **8** as shown in Fig. 1 and Table I. On the basis of these results, we speculated that **6** in $CHCl_3$ would produce **8** through oxidation (dehydrogenation) to the quaternary base followed by the addition of chloroform to the iminium double bond, since **6** was very labile and seemed susceptible to air-oxidation.

TABLE II. Results of Oxidation of Crude **6** to **7**

Run	Reaction conditions			Yield (%)[a]	
	Additive	O_2	Crown[b] ether	**7**	**9**
1	KCN	+	−	43.7	~3
2	KCN	+	+	47.7	1.5
3	KCN	−	−	17.7	1.6
4	—	+	−	Many spots on TLC	
5	$NaHCO_3$	+	−	Many spots on TLC	

a) Yields from methomethylsulfate (**5**) are given. *b*) Dicyclohexyl-18-crown-6 (*ca.* 10 mg) was used.

This speculation was confirmed by the production of **8** in 58% yield on stirring a solution of **6** in $CHCl_3$.[11,12] Subsequently, attempts were made to convert **8** to **7** by treatment with alkali or oxidizing reagents such as $K_3Fe(CN)_6$, MnO_2, pyridinium chlorochromate, pyridinium dichromate, and Ag_2O, but these reagents did not give satisfactory results.

In a previous paper,[13] we reported the preparation of the oxybase (F) by air-oxidation of the carbanion of the Ψ-cyanide (E) derived from the fully aromatized quaternary base (A). Since the Hofmann degradation product (**6**) was expected to produce the quaternary base by air-oxidation as mentioned above, we anticipated that the desired isocarbostyril (**7**) could be prepared in one-pot by sequential conversions involving quaternization by oxidation, addition of cyanide anion and reoxidation of the corresponding Ψ-cyanide. In practice, transformation of **6** to **7** was successfully carried out in the presence of potassium cyanide (KCN) in dimethylformamide (DMF). The results are given in Table II.

In conclusion, oxidation of **6** in the presence of KCN under an oxygen atmosphere (crown ether seems not to be required) provided the desired isocarbostyril (**7**) reproducibly, although in a moderate yield, along with a small amount of oxyberberine (**9**)[14] which was assumed to have arisen from dihydroberberine contaminating the crude Hofmann degradation product (**6**) (see runs 1 and 2 in Table II).

Experimental

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a Hitachi 215 spectrometer, and ^{1}H-NMR spectra in deuteriochloroform on JEOL FX-270 and/or JEOL GSX-400 spectrometers. The NMR data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants in hertz. Column chromatography was carried out on silica gel (Merck, Silica gel 60, No. 7734) or Florisil (Nacalai Tesque Inc., 100—200 mesh). Berberine chloride was purchased from Nacalai Tesque Inc. In general, the extract was dried over anhydrous potassium carbonate, then filtered, and the filtrate was evaporated to dryness under reduced pressure.

Dihydroberberine Methomethylsulfate (5) Berberine hydrochloride (8.63 g, 23.2 mmol) was added portionwise to a stirred suspension of LAH (4.09 g, 107.8 mmol)[10] in dry THF (340 ml) over a period of 15 min. The mixture was stirred for 1 h at room temperature under an argon atmosphere. The excess reagent was decomposed with ethyl acetate and wet ether, and the organic layer was decanted. The residue in benzene was chromatographed on Florisil (30 g). The benzene effluent (*ca.* 230 ml) was heated under reflux and dimethyl sulfate (21.99 g, 174.3 mmol) was added to the refluxing benzene solution. After refluxing for 2.5 h, the reaction mixture was cooled with ice-water and the resulting yellow precipitates were collected, then recrystallized from ethyl alcohol to provide the methomethylsulfate (**5**) (8.08 g, 73%), yellow prisms, mp 263—271 °C (dec.)

(lit.[15] mp 208—211 °C). *Anal.* Calcd for $C_{22}H_{25}NO_8S \cdot 3/4H_2O$: C, 55.38; H, 5.60; N, 2.94. Found: C, 55.37; H, 5.67; N, 2.65. ^{1}H-NMR (270 MHz in MeOH-d_4) δ: 3.12 (3H, s, NCH_3), 3.93 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.79 (1H, d, J=14.8 Hz, $NC\underline{H}_AH_B$), 5.10 (1H, d, J=14.8 Hz, $NCH_A\underline{H}_B$), 6.02 (1H, d, J=1.0 Hz, $-OC\underline{H}_AH_BO-$), 6.03 (1H, d, J=1.0 Hz, $-OCH_A\underline{H}_BO-$), 6.80 (1H, s, olefinic proton), 7.16 (1H, d, J=8.6 Hz, aromatic H), 7.27 (1H, d, J=8.6 Hz, aromatic H), 7.43 (1H, s, aromatic H), 7.48 (1H, s, aromatic H).

Hofmann Degradation of the Methomethylsulfate (5) The methomethylsulfate (**5**) (0.504 g, 1.06 mmol) was added at once to refluxing 25% methanolic potassium hydroxide (10 ml) and the mixture was heated under reflux for 20 min. The reaction mixture was poured into ice-water and extracted with ether. The crude Hofmann degradation product (**6**) (*ca.* 330 mg) was immediately used for the next step without purification because of its instability. ^{1}H-NMR (270 MHz in $CDCl_3$) δ: 2.50 (3H, s, NCH_3), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.47 (2H, s, C_1-H_2), 5.12 (1H, dd, J=11.0, 0.9 Hz, $C_{2''}$-H_A), 5.18 (1H, s, C_4-H), 5.57 (1H, dd, J=17.5, 0.9 Hz, $C_{2''}$-H_B), 5.97 (2H, s, $-OCH_2O-$),6.58 (1H, d, J=8.4 Hz, aromatic H), 6.70 (1H, d, J=8.4 Hz, aromatic H), 6.71 (1H, s, aromatic H), 6.85 (1H, dd, J=17.5, 11.0 Hz, $C_{1''}$-H), 7.08 (1H, s, aromatic H).

Oxidation of the Hofmann Degradation Product (6) with DDQ in $CHCl_3$ A solution of **6** (*ca.* 330 mg) and DDQ (0.472 g, 2.08 mmol) in $CHCl_3$ (10 ml) was stirred overnight at room temperature. After filtration, the $CHCl_3$ solution was washed with 5% aqueous NaOH solution and water. The residue was chromatographed on silica gel (10 g). Elution with hexane–ethyl acetate (2 : 1) gave **8** (34.8 mg, 7.0%), mp 161—163 °C, (colorless prisms from ether–hexane). *Anal.* Calcd for $C_{22}H_{20}Cl_3NO_4$: C, 56.37; H, 4.30; N, 2.99. Found: C, 56.38; H, 4.25; N, 2.90. ^{1}H-NMR (400 MHz in $CDCl_3$) δ: 2.94 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.09 (1H, dd, J=11.0, 0.9 Hz, $C_{2''}$-H_A), 5.45 (1H, s, C_1-H), 5.55 (1H, dd, J=17.4, 0.9 Hz, $C_{2''}$-H_B), 5.64 (1H, s, C_4-H), 5.98 (1H, d, J=1.5 Hz, $-OC\underline{H}_AH_BO-$), 6.01 (1H, d, J=1.5 Hz, $-OCH_A\underline{H}_BO-$), 6.87 (1H, d, J=8.2 Hz, C_5-H), 7.00 (1H, d, J=8.2 Hz, C_6-H), 7.07 (1H, dd, J=17.4, 11.0 Hz, $C_{1''}$-H), 7.10 (2H, s, $C_{3'}$-H and $C_{6'}$-H). Successive elution with the same solvent gave the isocarbostyril (**7**) (19.3 mg, 5.0%), mp 167—169 °C, (colorless plates from CH_2Cl_2–ether). (lit.,[9] mp 179—180 °C). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found C, 68.98; H, 5.34; N, 3.82. ^{1}H-NMR (270 MHz in $CDCl_3$) δ: 3.23 (3H, s, NCH_3), 3.95 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 5.12 (1H, dd, J=10.9, 0.7 Hz, $C_{2''}$-H_A), 5.60 (1H, dd, J=17.5, 0.7 Hz, $C_{2''}$-H_B), 6.04 (2H, s, $-OCH_2O-$), 6.28 (1H, s, C_4-H), 6.43 (1H, dd, J=17.5, 10.9 Hz, $C_{1''}$-H), 6.72 (1H, s, $C_{3'}$-H), 7.13 (1H, s, $C_{6'}$-H), 7.20 (1H, d, J=8.6 Hz, C_6-H), 7.33 (1H, d, J=8.6 Hz, C_5-H). IR (Nujol): ν_{max} 1645 (C=O).

The Chloroform Adduct (8) A solution of **6** prepared by Hofmann elimination of the methomethylsulfate (0.67 g, 1.40 mmol) in $CHCl_3$ (20 ml) was stirred overnight at room temperature. The reaction solution was evaporated to dryness under reduced pressure. The residue was chromatographed on Florisil (15 g). Elution with benzene provided **8** (0.38 g, 58%), mp 161—163 °C (colorless prisms from ether–hexane).

General Procedure for Oxidation of the Hofmann Product (6) KCN (88 mg, 1.36 mmol) for runs 1, 2, and 3 or $NaHCO_3$ (108 mg, 0.779 mmol) for run 5 was added to a DMF solution (5 ml) of the crude enamine (**6**) prepared from methomethylsulfate (**5**) (0.251 g, 0.53 mmol). The reaction mixture was stirred for 21 h at 50—60 °C under the reaction conditions indicated in Table I. The mixture was diluted with water and extracted with ether. The residue was chromatographed on silica gel (10 g). Elution with hexane–ethyl acetate (2 : 1) provided the isocarbostyril (**7**), mp 168 °C. Successive elution with hexane : ethyl acetate (1 : 1) provided oxyberberine (**9**), mp 206—208 °C, (colorless prisms from methanol). (lit.,[12] mp 201—203 °C).

X-Ray Structure Determination of 8 Crystal Data: $C_{22}H_{20}Cl_3NO_4$, M=468.36, monoclinic, space group P_21/n, a=17.540(13), b=7.365(1), c=16.806(12) Å, β=97.21(6)°, U=2154.1 Å^3, Z=4, and D_c=1445 g/cm^3. Single crystals of **8** were prepared by slow crystallization from ether–hexane. A crystal with dimensions of 0.10 × 0.15 × 0.20 mm was used for data collection. The intensity data were collected on a Rigaku AFC-5FU diffractometer with monochromated Cu K_α radiation (λ=1.54178 Å) using the $\omega < 30° < \omega$–2θ scan method at a 2θ scan speed of 4°/min. The structure was solved by the direct method using the MULTAN (UNICS-III system)[16] program and was refined by the full-matrix least-sequares method. The final R value was 0.075 for 3122 unique reflections [$F_O > 3\sigma(F_O)$].

References and Notes

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