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Studies on the Chemical Constituents of Rutaceous Plants. LX.[1] Development of a Versatile Method for Syntheses of the Antitumor Benzo[*c*]phenanthridine Alkaloids. (9).[1c] Efficient Syntheses and Antitumor Activities of Nitidine and Related Nonphenolic Benzo[*c*]-phenanthridine Alkaloids

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Several nonphenolic benzo[*c*]phenanthridine alkaloids including naturally occurring nitidine (**1a**) and avicine (**1e**) were synthesized in excellent yields through an efficient synthetic method developed by us. Antitumor activities of twelve alkaloids including four naturally occurring O_5-alkaloids [chelilutine (**1g**), chelirubine (**1h**), sanguilutine (**1k**), and sanguirubine (**1l**)] against Sarcoma 180 were tested. The structure–activity relationship of these alkaloids is discussed.

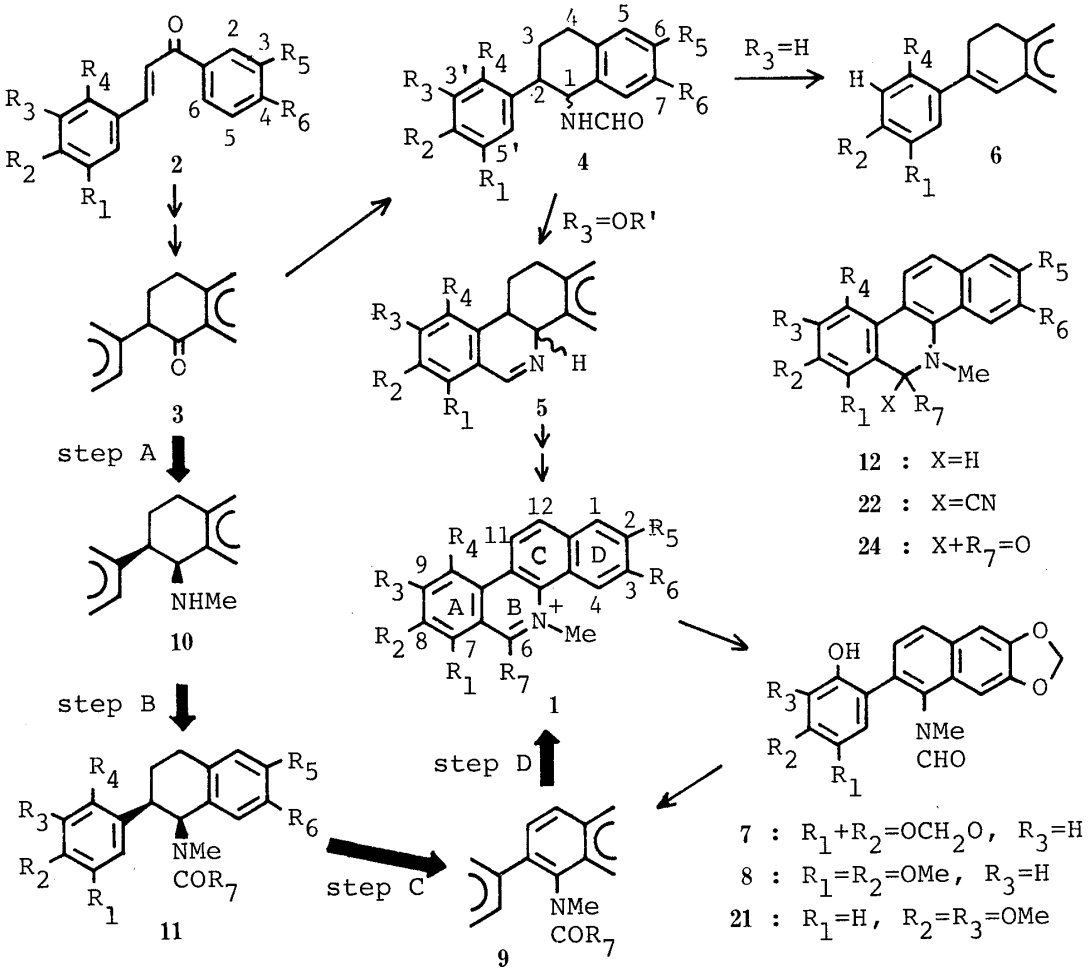
Keywords——benzo[*c*]phenanthridine alkaloid synthesis; nitidine; 6-methylnitidine; avicine; chloral; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ); antitumor activity; Sarcoma 180

It is well known that fully aromatized quaternary benzo[*c*]phenanthridine alkaloids[2] (**1**) occur naturally in Rutaceous and Papaveraceous plants. These alkaloids have attracted the interest of a number of chemists because of their antileukemic activities.[3] Recently, we[1c] have been able to establish an efficient synthetic sequence for the nonphenolic alkaloids as a general method, and we reported the syntheses of four naturally occurring O_5-benzo[*c*]phenanthridine alkaloids (**1g**, **1h**, **1k**, and **1l**). In this paper, we describe the syntheses of nitidine (**1a**), avicine (**1e**), and four related compounds (**1b**, **1c**, **1d**, and **1f**) and the antitumor activities of eight naturally occurring benzo[*c*]phenanthridine alkaloids (**1a**, **1e**, **1g**, **1h**, **1i**, **1j**, **1k**, and **1l**) and four synthetic materials (**1b**, **1c**, **1d**, and **1f**).

A. Synthetic Work

In 1937, Robinson *et al.*[4] reported a synthetic sequence for a fully aromatized benzo[*c*]phenanthridine alkaloid (**1**) from a chalcone derivative (**2**) through a 2-aryl-1-tetralone derivative (the tetralone) (**3**). The reaction sequence [**2**→**3**→**4**→**5**→**1**] shown in Chart 1 has become a standard method,[5] with some variations, for the synthesis of the 2,3,8,9-tetraalkoxybenzo[*c*]phenanthridine alkaloids (**1**: $R_2=R_3=R_5=R_6=$alkoxy; $R_1=R_4=R_7=H$) and their derivatives.

On the other hand, in the course of studies on the structural establishment of the naturally occurring 2,3,7,8,10-pentaalkoxybenzo[*c*]phenanthridine alkaloids[1c,6] (the O_5-benzo[*c*]phenanthridine alkaloids) (**1**: $R_1=R_2=R_4=R_5=R_6=$alkoxy; $R_3=R_7=H$), we[7] examined each step of the Robinson sequence for several compounds in detail, and found that the sequence had limited applicability to the synthesis of this type of alkaloids (**1**). In



	Substituents						
	R_1	R_2	R_3	R_4	R_5	R_6	R_7
a	H	OMe	OMe	H	OCH_2O		H
b	H	OMe	OMe	H	OCH_2O		Me
c	OMe	OMe	OMe	H	OCH_2O		H
d	H	OMe	OMe	OMe	OCH_2O		H
e	H	OCH_2O		H	OCH_2O		H
f	OMe	H	OCH_2O		OCH_2O		H
g	OMe	OMe	H	OMe	OCH_2O		H
h	OCH_2O		H	OMe	OCH_2O		H
i	OMe	OMe	H	H	OCH_2O		H
j	OCH_2O		H	H	OCH_2O		H
k	OMe	OMe	H	OMe	OMe	OMe	H
l	OCH_2O		H	OMe	OMe	OMe	H
m	H	OMe	OMe	H	OH	OMe	H

Chart 1

particular, the existence of an alkoxy group para to the position to be cyclized in the molecule of the starting *N*-(2-aryl-1,2,3,4-tetrahydro-1-naphthyl)formamide (the aliphatic formamide) (**4**), the C_3-position, is a minimum requirement[7d] for success in cyclization to the desired 4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (the 2*H*-isoquinoline) (**5**) by means of the Bischler–Napieralski reaction. Otherwise, the *β*-elimination product[7d] (the stilbene) (**6**) formed by loss of a formamide molecule ($HCONH_2$) becomes the sole product, instead of the

desired cyclized product (**5**). This means that the naturally occurring O_5-benzo[*c*]phenanthridine alkaloids (**1g**, **1h**, **1k**, and **1l**) can not be prepared by the Robinson sequence.

Later, we isolated two seco-amide alkaloids, integriamide[8] (**7**) and isoarnottianamide[9] (**8**), from several Rutaceous plants [*Xanthoxylum* (*Fagara*)] and succeeded in the synthesis[1d,8b,9b] of these compounds (**7** and **8**) from nitidine (**1a**) and avicine (**1e**) by the Baeyer–Villiger type oxidation of their immonium groups. The Bischler–Napieralski reaction[1c,6b] of their *O*-methyl products (**9g** and **9h**) provided two naturally occurring quaternary O_5-benzo[*c*]phenanthridine alkaloids, chelirubine (**1h**) and chelilutine (**1g**), in reasonable yields, respectively. Further, we could establish a general synthetic method[1c,6b,c] for the *O*-methyl compounds (**9**) from the tetralone (**3**) through the following synthetic sequence: i) treatment of the tetralones (**3**) with methylamine and titanium tetrachloride followed by reduction with sodium borohydride (step A); ii) conversion of the resulting *cis*-2-aryl-*N*-methyl-1,2,3,4-tetrahydro-1-naphthylamines (the *N*-methylamines) (**10**) to the *N*-formyl derivatives (the aliphatic *N*-methylformamides) (**11**) by treatment with freshly prepared chloral (step B); iii) dehydrogenation of the aliphatic *N*-methylformamide (**11**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the fully aromatized amide products (the aromatic formamides) (**9**) (step C). This success has provided an efficient method for the synthesis of the O_5-benzo[*c*]phenanthridine alkaloids (**1**).

Since two other O_5-benzo[*c*]phenanthridine alkaloids, sanguirubine[1c,6c] (**11**) and sanguilutine[1c,6c] (**1k**), could be prepared by this method in excellent yields, we undertook an

TABLE I. Overall Yields of Nitidine (**1a**) Obtained by Various Methods

Starting material	Research group	Yield (%) / Counter anion	Method
3a	This paper	69.3/Cl	Ours
	Arthur *et al.*[5a]	18.4/$MeSO_4$	Robinson's
	Gopinath *et al.*[5b]	10.2/$MeSO_4$	A
	Kametani *et al.*[5c]	5.0/$MeSO_4$	B
	Zee-Cheng *et al.*[5d]	23.9/Cl	Robinson's
13	Kessar *et al.*[11a]	—	C
	Begley *et al.*[11b]	14.0/BF_4	D
14	Ninomiya *et al.*[11c] / Ishii *et al.*[7e]	7.3/Cl	E
15	Ninomiya *et al.*[11c] / Ishii *et al.*[7e]	16.7/Cl	F
16	Cushman *et al.*[11d]	11.3/Cl	G
17	Dyke *et al.*[11e] (Ishii *et al.*[7e])	7.8/Cl[a]	H
18[12]	Hanaoka *et al.*[11f]	8.0/Cl	I

A: i) $NH_2OH \cdot HCl$/pyridine, ii) Ac_2O, iii) Ac_2O/AcOH, iv) SeO_2/AcOEt, v) $Me_2SO_4/PhNO_2$. B: i) $NH_2OH \cdot HCl$/pyridine, ii) H_2/Raney Ni/EtOH, iii) $HCHO \cdot HCl$/EtOHaq, iv) Pd–C, v) $Me_2SO_4/PhNO_2$–xylene. C: i) *hν*/MeCNaq containing NaOH, ii) the quaternization yield is not described. D: i) *hν*/MeCN, ii) $LiAlH_4$/THF, iii) H_2O_2/HBF_4. E: i) *hν*/I_2/MeOH,[11c] ii) 30% Pd–C/*p*-cymene,[11c] iii) $LiAlH_4$/THF,[11c] iv) Jones reagent.[7e] F: i) *hν*/abs. Et_2O,[11c] ii) 30% Pd–C/*p*-cymene,[11c] iii) $LiAlH_4$/THF,[11c] iv) Jones reagent.[7e] G: i) $SOCl_2$/PhH, ii) CH_2N_2, iii) Me_3N/MeOH–THF, iv) PPA, v) $LiAlH_4$/THF, vi) 5%Pd–C/AcOH. H: i) $FeSO_4$,[11e] ii) $NaNO_2$/HCl,[11e] iii) Cu,[11e] iv) Me_2SO_4–$NaBH_4$/HMPA,[7e] v) Jones reagent.[7e] I: i) HCHO/AcOH,[12] ii) I_2/EtOH, iii) $LiAlH_4$/THF, iv) Me_2SO_4, v) 25% KOH/MeOH, vi) DDQ, vii) $K_4Fe(CN)_6$, viii) $Tl(NO_3)_2$/MeOH, ix) 10% HCl, x) $LiAlH_4$/THF, xi) DDQ. *a*) The yield was calculated by application of our method[7e] to synthetic nornitidine.[11e]

examination of the utility of our synthetic sequence in the synthesis of other benzo[*c*]-phenanthridine alkaloids (**1**) which could be expected to have antitumor activity.

Synthetic Targets

a) Nitidine (1a) Chloride——Nitidine (**1a**) was first isolated from *X. nitidum* collected in Hong Kong by Arthur *et al.*[10] The structure[10] (**1a**) was established by the conversion of nitidine to a known 2,3,8,9-tetramethoxybenzo[*c*]phenanthridine derivative, and thus nitidine was classified as a new type of benzo[*c*]phenanthridine alkaloid having alkoxy groups at the 2,3,8,9-positions. Subsequently, dihydronitidine[5a,b] (**12a**) was synthesized by the Robinson method.

Fourteen years later, Wall *et al.*[3a] disclosed that nitidine (**1a**), isolated from *F. macrophylla*, was the active principle in the extract showing strong antileukemic activity against L1210 in mice. Therefore, many research groups[5a-d,11] prepared nitidine (**1a**) from various starting materials (**3a**, **13**, **14**, **15**, **16**, **17**, and **18**[12]) by their own methods.

The yields of nitidine (**1a**) from the starting materials achieved by these groups and by ourselves are listed in Table I.

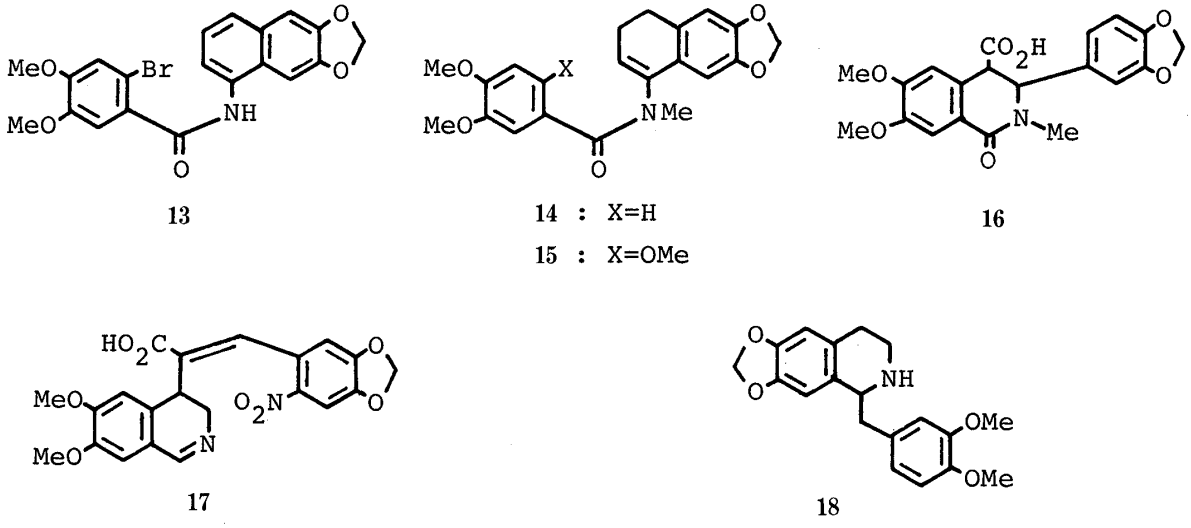


Chart 2

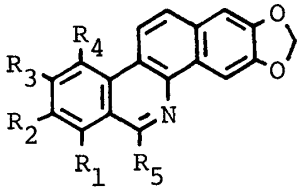
b) 6-Methylnitidine (1b) Chloride——In 1959, Gopinath *et al.*[5b] reported the synthesis of 6-methylnornitidine (**19a**) by treatment[13] of the tetralone acetoxime (**20**) with acetic anhydride in acetic acid. About twenty years later, Cheng and Zee-Cheng[3b] tried to prepare 6-methylnitidine (**1b**) by quaternization of the norbase (**19a**) with various alkylating agents in order to compare the antileukemic activity of nitidine (**1a**) and that of the 6-methyl derivative (**1b**) but their attempts failed. However, since 6-methylnitidine (**1b**) would be useful in connection with an examination of the structure–cytotoxicity relationship of benzo[*c*]-phenanthridine alkaloids, we applied our method to the acetamide derivative (**9b**).

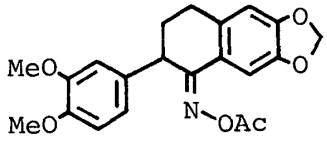
c) 7-Methoxynitidine (1c) Chloride——In 1973, Stermitz *et al.*[3e] examined the cytotoxicities of chelerythrine (**1i**) and sanguinarine (**1j**) and stated that the activities were in the order of sanguinarine (**1j**)>chelerythrine (**1i**). Their result made it of interest to study the cytotoxicity of the 7,8,9-trimethoxy quaternary base (7-methoxynitidine) (**1c**). Therefore, in our detailed examination of the Robinson method, we adopted 7-methoxynitidine (**1c**) as a synthetic model compound in our studies. Since the standard quaternization method for the norbase (**19b**) in the Robinson sequence gave the desired quaternary base (**1c**) only in very low yield, we applied our new synthetic pathway to the synthesis of 7-methoxynitidine (**1c**) from the corresponding tetralone (**3c**) for biological testing.

d) 10-Methoxynitidine (1d) Chloride——In the course of structural establishment[1d,9b] of

arnottianamide (**21**), it was prepared from chelerythrine (**1i**) by Baeyer–Villiger type oxidation of its immonium group, and the resulting arnottianamide (**21**) was methylated to *O*-methylarnottianamide (**9d**). The formation of this material suggested that 10-methoxynitidine (**1d**) might be obtainable by application of our method. The Bischler–Napieralski reaction of the *O*-methyl derivative (**9d**) gave the desired 10-methoxynitidine (**1d**).

e) Avicine (1e) Chloride——Avicine (**1e**) was isolated from *X. avicennae* collected in Hong Kong by Arthur *et al.*[14] They[14] established its structure (**1e**) by its conversion to a known compound. In 1961, Gopinath *et al.*[5f] synthesized oxyavicine (**24e**) by the Robinson method with some variations. We chose avicine (**1e**) as a synthetic target, because, during our detailed examination of the Robinson method, we[7e] occasionally found that the norbases (**19c**) persistently resisted quaternization according to the reported standard method,[3b,d,5d,g] involving dimethyl sulfate in xylene and/or nitrobenzene. Moreover, we were also interested in the biological activity of this material (**1e**).





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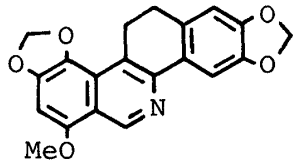

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19a: $R_1=R_4=H$, $R_2=R_3=OMe$, $R_5=Me$
19b: $R_1=R_2=R_3=OMe$, $R_4=R_5=H$
19c: $R_1=R_4=R_5=H$, $R_2+R_3=OCH_2O$
19d: $R_1=OMe$, $R_2=R_5=H$, $R_3+R_4=OCH_2O$

Chart 3

f) 7-Methoxy-2,3;9,10-bis(methylenedioxy)benzo[*c*]phenanthridinium (Model I) (1f) Chloride——The natural occurrence of a variety of fully aromatized O_5-benzo[*c*]phenanthridine alkaloids[2] in Papaveraceous plants is well known. In 1955, Slavík *et al.*[15] isolated chelirubine (**1h**) from *Chelidonium majus* as the first such alkaloid. In 1965, Onda *et al.*[16] isolated the same alkaloid from *Macleaya cordata* (*Bocconia cordata*) and, in 1970, they[17] tentatively proposed the formula (**1f**) as the structure of the alkaloid (**1h**) under the name of bocconine. During our studies on the structural establishment of chelirubine (**1h**), we tried to synthesize the compound having Onda's structure (**1f**) by the Robinson[7a–d] and Dyke[1e] methods. However, all efforts were unsuccessful. In the Robinson method, dehydrogenation[7d] of the 2*H*-isoquinoline derivative (**5f**) afforded only the 11,12-dihydrobenzo[*c*]-phenanthridine product (**23**), but not the desired norbase (**19d**) at all (Chart 3). Therefore, in order to examine the range of applicability of our synthetic sequence for the benzo[*c*]-phenanthridine alkaloids, this compound (**1f**) was adopted as a target compound.

Conclusion

In the preceding paper,[7b] we reported syntheses of a number of the starting tetralones (**3**). We describe here syntheses of six quaternary bases (**1a**, **1b**, **1c**, **1d**, **1e**, and **1f**) from the five corresponding tetralones (**3a**, **3c**, **3d**, **3e**, and **3f**). Each step except one proceeded in reasonable yield, as summarized in Table II. Unfortunately, the dehydrogenation of the *N*-methylacetamide derivative (**11b**) with DDQ (step C) resulted in formation of the desired fully aromatized product (**9b**) in only 32.7% yield, although the similar reaction of the ali-

TABLE II. The Yield (%) at Each Step in Our Method

Quaternary base	Step A 3→10	Step B 10→11	Step C 11→9	Step D 9→1
Nitidine (**1a**)	91.6	87.3	86.5	Quant.
6-Methylnitidine (**1b**)	(91.6)	R_7=Me 97.9	R_7=Me 32.7	R_7=Me Quant.
7-Methoxynitidine (**1c**)	88.7	87.6	66.3	86.1
10-Methoxynitidine (**1d**)	—	—	—	78.8
Avicine (**1e**)	91.2	83.8	71.4	99.7
Model I (**1f**)	82.4	81.2	74.1	Quant.

phatic *N*-methylformamide derivatives (**11**) always produced the desired corresponding products (**9**) in excellent yields. Moreover, all attempts to improve the yield of the product (**9b**) by using other reagents (for example, chloranil, 30% palladium–charcoal, *etc.*) failed.

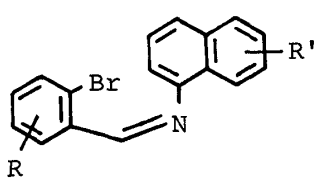
Since, generally speaking, the quaternary bases (**1**) tended to incorporate undefined contents of water of crystallization, the newly derived quaternary bases (**1**) were characterized as the dihydrobases (**12**), the ψ-cyanide (**22**), and/or the oxybase (**24**).

As shown in Table I, our synthetic sequence provides the desired nitidine (**1a**) in excellent yield, as compared with other methods. Our method has the following advantages: i) easily accessible starting materials, an aryl aldehyde and an acetophenone derivative, ii) facile operation on a large scale, iii) an excellent overall yield, and iv) wide applicability. The success in establishment of our versatile synthetic method should allow us to study the structure–cytotoxicity relationship of the benzo[*c*]phenanthridine alkaloids.

B. Biological Results and Discussion

Several groups have carried out biological tests of benzo[*c*]phenanthridine alkaloids and related compounds since Wall *et al.*[3a] discovered the antileukemic activity of nitidine (**1a**) against L1210. In 1975, Cheng and Zee-Cheng[3b] reported that nitidine (**1a**) and related compounds possessed antileukemic activity against both L1210 and P388, and showed growth inhibition of Lewis lung carcinoma.

In 1972, Farnsworth and collaborators[3c,18] isolated a phenolic benzo[*c*]phenanthridine alkaloid, which they designated as fagaronine (**1m**), from *F. zanthoxyloides* as the principle possessing the antileukemic activity against P388 leukemia. Later, Stermitz *et al.*[3d,19] established a synthetic method for phenolic benzo[*c*]phenanthridine alkaloids[20] by photocyclization of anil derivatives (**25**) and prepared many phenolic quaternary bases related to fagaronine (**1m**). They also reported the antileukemic activities[3d] of these compounds[19] as well as synthetic fagaronine[3d] (**1m**) against both L1210 and P388, but not against B16 melanoma. They[3d] further found that nitidine (**1a**) is marginally active against B16 melanoma.



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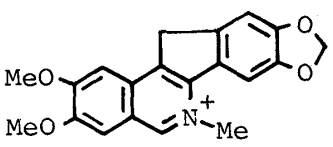

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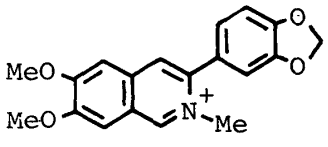

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Chart 4

Moreover, in 1960, Hartwell[21] described the cytotoxicity of sanguinarine (**1j**). Later, Stermitz *et al.*[3e] examined the cytotoxicities of sanguinarine (**1j**) and chelerythrine (**1i**), having two methoxy groups in ring A in place of the methylenedioxy group of sanguinarine (**1j**), *in vitro* against KB cell and *in vivo* against L1210 and P388 leukemias, and found that the latter (**1i**) is less cytotoxic than the former (**1j**).

In addition, the interaction[22] of fagaronine (**1m**) with nucleic acids was recently examined. Cushman *et al.*[23] reported the synthesis of structural analogues (**26** and **27**) bearing modified skeletons of nitidine (**1a**) and their biological activities.

TABLE III. The Antitumor Activities of Several Benzo[*c*]phenanthridine Alkaloids against Sarcoma 180

Alkaloid	Antitumor activity		Alkaloid	Antitumor activity	
	Dose (mg/kg/5 d)	$T/C^{a)}$ (%)		Dose (mg/kg/5 d)	$T/C^{a)}$ (%)
	100	Toxic (6/6)		10	Toxic (4/6)
	30	4	**1g**	3	120
1a	10	15		30	Toxic (6/6)
	3	40	**1h**	10	7
	1	80		3	46
	100	17		30	Toxic (6/6)
1b	30	53		10	4
	10	78	**1i**	3	26
	100	Toxic (5/6)		1	81
1c	30	44		30	Toxic (6/6)
	10	83	**1j**	10	1
1d	10	Toxic (3/6)		3	87
	3	27	**1k**	100	Toxic (6/6)
1e	100	38		30	27
	30	58	**1l**	30	2
	30	Toxic (4/6)			
1f	10	9			
	3	48			

a) Tumor growth relative to the control.

During our studies, we have acquired relatively large amounts of naturally occurring, fully aromatized nonphenolic benzo[*c*]phenanthridine alkaloids and some related model compounds in our laboratory. Therefore, we began to study the structure–activity relationships of benzo[*c*]phenanthridine alkaloids systematically. The results of tests on antineoplastic activities against Sarcoma 180 are given in Table III.

It is clear that alkaloids of this type show some antineoplastic activities, but their toxicities are a serious problem, as exemplified by the cases of Model I (**1f**), chelerythrine (**1i**), sanguinarine (**1j**), and chelirubine (**1h**). The result on 6-methylnitidine (**1b**) indicates that the immonium group ($N^+=C_6$) of the benzo[*c*]phenanthridine skeleton plays an important role in the appearance of the activity, because introduction of a methyl group at the C_6-position in the nitidine molecule decreased the activity. Comparison of the toxicities of pairs of compounds [nitidine–fagaronine[20] (**1a** and **1m**), chelirubine–sanguirubine (**1h** and **1l**), and chelilutine–sanguilutine (**1g** and **1k**)] suggests that the existence of a methylenedioxy group at the C_2–C_3 positions increases the toxicity. On the other hand, comparisons of the toxicities of chelilutine–chelirubine (**1g** and **1h**), chelerythrine–sanguinarine (**1i** and **1j**), sanguilutine–

sanguirubine (**1k** and **1l**), and nitidine–avicine (**1a** and **1e**) suggest that replacement of two methoxy groups on ring A by a methylenedioxy group reduces the toxicity to mice or leaves it unchanged, but enhances the antitumor activity except in the last pair (**1a** and **1e**).

The effects of the number and arrangement of alkoxy groups on ring A remain unclear. For example in the case of nitidine–10-methoxynitidine (**1a** and **1d**), the introduction of an additional methoxy group at the C_{10} position resulted only in increased toxicity to the host, while in the case of chelerythrine–chelilutine (**1i** and **1g**), the antitumor activity is lowered and the toxicity to the host is increased. On the other hand, in the case of sanguinarine–chelirubine (**1j** and **1h**), the antitumor activity and toxicity to the host remained unaffected. Furthermore, comparison of the results for nitidine–7-methoxynitidine–chelerythrine (**1a**, **1c**, and **1i**) suggests that the existence of an alkoxy group at the C_9 position in nitidine (**1a**) or fagaronine (**1m**) or at the C_7 position in chelerythrine (**1c**) may not be a minimum requirement for the appearance of antitumor activity in this type of alkaloid.

These considerations should offer some hints for the design of compounds which are more effective against human neoplasms. The results on the naturally occurring O_5-benzo[*c*]phenanthridine alkaloids again suggest interesting antitumor activity of derivatives having a 2,3,7,8-tetraoxygenated benzo[*c*]phenanthridine skeleton. Further works is in progress.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-G3 spectrometer in Nujol. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-4H-100 or Hitachi R-24B spectrometer in deuteriochloroform, with tetramethylsilane as an internal reference. All NH and OH signals were confirmed by their disappearance after addition of deuterium oxide. Mass spectra (MS) were measured on a Hitachi RMU-6E spectrometer at 70 eV chamber voltage with a direct inlet system. For chromatography (column), Silica gel 60 (70—230 mesh ASTM), Merck, or silicic acid (100 mesh), Mallinckrodt Chemical Works, and for preparative thin layer chromatography (TLC), Silica gel GF_{254}, Merck, were used. All identification of products was done by IR and TLC comparisons and mixed melting point determination. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; dd, double doublet; dt, double triplet; q, quartet; m, multiplet; br, broad; dif, diffused.

General Method[1c] for Preparation of *cis*-2-Aryl-*N*-methyl-1,2,3,4-tetrahydro-1-naphthylamines (10) from the 2-Aryl-1-tetralone Derivatives (3)——A solution of a 1-tetralone derivative[7b] (**3**) and $MeNH_2$ in abs. $CHCl_3$ was gradually added to a solution of titanium tetrachloride[1c,24] ($TiCl_4$) in abs. $CHCl_3$ under ice-cooling, and then the mixture was refluxed. After removal of the precipitates by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in MeOH or in a mixed solution of dimethylformamide (DMF) and MeOH. The reaction mixture was treated with $NaBH_4$ at room temperature until the reaction was complete, then diluted with a large amount of H_2O and extracted with $CHCl_3$. When the mixed solvent was used, the reaction mixture was evaporated to dryness *in vacuo*. A large amount of H_2O was added to the residue and the mixture was extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Recrystallization of the residue from an appropriate solvent gave the desired *cis*-tetrahydro-1-naphthylamine (**10**).[1c,7c,25]

***cis*-2-(3,4-Dimethoxyphenyl)-*N*-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-naphthylamine (10a)**——A solution of the tetralone[7b] (**3a**) (colorless prisms; mp 176—177.5 °C) (5.00 g) and $MeNH_2$ (15 g) in abs. $CHCl_3$ (100 ml) and a solution of $TiCl_4$ (1.7 ml) in abs. $CHCl_3$ (50 ml) were mixed and refluxed for 0.5 h. A solution of the crude iminium salt in abs. MeOH (150 ml) was treated with $NaBH_4$ (0.876 g) for 1 h to give colorless needles (4.79 g), mp 117—119 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.18; H, 6.81; N, 4.11. IR ν_{max} cm^{-1}: 3300 (NH). ^{1}H-NMR δ: 1.22 (1H, s, NH), 1.80—2.64 (2H, m, C_3-H_2), 2.19 (3H, s, NMe), 2.68—3.02 (2H, m, C_4-H_2), 3.13 (1H, dt, J=11.0, 4.0 Hz, C_2-H), 3.57 (1H, d, J=4.0 Hz, C_1-H), 3.87 (6H, s, OMe×2), 5.89 (2H, s, OCH_2O), 6.61 (1H, s, C_5-H), 6.73 (1H, s, arom. H), 6.81 (3H, s, $C_{5'}$- and $C_{6'}$-H, arom. H).

***cis*-*N*-Methyl-6,7-methylenedioxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine (10c)**——A solution of the tetralone[7b] (**3c**) (colorless needles; mp 189—191 °C) (5.00 g) and $MeNH_2$ (12 g) in abs. $CHCl_3$ (100 ml) and a solution of $TiCl_4$ (1.5 ml) in abs. $CHCl_3$ (50 ml) were mixed and refluxed for 1 h. A solution of the crude iminium salt in abs. MeOH (100 ml) was treated with $NaBH_4$ (0.534 g) for 0.5 h to give colorless prisms (4.62 g), mp 138—139 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.86; H, 6.82; N, 3.64. ^{1}H-NMR δ: 1.16 (1H, br s, NH), 1.80—2.68 (2H, m, C_3-H_2), 2.25 (3H, s, NMe), 2.80—3.28 (3H, m, C_2-H and C_4-H_2), 3.62 (1H, d, J=4.0 Hz, C_1-H), 3.88 (9H, s, OMe×3), 5.92 (2H, s, OCH_2O), 6.55 (2H, s, $C_{2'}$-, $C_{6'}$-H), 6.65

(1H, s, C_5-H), 6.77 (1H, s, C_8-H).

***cis*-*N*-Methyl-6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine (10e)**——A solution of the tetralone[7b] (**3e**) (colorless needles; mp 176—179 °C) (2.49 g) and $MeNH_2$ (6.0 g) in abs. $CHCl_3$ (86 ml) and a solution of $TiCl_4$ (0.88 ml) in abs. $CHCl_3$ (30 ml) were mixed and refluxed for 0.5 h. A solution of the crude iminium salt in a mixed solvent of DMF (40 ml) and abs. MeOH (40 ml) was treated with $NaBH_4$ (0.608 g) for 2 h to give colorless prisms (2.38 g), mp 119.5—121.5 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.00; H, 5.86; N, 4.19. ^{1}H-NMR δ: 1.16 (1H, s, NH), 1.73—2.11 (1H, m, C_3-H_A), 2.10 (3H, s, NMe), 2.10—2.71 (1H, m, C_3-H_B), 2.73—3.00 (2H, m, C_4-H_2), 3.10 (1H, dt, J=12.0, 3.8 Hz, C_2-H), 3.54 (1H, d, J=3.8 Hz, C_1-H), 5.89 and 5.92 (each 2H, s, OCH_2O), 6.60 (1H, s, C_5-H), 6.70 (1H, s, arom. H), 6.76 (2H, s, $C_{5'}$-, $C_{6'}$-H), 6.80 (1H, s, arom. H).

cis-2-(5-Methoxy-2,3-methylenedioxyphenyl)-*N*-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-naphthylamine (10f)——A solution of the tetralone[7b] (**3f**) (colorless pillars; mp 144—147 °C) (5.50 g) and $MeNH_2$ (14 g) in abs. $CHCl_3$ (155 ml) and a solution of $TiCl_4$ (1.8 ml) in abs. $CHCl_3$ (65 ml) were mixed and refluxed for 0.5 h. A solution of the crude iminium salt in a mixed solvent of DMF (100 ml) and abs. MeOH (50 ml) was treated with $NaBH_4$ (1.33 g) for 15 h to give colorless prisms (4.73 g), mp 137.5—138.5 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.51; H, 5.92; N, 3.87. ^{1}H-NMR δ: 1.12 (1H, br s, NH), 1.74—2.10 (1H, m, C_3-H_A), 2.25 (3H, s, NMe), 2.10—2.70 (1H, m, C_3-H_B), 2.70—3.10 (2H, m, C_4-H_2), 3.28 (1H, dt, J=11.0, 3.5 Hz, C_2-H), 3.70 (4H, s, OMe, C_1-H), 5.78—6.02 (4H, m, OCH_2O × 2), 6.27 (1H, d, J=3.0 Hz, $C_{4'}$-H), 6.37 (1H, d, J=3.0 Hz, $C_{6'}$-H), 6.58 (1H, s, C_5-H), 6.72 (1H, s, C_8-H).

General Method[1c] for Formylation of *cis*-2-Aryl-*N*-methyl-1,2,3,4-tetrahydro-1-naphthylamines (10) [*cis*-2-Aryl-1-(*N*-methylformamido)-1,2,3,4-tetrahydronaphthalenes (Aliphatic *N*-Methylformamides) (11: R_7=H)]——A mixture of an amine (**10**) and freshly prepared chloral[1c,26] in abs. $CHCl_3$ was refluxed, then washed with H_2O, dried over K_2CO_3, and evaporated to dryness *in vacuo*. Purification of the residue by column chromatography followed by recrystallization from an appropriate solvent gave the desired aliphatic *N*-methylformamide (**11**: R_7=H). In some cases, the product was obtained as a mixture of rotational isomers.

***cis*-2-(3,4-Dimethoxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)-1,2,3,4-tetrahydronaphthalene (11a)**——A solution of the amine (**10a**) (2.00 g) and freshly prepared chloral (1.2 ml) in abs. $CHCl_3$ (20 ml) was refluxed for 2 h. Column chromatography was run with $CHCl_3$. Colorless prisms (1.89 g), mp 159—162 °C (iso-PrOH). *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.33; H, 6.29; N, 3.76. IR ν_{max} cm^{-1}: 1665 (CO). ^{1}H-NMR δ: 1.92—2.30 (2H, m, C_3-H_2), 2.50 (3H, s, NMe), 2.84—3.30 (3H, m, C_2-H, C_4-H_2), 3.86 (6H, s, OMe × 2), 4.56 (1H, d, J=5.0 Hz, C_1-H), 5.90 (2H, s, OCH_2O), 6.46—6.92 (5H, m, arom. H × 5), 7.58 (4/5H, s, CHO), 7.73 (1/5H, s, CHO).

***cis*-6,7-Methylenedioxy-1-(*N*-methylformamido)-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (11c)**——A solution of the amine (**10c**) (0.765 g) and freshly prepared chloral (0.4 ml) in abs. $CHCl_3$ (8 ml) was refluxed for 1 h. Column chromatography was run with $CHCl_3$ followed by benzene–AcOEt [20 : 1 (v/v)]. Pale yellow amorphous solid (0.721 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (CO). ^{1}H-NMR (CCl_4) δ: 1.78—2.40 (2H, m, C_3-H_2), 2.52 (3H, s, NMe), 2.84—3.26 (3H, m, C_2-H, C_4-H_2), 3.82, 3.88, 3.90 (each 3H, s, OMe), 4.59 (1H, d, J=5.0 Hz, C_1-H), 6.03 (4/7H, s, OCH_2O), 6.04 (10/7H, s, OCH_2O), 6.41 (10/7H, s, arom. H), 6.64 (2/7H, s, arom. H), 6.67 (9/7H, s, arom. H), 6.73 (1H, s, arom. H), 7.64 (5/7H, s, CHO), 7.88 (2/7H, s, CHO).

***cis*-6,7-Methylenedioxy-2-(3,4-methylenedioxyphenyl)-1-(*N*-methylformamido)-1,2,3,4-tetrahydronaphthalene (11e)**——A solution of the amine (**10e**) (1.00 g) and freshly prepared chloral (0.6 ml) in abs. $CHCl_3$ (10 ml) was refluxed for 7 h. Column chromatography was run with benzene–AcOEt [10 : 1 (v/v)]. Colorless prisms (0.910 g), mp 165—167.5 °C (iso-PrOH). *Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.48; H, 5.36; N, 3.78. IR ν_{max} cm^{-1}: 1670 (CO). ^{1}H-NMR δ: 1.80—2.32 (2H, m, C_3-H_2), 2.51 (15/6H, s, NMe), 2.57 (3/6H, s, NMe), 2.70—3.40 (3H, m, C_2-H, C_4-H_2), 4.56 (1H, d, J=5.5 Hz, C_1-H), 5.91 (4H, s, OCH_2O × 2), 6.47—6.85 (5H, m, arom. H × 5), 7.61 (5/6H, s, CHO), 7.78 (1/6H, s, CHO).

***cis*-2-(5-Methoxy-2,3-methylenedioxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)-1,2,3,4-tetrahydronaphthalene (11f)**——A solution of the amine (**10f**) (0.972 g) and freshly prepared chloral (0.6 ml) in abs. $CHCl_3$ (9.7 ml) was refluxed for 7.5 h. Column chromatography was run with benzene–AcOEt [5 : 1 (v/v)]. Colorless prisms (0.851 g), mp 182—184 °C (iso-PrOH). *Anal.* Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.67; H, 5.54; N, 3.59. IR ν_{max} cm^{-1}: 1665 (CO). ^{1}H-NMR δ: 1.90—2.40 (2H, m, C_3-H_2), 2.55 (12/5H, s, NMe), 2.63 (3/5H, s, NMe), 2.70—3.10 (2H, br t, J=14.0 Hz, C_4-H_2), 3.10—3.60 (1H, m, C_2-H), 3.70 (3H, s, OMe), 4.77 (1H, d, J=5.5 Hz, C_1-H), 5.80—6.00 (4H, m, OCH_2O × 2), 6.14 (1H, d, J=3.0 Hz, $C_{4'}$-H), 6.39 (1H, d, J=3.0 Hz, $C_{6'}$-H), 6.49 (1H, s, C_5-H), 6.60 (1H, s, C_8-H), 7.77 (1H, s, CHO).

General Method[1c] for Dehydrogenation of *cis*-2-Aryl-1-(*N*-methylformamido)-1,2,3,4-tetrahydronaphthalenes (11) [2-Aryl-1-(*N*-methylformamido)naphthalenes[27] (Aromatic Formamides) (9: R_7=H)]——A solution of an aliphatic *N*-methylformamide (**11**) and DDQ in benzene was refluxed. After removal of the precipitates by filtration, a large amount of 5% NaOH aq. was added to the filtrate and the mixture was extracted with $CHCl_3$. The chloroform solution was washed with 5% NaOH aq., dried over K_2CO_3, and then evaporated to dryness *in vacuo*. Purification of the residue by column chromatography with $CHCl_3$ followed by recrystallization from an appropriate solvent gave

the desired 2-aryl-1-(*N*-methylformamido)naphthalene (aromatic formamide) (**9**: $R_7 = H$).

2-(3,4-Dimethoxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (9a)——Refluxing of a solution of the aliphatic *N*-methylformamide (**11a**) (1.94 g) and DDQ (3.59 g) in benzene (120 ml) for 1 h gave colorless prisms (1.66 g), mp 196—198.5 °C ($CHCl_3$–EtOH). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.18; H, 5.18; N, 3.84. IR ν_{max} cm^{-1}: 1680 (CO). ^{1}H-NMR δ: 3.01 (3H, s, NMe), 3.88, 3.92 (each 3H, s, OMe), 6.06 (2H, s, OCH_2O), 6.80 (1H, d, J=2.0 Hz, $C_{2'}$-H), 6.87 (2H, dif d, J=2.0 Hz, $C_{5'}$-, $C_{6'}$-H), 7.08 (1H, s, C_5-H), 7.18 (1H, s, C_8-H), 7.36 (1H, d, J=8.0 Hz, C_4-H), 7.71 (1H, d, J=8.0 Hz, C_3-H), 8.15 (1H, s, CHO).

6,7-Methylenedioxy-1-(*N*-methylformamido)-2-(3,4,5-trimethoxyphenyl)naphthalene (9c)——Refluxing of a solution of the aliphatic *N*-methylformamide (**11c**) (0.721 g) and DDQ (1.06 g) in benzene (60 ml) for 1 h gave colorless prisms[28] (0.473 g), mp 168—172 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.54. Found: C, 66.39; H, 5.25; N, 3.55. IR ν_{max} cm^{-1}: 1670 (CO). ^{1}H-NMR δ: 2.94 (9/5H, s, NMe), 3.04 (6/5H, s, NMe), 3.86 (27/5H, s, OMe × 3), 3.91 (18/5H, s, OMe × 3), 6.03 (4/5H, d, J=2.0 Hz, OCH_2O), 6.05 (6/5H, d, J=2.0 Hz, OCH_2O), 6.49 (4/5H, s, $C_{2'}$-, $C_{6'}$-H), 6.65 (6/5H, s, $C_{2'}$-, $C_{6'}$-H), 7.00 (3/5H, s, C_5-H), 7.08 (2/5H, s, C_5-H), 7.16 (3/5H, s, C_8-H), 7.18 (2/5H, s, C_8-H), 7.32 (3/5H, d, J=8.0 Hz, C_4-H), 7.36 (2/5H, d, J=8.0 Hz, C_4-H), 7.68 (3/5H, d, J=8.0 Hz, C_3-H), 7.72 (2/5H, d, J=8.0 Hz, C_3-H), 8.17 (2/5H, s, CHO), 8.36 (3/5H, s, CHO).

6,7-Methylenedioxy-2-(3,4-methylenedioxyphenyl)-1-(*N*-methylformamido)naphthalene (9e)——Refluxing of a solution of the aliphatic *N*-methylformamide (**11e**) (0.744 g) and DDQ (1.43 g) in benzene (48 ml) for 1.5 h gave colorless prisms (0.525 g), mp 209—211.5 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found: C, 69.25; H, 4.37; N, 4.02. IR ν_{max} cm^{-1}: 1670 (CO). ^{1}H-NMR δ: 3.03 (3H, s, NMe), 5.96, 6.04 (each 2H, s, OCH_2O), 6.68 (1H, dd, J=8.5, 2.0 Hz, $C_{6'}$-H), 6.74 (1H, s, $C_{2'}$-H), 6.84 (1H, d, J=8.5 Hz, $C_{5'}$-H), 7.04 (1H, s, C_5-H), 7.16 (1H, s, C_8-H), 7.28 (1H, d, J=8.5 Hz, C_4-H), 7.67 (1H, d, J=8.5 Hz, C_3-H), 8.07 (1H, s, CHO).

2-(5-Methoxy-2,3-methylenedioxyphenyl)-6,7-methylenedioxy-1-(*N*-methylformamido)naphthalene (9f)——A solution of the aliphatic *N*-methylformamide (**11f**) (1.50 g) and DDQ (2.67 g) in benzene (125 ml) was refluxed for 1.5 h. Purification by column chromatography with benzene–AcOEt [5 : 1 (v/v)] gave colorless prisms (1.10 g), mp 174—176 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{21}H_{17}NO_6$: C, 66.48; H, 4.52; N, 3.69. Found: C, 66.32; H, 4.46; N, 3.53. IR ν_{max} cm^{-1}: 1670 (CO). ^{1}H-NMR δ: 3.01 (3H, s, NMe), 3.76 (3H, s, OMe), 5.85, 6.06 (each 2H, s, OCH_2O), 6.23 (1H, d, J=3.0 Hz, $C_{4'}$-H), 6.49 (1H, d, J=3.0 Hz, $C_{6'}$-H), 7.08 (1H, s, C_5-H), 7.17 (1H, s, C_8-H), 7.34 (1H, d, J=8.5 Hz, C_4-H), 7.72 (1H, d, J=8.5 Hz, C_3-H), 8.15 (1H, s, CHO).

General Method[1c] for Bischler–Napieralski Reaction of 2-Aryl-1-(*N*-methylformamido)naphthalenes (Aromatic Formamides) (9: R_7 = H) [Quaternary Bases (1: R_7 = H)]——A solution of an aromatic formamide (**9**: $R_7 = H$) and $POCl_3$ in MeCN was refluxed. The reaction mixture was poured into ice-water, and the resulting precipitates were collected by filtration and recrystallized from an appropriate solvent to give the desired quaternary base (**1**: $R_7 = H$) as the chloride. This material was characterized as a dihydrobase (**12**), a ψ-cyanide (**22**), and/or an oxybase (**24**).

Nitidine (1a) Chloride——A solution of the aromatic formamide (**9a**) (3.00 g) and $POCl_3$ (5.1 ml) in MeCN (120 ml) was refluxed for 50 min. Yellow fine needles, quantitative, mp 285—292 °C (dec.) (H_2O) [lit. mp 274—275 °C,[29] mp 275—277 °C (dec.),[5d] and mp 286—292 °C (dec.)[7e]].

This material was identical with an authentic sample of nitidine[7e] (**1a**) chloride.

7-Methoxynitidine (9-Methoxychelerythrine: 7,8,9-Trimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium) (1c) Chloride——A solution of the aromatic formamide (**9c**) (0.101 g) and $POCl_3$ (0.16 ml) in MeCN (4 ml) was refluxed for 2 h. Pale yellow needles (0.091 g), mp 196—200 °C (dec.) (MeOH) [lit.[7e] mp 225—232 °C (dec.)]. This material was identical with an authentic sample of the quaternary base (**1c**) chloride which was prepared by an alternative method.[7e]

10-Methoxynitidine (8,9,10-Trimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium) (1d) Chloride——The Quaternary Base (**1d**): A solution of *O*-methylarnottianamide[1d] (**9d**) (0.169 g) and $POCl_3$ (0.27 ml) in MeCN (6 ml) was refluxed for 1.5 h. Yellow prisms (0.150 g), mp 149—155 °C (dec.) (MeOH–Et_2O). ^{1}H-NMR δ: 3.98, 4.17 (each 3H, s, OMe), 4.14 (3H, dif s, OMe), 5.10 (3H, s, N^+Me), 6.20 (2H, s, OCH_2O), 7.37, 7.96 (each 1H, s, C_1- and C_7-H), 8.00 (1H, d, J=9.0 Hz, C_{12}-H), 8.34 (1H, br s, C_4-H), 9.31 (1H, d, J=9.0 Hz, C_{11}-H), 11.48 (1H, br s, C_6-H).

The Dihydrobase (8,9,10-Trimethoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine) (**12d**): A solution of the quaternary base (**1d**) chloride (0.042 g) and $NaBH_4$ (0.024 g) in abs. MeOH (4 ml) was stirred at room temperature for 30 min. After the reaction mixture had been evaporated to dryness *in vacuo*, H_2O was added to the residue and the solution was extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Recrystallization of the residue from $CHCl_3$–MeOH followed by benzene–hexane gave colorless prisms (0.030 g), mp 167—171 °C. *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.61; H, 5.51; N, 3.58. ^{1}H-NMR δ: 2.55 (3H, s, NMe), 3.80, 3.90, 3.93 (each 3H, s, OMe), 4.02 (2H, s, C_6-H_2), 5.99 (2H, s, OCH_2O), 6.60 (1H, s, C_7-H), 7.08 (1H, s, C_1-H), 7.44 (1H, d, J=9.0 Hz, C_{12}-H), 7.64 (1H, s, C_4-H), 8.29 (1H, d, J=9.0 Hz, C_{11}-H).

Avicine (1e) Chloride——A solution of the aromatic formamide (**9e**) (1.00 g) and $POCl_3$ (1.8 ml) in MeCN (40 ml) was refluxed for 20 min. Yellow needles, quantitative, mp > 300 °C (MeOH) (lit.[7e] mp > 300 °C).

This material was identical with an authentic sample of avicine[7e] (**1e**) chloride.

7-Methoxy-5-methyl-2,3;9,10-bis(methylenedioxy)benzo[*c*]phenanthridinium (Model I) (1f) Chloride——The

Quaternary Base (**1f**): A solution of the aromatic formamide (**9f**) (0.700 g) and $POCl_3$ (1.1 ml) in MeCN (28 ml) was refluxed for 1.5 h. Orange fine needles, quantitative, mp 293—296 °C (dec.) (MeOH). ^{1}H-NMR (D_2O) δ: 4.00 and 4.11 (each 3H, s, N^+Me and OMe), 6.08 and 6.16 (each 2H, s, OCH_2O), 6.32 (1H, s, C_8-H), 6.84 (1H, d, J=9.5 Hz, C_{12}-H), 6.86 (1H, s, C_1-H), 7.20 (1H, s, C_4-H), 7.26 (1H, d, J=9.5 Hz, C_{11}-H), 8.82 (1H, s, C_6-H).

The Dihydrobase [7-Methoxy-5-methyl-2,3;9,10-bis(methylenedioxy)-5,6-dihydrobenzo[*c*]phenanthridine] (**12f**): A solution of the quaternary base (**1f**) chloride (0.049 g) and $NaBH_4$ (0.015 g) in MeOH (5 ml) was stirred at room temperature for 30 min. After addition of H_2O, the mixture was extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Recrystallization of the residue from $CHCl_3$–MeOH gave colorless prisms (0.036 g), mp 212.5—214 °C. *Anal.* Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.33; H, 4.52; N, 3.74. ^{1}H-NMR δ: 2.60 (3H, s, NMe), 3.81 (3H, s, OMe), 4.18 (2H, s, C_6-H), 6.01 (4H, s, $OCH_2O\times2$), 6.55 (1H, s, C_8-H), 7.08 (1H, s, C_1-H), 7.44 (1H, d, J=8.5 Hz, C_{12}-H), 7.67 (1H, s, C_4-H), 8.06 (1H, d, J=8.5 Hz, C_{11}-H).

The ψ-Cyanide [6-Cyano-7-methoxy-5-methyl-2,3;9,10-bis(methylenedioxy)-5,6-dihydrobenzo[*c*]phenanthridine] (**22f**): Potassium cyanide (0.071 g) was added to a hot solution of the quaternary base (**1f**) chloride (0.190 g) in H_2O (19 ml) under heating at 75 °C. The mixed solution was stirred at 75 °C for 1.5 h. The resulting precipitates were collected by filtration and washed with H_2O. Recrystallization of the precipitates from $CHCl_3$–MeOH gave colorless prisms (0.149 g), mp 248—251 °C (dec.). *Anal.* Calcd for $C_{22}H_{16}N_2O_5$: C, 68.03; H, 4.15; N, 7.21. Found: C, 67.75; H, 4.03; N, 6.96. ^{1}H-NMR (DMSO-d_6) δ: 2.59 (3H, s, NMe), 3.88 (3H, s, OMe), 5.73 (1H, s, C_6-H), 6.04—6.28 (4H, m, $OCH_2O\times2$), 6.94 (1H, s, C_8-H), 7.33 (1H, s, C_1-H), 7.51 (1H, s, C_4-H), 7.63 (1H, d, J=9.0 Hz, C_{12}-H), 8.01 (1H, d, J=9.0 Hz, C_{11}-H).

The Oxybase [7-Methoxy-5-methyl-2,3;9,10-bis(methylenedioxy)benzo[*c*]phenanthridin-6(5*H*)-one] (**24f**): Sodium hydride[30] (0.012 g) was added to a stirred solution of the ψ-cyanide (**22f**) (0.051 g) in hexamethylphosphoric triamide (3 ml) at room temperature. The mixed solution was stirred at room temperature for 2.5 h. After addition of H_2O, the resulting precipitates were collected by filtration. The filtrate was extracted with AcOEt. The organic layer was washed with H_2O, dried over K_2CO_3, and evaporated to dryness *in vacuo*. The residue was combined with the precipitates. Recrystallization of the crude material from $CHCl_3$–MeOH gave colorless needles (0.040 g), mp 262—264 °C. *Anal.* Calcd for $C_{21}H_{15}NO_6$: C, 66.84; H, 4.01; N, 3.71. Found: C, 66.71; H, 3.95; N, 3.46. IR ν_{max}^{KBr} cm^{-1}: 1645 (CO). ^{1}H-NMR δ: 3.83 and 3.99 (each 3H, s, OMe, NMe), 6.05 and 6.14 (each 2H, s, OCH_2O), 6.70 (1H, s, C_8-H), 7.11 (1H, s, C_1-H), 7.43 (1H, d, J=9.5 Hz, C_{12}-H), 7.51 (1H, s, C_4-H), 8.50 (1H, d, J=9.5 Hz, C_{11}-H).

***cis*-2-(3,4-Dimethoxyphenyl)-1-(*N*-methylacetamido)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (11b)**——A solution of the *cis*-amine (**10b**) (1.00 g) in acetic anhydride (20 ml) and pyridine (20 ml) was stirred at room temperature for 3 h and poured into a large amount of ice-water. The mixture was made alkaline with conc. NH_4OH, and then extracted with AcOEt. The organic layer was washed with saturated $CuSO_4$ aq. solution and with H_2O, and then dried over K_2CO_3. The ethyl acetate solution was evaporated to dryness *in vacuo*. Recrystallization of the residue from EtOH gave colorless prisms (1.10 g), mp 168—171 °C. *Anal.* Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.90; H, 6.56; N, 3.60. IR ν_{max} cm^{-1}: 1630 (CO). ^{1}H-NMR δ: 1.55 (9/7H, s, COMe), 1.72 (12/7H, s, COMe), 1.88—2.22 (2H, m, C_3-H_2), 2.54 (12/7H, s, NMe), 2.69 (9/7H, s, NMe), 2.80—3.40 (3H, m, C_2-H, C_4-H_2), 3.85 (24/7H, s, OMe), 3.88 (18/7H, s, OMe), 4.91 (3/7H, d, J=5.0 Hz, C_1-H), 5.87, 5.90 (total 2H, each s, OCH_2O), 6.23 (4/7H, d, J=6.5 Hz, C_1-H), 6.44—6.90 (5H, m, arom. H×5).

2-(3,4-Dimethoxyphenyl)-1-(*N*-methylacetamido)-6,7-methylenedioxynaphthalene (9b)——A solution of the aliphatic acetamide (**11b**) (0.102 g) and DDQ (0.181 g) in abs. benzene (8 ml) was refluxed for 1 h, made alkaline with 5% NaOH aq., and extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. After removal of the portion insoluble in benzene, the residue was purified by preparative TLC with benzene–AcOEt [1 : 1 (v/v)] (double development) to give colorless prisms (0.033 g), mp 154—155 °C, which were recrystallized from EtOH. *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.58; H, 5.58; N, 3.86. IR ν_{max} cm^{-1}: 1660 (CO). ^{1}H-NMR δ: 1.76 (3H, s, COMe), 3.09 (3H, s, NMe), 3.90, 3.93 (each 3H, s, OMe), 6.08 (2H, s, OCH_2O), 6.87 (1H, dif s, C_2-H), 6.92 (2H, dif s, C_5- and C_6-H), 7.07 (1H, s, C_5-H), 7.19 (1H, s, C_8-H), 7.38 (1H, d, J=8.0 Hz, C_4-H), 7.71 (1H, d, J=8.0 Hz, C_3-H).

6-Methylnitidine (8,9-Dimethoxy-5,6-dimethyl-2,3-methylenedioxybenzo[*c*]phenanthridinium) (1b) Chloride——The Quaternary Base (**1b**): A solution of the aromatic acetamide (**9b**) (0.368 g) in MeCN (15 ml) containing $POCl_3$ (0.7 ml) was heated at 85—90 °C for 2.5 h. The reaction mixture was poured into a large amount of ice-water and the resulting precipitates were collected by filtration. Recrystallization of the precipitates from H_2O–MeOH gave yellow needles quantitative, mp 221—223 °C. ^{1}H-NMR (CF_3CO_2H) δ: 3.42 (3H, s, CMe), 4.24, 4.33 (each 3H, s, OMe), 4.73 (3H, s, N^+Me), 6.21 (2H, s, OCH_2O), 7.47, 7.82, 7.85 (each 1H, s, arom. H), 8.12 (1H, d, J=9.0 Hz, C_{12}-H), 8.16 (1H, s, arom. H), 8.41 (1H, d, J=9.0 Hz, C_{11}-H).

The Dihydrobase [6-Methyldihydronitidine (8,9-Dimethoxy-5,6-dimethyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine)] (**12b**): A solution of 6-methylnitidine (**1b**) chloride (0.050 g) and $NaBH_4$ (0.016 g) in MeOH (7 ml) was stirred at room temperature for 30 min. After addition of H_2O, the mixture was extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Recrystallization of the residue from $CHCl_3$–MeOH gave colorless prisms (0.037 g), mp 205—207 °C. *Anal.* Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N,

3.85. Found: C, 72.80; H, 5.74; N, 3.93. ^{1}H-NMR δ: 1.16 (3H, d, J=7.0 Hz, $CHC\underline{H}_3$), 2.56 (3H, s, NMe), 3.93, 3.97 (each 3H, s, OMe), 4.04 (1H, q, J=7.0 Hz, C_6-H), 6.00 (2H, s, OCH_2O), 6.72 (1H, s, C_7-H), 7.08 (1H, s, C_1-H), 7.31 (1H, s, C_{10}-H), 7.45 (1H, d, J=9.0 Hz, C_{12}-H), 7.68 (1H, d, J=9.0 Hz, C_{11}-H), 7.68 (1H, s, C_4-H).

Antitumor Activity——A group of six female ddY mice weighing 20±2 g were implanted intraperitoneally (*i.p.*) with 1×10^7 cells of Sarcoma 180. Compounds to be tested were suspended in 0.5% carboxymethylcellulose in 0.9% NaCl solution and injected *i.p.* at various doses once daily for 5 d, starting 24 h after transplantation. Antitumor activity was evaluated in terms of the total packed cell volume (TPCV) ratio (T/C, %) on the seventh day after transplantation.[31]

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