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Synthesis of Benzo[*c*]phenanthridine Derivatives and their *In Vitro* Antitumor Activities

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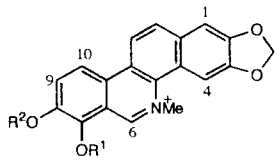
Aiming at the development of anticancer agents by modification of phenolic benzo[*c*]phenanthridine alkaloid, additional hydroxyl group was put on C10 position of fagaridine (**1**) by a biomimetic synthetic procedure to afford 10-hydroxyfagaridine (**12**). All of the synthetic intermediates were also screened *in vitro* antitumor activities against five different cell lines as well as **12**. Among them the representative cytotoxic results are shown as follows; *p*-quinone (**11**) [ED_{50} (A549=0.22 μg/ml), (HCT15=0.21 μg/ml), fagaridine (**1**) (HCT 15=0.41 μg/ml), olefin (**6**) (HCT 15=0.06 μg/ml), acetal (**7**) (SKMEL-2=0.07 μg/ml), dihydrofagaridne (**10**) (A549=0.38 μg/ml), 10-hydroxyfagaridine (**12**) (A 549=0.45μg/ml). From these observation three main remarks can be drawn; (i) the iminium part of benzo[*c*]phenanthridine is not essential for showing acitvities, (ii) the additional hydroxyl group did not contribute to enhance the cytotoxicity, (iii) the 3-arylisoquinolin-1(*2H*)-one derivatives were found to display significant *in vitro* antitumor activity.

Key words : Anticancer agents, Phenolic benzo[c]phenanthridine alkaloids, Fagaridine, 10-Hydroxyfagaridine, 3-Arylisoquinolin-1(*2H*)-ones

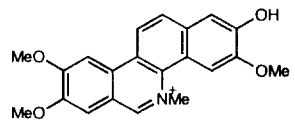
INTRODUCTION

Benzo[*c*]phenanthridine alkaloids occupy an increasingly important position from the finding of the marked potencies of some of these alkaloids against leukemia (Simeon *et al.*, 1989). However, the toxicity, narrow spectrum and unstability were the barriers to be developed these alkaloids as plausible anticancer agents (Sufness *et al.*, 1979). Recently, several alkaloids isolated from *Zanthoxylum nitidum* were also reported to inhibit topoisomerase I, II enzymes (Fang *et al.*, 1993) and the total synthesis of isofagaridine (**2**) was achieved (Cho *et al.*, 1996). Among these alkaloids, phenolic benzo[*c*]phenanthridine alkaloid, fagaridine (**1**), is now being developed to the phase II clinical stage (Kobayashi *et al.*, 1993). Because of a strong interest in their biological activites, synthesis of the benzo[*c*]phenanthridines has been an important area of heterocylic chemistry (Cushman *et al.*, 1985). We already reported the biomimetic synthesis of benzo[*c*]phenanthridine alkaloids by using the protoberberines as synthetic precursors and applied it to the syntheses of all kinds of benzo[*c*]phenanthridine alkaloids, B/C hexahydro or totally aromatized compounds (Hanaoka *et al.*, 1994). However, in our laboratory efforts have never been made to find bioactive compounds instead of concentrating on total synthesis of natural compounds.

Aiming at the synthesis and biological studies of new anticancer compounds, we decided to prepare the 10-hydroxyfagaridine in order to increase the antitumor properties of fagaridine. The common property of antitumor benzo[*c*]phenanthridine alkaloids is a mono-hydroxyl moiety on aromatic ring (Janin *et al.*, 1993) as shown in scheme I. By adding two hydroxy group on the aromatic ring, the function of phenolic hydroxyl group could be clarified. In this



Fagaridine (**1**) : R^1 =H, R^2 = Me
Isofagaridine (**2**) : R^1 = Me, R^2 = H



Fagaronine (**3**)

Scheme I.

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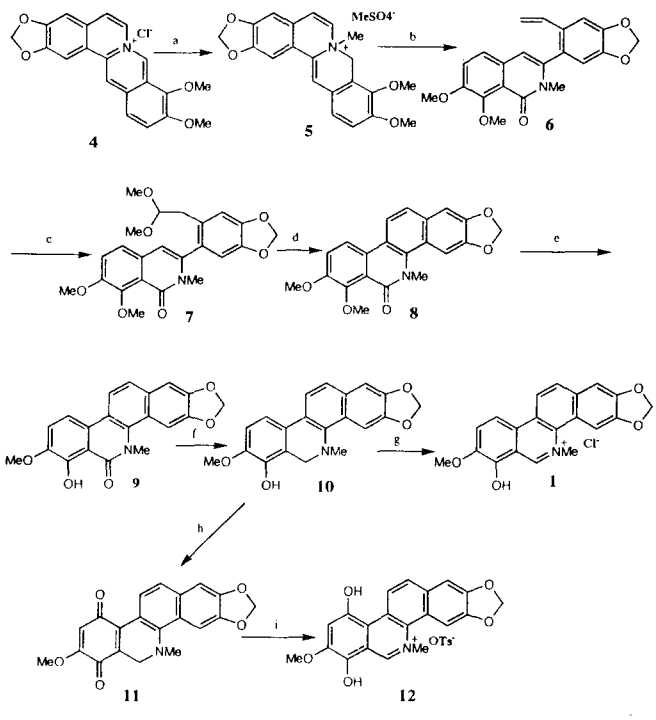

a; $LiAlH_4$/ THF, Me_2SO_4/PhH 78% b; 10% KOH/MeOH reflux, then DDQ $CHCl_3$ 31% c; TTN/ MeOH 80% d; 10% HCl/MeOH 86% e; *p*-TsOH/toluene 95% f; $LiAlH_4$/THF, $NaBH_4$/MeOH 83% g; DDQ/PhH 25% h; salcomine, O_2 57% i; *p*-TsOH/toluene 65%

Scheme 2.

paper we describe the synthesis and the biological evaluation of 10-hydroxyfagaridine as well as *in vitro* screeing results of the synthetic intermediates against five different human tumor cell lines.

MATERIALS AND METHODS

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AC 80 instrument. Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl; dry methylene chloride was obtained by distillation over phospholous pentoxide; dry benzene was obtained by distillation from calcium hydride. Column chromatography was performed on Merck silica gel 60 (230-400 mesh). The organic extract was dried with sodium sulphate.

Synthesis of compounds

5,6,7,8-Tetrahydro-9,10-dimethoxy-7-methyl-1,2-methylenedioxy-dibenzo[a,g]quinolizinium Methylsulfate (5) : Berberine chloride (**4**) (10 g, 26.89 mmol) was added portionwise to a stirring suspension of $LiAlH_4$ (3.07 g, 81.1 mmol) in dry THF (340 ml) in a stream of nitrogen at 0°C, and the mixture was stirred for additional 2h at room temperature. Water was added to the reaction, and the precipitates were filtered off. The filtrate was concentrated to give the dihydrogenated derivative, which was dissolved in dry benzene (200 ml) and the solution was heated under reflux. Dimethyl sulphate (10.2 g, 81.1 mmol) was added to the refluxing benzene solution and the mixture was refluxed for a further 1.5h. After the mixture had cooled, the resulting precipitates were collected by filtration and dried to afford the methylsulphate (**5**) (9.75 g, 78%) as a yellow solid. mp 209-210°C (EtOH) [208-211°C (EtOH), Onda *et al.*, 1971). ^{1}H-NMR (DMSO-d_6) δ 7.75, 7.44, 6.90 (each 1H, each s, C1-H, C4-H and C13-H), 7.33, 7.24 (each 1H, AB-q, *J*=8.5 Hz, C11-H and C12-H), 6.01 (2H, s, OCH_2O), 5.10, 4.88 (each 1H, AB-q, *J*=8.5 Hz, C8-H), 4.28-3.95 (2H, m, C6-H), 3.90, 3.85 (each 3H, OMe x 2), 3.40-3.10 (2H, m, C5-H), 3.37 (3H, s, $MeSO_4$), 3.05 (3H, s, NMe).

7,8-Dimethoxy-2-methyl-3-(4,5-methylenedioxy-2-vinylphenyl)-isoquinolin-1 (2*H*)-one (6) : The methylsulphate (**5**) (2 g, 4.4 mmol) was added to refluxing 25% potassium hydroxide-methanol (50 ml) and the mixture was heated under reflux for 10 min, then poured into ice-water and extracted with chloroform (200 ml). The organic layer was washed successively with water and brine, dried, and filtered. To the filtrate was added DDQ (1.18 g, 5.18 mmol) portionwise at room temperature. The mixture was stirred overnight and was added sat.aq. $NaHCO_3$. The organic layer was separated and washed brine, dried, concentrated to give the residue which was purified by column chromatograhpy with methylene dichloride-methanol (100 : 1) to afford the enamide (6) 490 mg (31%). mp 176-177°C (EtOH) (179-180°C, Onda *et al.*, 1979). ^{1}H-NMR ($CDCl_3$) δ 7.30, 7.18 (each 1H, AB-q, *J*=9.0 Hz, C5-H and C6-H), 7.12 (1H, s, C6'-H), 6.70 (1H, s, C3'-H), 6.28 (1H, s, C4-H), 6.01 (2H, s, OCH_2O), 6.23 (1H, dd, *J*=17 Hz, *J*=1 Hz, vinylic H), 5.58 (1H, dd, *J*=17 Hz, *J*=1.0 Hz, vinylic H), 5.10 (1H, dd, *J*=11 Hz, *J*=1.0 Hz, vinylic H), 4.03, 3.95 (each 3H, each s, OMe x 2), 3.23 (3H, s, NMe).

7,8-Dimethoxy-3-[2-(2,2-dimethoxyethyl)-4,5-methylenedioxyphenyl]-2-methylisoquinolin-1(2*H*)-one (7) : A solution of $Tl(NO_3)_3 \cdot 3H_2O$ (1.84 g, 4.13 mmol) in MeOH (12 ml) was added to a stirred solution of enamide (**6**) (860 mg, 2.34 mmol) in MeOH (10 ml) at room temperature. After stirred for 15 min, the reaction mixture was basified with sat. aq. $NaHCO_3$ soln. and extracted with methylene dichloride. The organic layer was separated and washed with brine, dried, concentrated to afford the residue which was purified by column chromatography with methylene dichloride-methanol (100 : 2) to give the acetal (**8**) (800 mg, 80%). mp 180-181°C (MeOH) (181-182°C, Hanaoka *et al.*, 1986). ^{1}H-NMR ($CDCl_3$)

δ 7.33, 7.19 (each 1H, AB-q, *J*=9.0 Hz, C5-H and C6-H), 6.95, 6.69, 6.26 (each 1H, each s, C6-H, C3-H and C4-H), 6.01 (2H, s, OCH_2O), 4.39 [1H, dd, *J*=5.0 and 6.0 Hz, $CH(OMe)_2$], 4.00, 3.95, 3.24 and 3.20 (each 3H, each s, OMe x 4), 3.19 (3H, s, NMe), 2.88 (1H, dd, *J*=6.0 and 15 Hz, benzylic H), 2.68 (1H, dd, *J*=5.0 and 15 Hz, benzylic H).

7,8-Dimethoxy-2,3-methylenedioxy-5-methylbenzo[*c*]phenanthridin-6(5*H*)-one (oxychelerythrine) (8) : To a solution of acetal (**7**) (760 mg, 1.77 mmol) in MeOH (40 ml) was added 10% HCl (8 ml). The mixture was refluxed for 2 hrs. After cooling down the mixture, the reaction mixture was basified with sat. aq. $NaHCO_3$ and the methanol was evaporated off. The resultant residue was taken up in methylene dichloride, and the solution was washed with water, dried, concentrated to dryness which was chromatographed with methylene dichloride-methanol (100 : 2) to afford the oxychelerythrine (**9**) (550 mg, 86%). mp 198-199°C (MeOH) (197-198°C, Hanaoka *et al.*, 1986). ^{1}H-NMR ($CDCl_3$) δ 8.00, 7.58 (each 1H, AB-q, *J*=9.0 Hz, C11-H and C12-H), 7.98, 7.38 (each 1H, AB-q, *J*=9.0 Hz, C9-H and C10-H), 7.52, 7.11 (each 1H, each s, C1-H, C4-H), 6.02 (2H, s, OCH_2O), 3.97, 3.88 (each 3H, each s, OMe x 2), 3.97 (3H, s, NMe).

7-Hydroxy-8-methoxy-2,3-methylenedioxy-5-methylbenzo[*c*]phenanthridin-6(5H)-one (oxyfagaridine) (9) : The solution of oxychelerythrine (**8**) (500 mg, 2.05 mmol) and *p*-TsOH (391 mg, 2.05 mmol) in toluene (50 ml) was refluxed for 3 hrs. The toluene was evapoated off and the residue was dissolved in methylene dichloride. The organic layer was washed with brine, dried, evaporated *in vacuo* to dryness which was purified by column chromatography with methylene dichloride-methanol (100 : 2) to provide the oxyfagaridine (**9**) (460 mg, 95 %). mp 245-246°C (MeOH) (246-247°C, Hanaoka *et al.*, 1985). ^{1}H-NMR ($CDCl_3$) δ 7.90, 7.46 (each 1H, AB-q, *J*=9.0 Hz, C11-H and C12-H), 7.58, 7.26 (each 1H, AB-q, *J*=9.0 Hz, C9-H and C10-H), 7.40, 7.11 (each 1H, each s, C1-H, C4-H), 6.04 (2H, s, OCH_2O), 3.97, 3.84 (3H, each s, Me x 2), 3.30 (1H, s, OH).

5,6-Dihydro-7-hydroxy-8-methoxy-5-methylbenzo[*c*]phenanthridine (dihydrofagaridine) (10) : $LiAlH_4$ (324 mg, 8.53 mmol) was added to a solution of oxyfagaridine (**9**) (300 mg, 0.86 mmol) in dry THF (40 ml) under a stream of nitrogen at 0°C. The reaction mixture was stirred for 1h at room temperature, then water was added and the mixutre was passed through celite. The filtrate was concentrated and the residue was dissloved in methanol (40 ml). $NaBH_4$ (323 mg, 8.53 mmol) was added to the solution and the mixture was kept for 30 min at room temperature. Methanol was evaporated off, the residue was taken up in methylene dichloride, and the solution was washed successively with water and brine, dried, and concentrated to dryness. Chromatography of the residue with methylene dichloride-methanol (100 : 1) provided dihydrofagaridine (**10**) (240 mg, 83 %). mp 236-238°C (MeOH) (239-240°C, Hanaoka *et al.*, 1985). ^{1}H-NMR ($CDCl_3$) δ 8.75 (1H, s, OH), 7.75, 7.52 (each 1H, AB-q, *J*=9.0 Hz, C11-H and C12-H), 7.30, 6.98 (each 1H, AB-q, *J*=9.0 Hz, C9-H and C10-H), 7.50, 7.25 (each 1H, each s, C1-H and C4-H), 6.10 (2H, s, OCH_2O), 4.10 (2H, s, benzylic H), 3.98 (3H, s, OMe), 2.46 (3H, s, NMe).

7-Hydroxy-8-methoxy-5-methylbenzo[*c*]phenanthridium chloride (fagaridine chloride) (1) : DDQ (150 mg, 0.90 mmol) was added dropwise to a stirred solution of dihydrofagaridine (**10**) (300 mg, 0.85 mmol) and 5 % NaOH (2 ml) in benzene (20 ml) at room temperature. The reaction mixture was stirred for 2h at room temperatute, then the organic layer was separated. The water layer was extracted with ethyl acetate and the combined organic layer was washed, dried, concentrated to dryness. To the residue was added a small amount of conc. hydrochloric acid, and the resulting precipitate was collected by filtration and recrystallized from ethanol to give fagaridine chloride (**1**) (120 mg, 25%). mp 200-203°C (206-208°C, Hanaoka *et al.*, 1985). ^{1}H-NMR (DMSO-d_6) δ 9.80 (1H, s, imine), 8.49, 8.07 (each 1H, AB-q, *J*=9.0 Hz, C11-H and C12-H), 8.46, 8.25 (each 1H, AB-q, *J*=9.0 Hz, C9-H and C10-H), 8.06, 7.48 (each 1H, each s, C1-H and C4-H), 6.25 (2H, s, OCH_2O), 5.10 (3H, s, OMe), 4.23 (3H, s, NMe).

5,6,7,10-Tetrahydro-8-methoxy-5-methyl-2,3-methylenedioxy-7,10-dioxobenzo[*c*]phenanthridine (11) : To a stirred solution of dihydrofagaridine (**10**) (220 mg, 0.66 mmol) in dry THF (30 ml) was added salcomine (215 mg, 0.66 mmol). The mixture was stirred for 2 hrs under the stream of oxygen at room temperature, then the precipitate was filtered off. The filtrate was concentrated in vacuo to dryness which was purified by column chlomatography with methylene dichloride-methanol (100 : 3) to give the quinone (**11**) (130 mg, 57%). mp 195-199°C (dec.) (hexane) (198-205°C, Hanaoka *et al.*, 1991). ^{1}H-NMR ($CDCl_3$) δ 8.16, 7.50 (each 1H, AB-q, *J*=9.0 Hz, C11-H and C12-H), 7.50, 7.34 (each 1H, each s, C1-H and C4-H), 6.04 (2H, s, OCH_2O), 5.95 (1H, s, C9-H), 4.12 (2H, s, C6-H), 3.88 (3H, s, OMe), 2.70 (3H, s, NMe).

7,10-Dihydroxy-8-methoxy-5-methylbenzo[*c*]phenanthridium Tosylate (10-hydroxyfagaridine tosylate) (12) : *p*-TsOH (130 mg, 0.75 mmol) was added the solution of *p*-quinone (250 mg, 0.75 mmol) in toluene (15 ml). The reaction mixture was refluxed for 2 hrs. The resultant precipitate was collected and dried to give the tosylate (**12**) (230 mg, 65%) as a red solid. ^{1}H-NMR (DMSO-d_6) δ 9.80 (1H, s, imine), 8.55,

8.04 (each 1H, AB-q, J=9.0Hz, C11-H and C12-H), 8.01, 8.06, 7.51 (each 1H, each s, C1-H, C4-H and C9-H), 6.24 (2H, s, OCH_2O), 5.01 (3H, s, OMe), 4.12 (3H, s, NMe).

Antitumor test *in vitro*

The experiment was carried out using the five different human cancer cell lines, A-549 (human non-small cell lung), SKOV-3 (ovarian carcinoma), HCT-15 (colon), XF-498 (CNS), SK-MEL-2 (melanoma) which were purchased from National Cancer Institute (NCI) in U.S.A.

The cells were grown at 37°C in RPMI 1640 medium supplemented with 10% FBS and separated using PBS containing 0.25% trypsin and 3 mM EDTA. 5×10^3-2×10^4 cells were added to each well of 96 well plate and incubated at 37°C for 24 hrs. Each compounds was dissolved in DMSO and diluted with the above medium at five different concentrations with the range of 0.1-30 μg/ml. The DMSO concentration was set to be below 0.5% and filtrated using 0.22 mg filter. After removing the well medium by aspiration, a portion 200 ml of the solution was added to above well plates which were placed in 5% CO_2 incubator for 48 hrs. The protein stain assay was performed according to SRB method (Skehan *et al.*, 1990, Rubinson *et al.*, 1990).

RESULTS AND DISCUSSION

Chemistry

The berberine (**4**) was reduced with lithium aluminum hydride ($LiAlH_4$) in dry tetrahydrofuran (THF) followed by treatment with dimethyl sulphate in refluxing benzene to afford the methylsulphate (**5**) in good yield. Hofmann degradation of compound **5** with 25% methanolic potassium hydroxide resulted in C6-N bond cleavage to furnich an unstable enamine, which was subsequently oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in chloroform to provide the enamide (**6**). Oxy-functionalization of the styrene moiety in compound was attained by treatment with thallium trinitrate (TTN) trihydrate in methanol to give the dimethyl acetal (**7**), exposure of which to 10 % hydrochloric acid yielded oxychelerythrine (**8**). The benzo[*c*]phenanthridine structure of oxychelerythrine was apparent from the signals due to 11-H and 12-H at d 8.00 and d 7.58 as an AB quartet (J=9 Hz) in its ^{1}H-NMR spectrum. The selective demethylation was accomplished in the condition with *p*-TsOH in refluxing toluene. Sequential reduction of **9** with $LiAlH_4$ in dry THF, and $NaBH_4$ in methanol, at room temperature afforded dihydrfagaridine (**10**) in 83% yield. DDQ dehydrogenaton of dihydrofagaridine in benzene gave rise to the fagaridine (**1**). The structure of compounds were elucidated from the spectral data. The synthetic compounds were shown to be identical with authentic compounds by comparison of NMR and MP. Treatment of **10** with salcomine in a stream of oxygen afforded the desired *p*-quinone (**11**). Finally, the dihydroxylation of A ring was accomplished by adding *p*-TsOH to a refluxing solution of **11** as a proton donor of quinone moiety to produce the oxidized form, 10-hydroxyfagaridine (**12**), of dihydrocompound.

Biological avtivity

10-Hydroxyfagaridine (**12**) and dihydrofagaridine (**10**) showed little bit lower *in vitro* antitumor activities than fagaridine (**1**). On the other hand, *p*-quinone (**11**) exhibited stronger broad spectrum against five different cancer cells than fagaridine. Oxychelerythrine (**8**) and oxyfagaridine (**9**) were not found to display good activity. The most significant attention of this research should be focused on the finding of the 3-arylisoquinolin-1(2*H*)-one derivatives, olefin (**6**) and acetal (**7**), the former showed 0.06 mg/ml (ED50) cytotoxicity against human cancer colon cell (HCT 15) and the latter also exhibited comparable activities as shown in Table. From the results of the above biological evaluation of benzo[*c*] phenanathridine derivatives, three main remarks can be drawn : (i) the iminium charge on the benzo[*c*] phenanthridine skeleton seems not to be essential for their biological action (ii) the additional hydroxyl function on C10 position does not contribute to increase the *in vitro* antitumor action (iii) the 3-arylisoquinolin-1(2H)-one, bioisostere of benzo[*c*] phenanthridines, could be lead compound for the new area of antitumor agents. The systematic study for quantitative structure-activity relationships (QSAR) of 3-arylisoquinolins is in progress.

Table. *In Vitro* Antitumor Activity

No.	ED_{50} (μg/ml)				
	HCT 15	XF 498	SKMEL-2	SKOV-3	A 549
fagaridine (1)	0.41	0.41	1.03	0.50	0.38
ofefin (6)	0.06	4.09	<0.10[1)]	0.33	<0.10
acetal (7)	1.21	0.54	0.07	1.16	0.13
dihydrofagaridine (10)	0.52	0.49	2.22	0.56	0.34
p-quinone (11)	0.21	0.23	0.45	0.36	0.22
10-hydroxyfagaridine (12)	0.67	0.60	0.97	0.59	0.45
methosulfate (5)	24.20	5.00	10.80	13.70	11.10
oxychelerythrine (8)	nd[2)]	nd	nd	nd	nd
oxyfagaridine (9)	nd	nd	nd	nd	nd

1)The exact activity should be determined after diluting the compound.
2)nd exhibits not determined (ED_{50}(μg/ml)=>30.00)

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