[Chem. Pharm. Bull. 32(8)2984—2994(1984)]

Studies on the Chemical Constituents of Rutaceous Plants. LV.[1] The Development of a Versatile Method for the Synthesis of Antitumor-Active Benzo[*c*]phenanthridine Alkaloids. (5).[1] A New Method for Quaternization of the Benzo[*c*]phenanthridine Nucleus

HISASHI ISHII,* TSUTOMU ISHIKAWA, YUH-ICHIRO ICHIKAWA, MITSUGI SAKAMOTO, MUNEKAZU ISHIKAWA, and TSUTOMU TAKAHASHI (deceased)

Faculty of Pharmaceutical Sciences, Chiba University, 1–33, Yayoi-cho, Chiba 260, Japan

(Received November 18, 1983)

A versatile method of synthesis of the quaternary benzo[*c*]phenanthridine alkaloid (**1**), having a tertiary benzo[*c*]phenanthridine skeleton, from the norbase (**3**) is described.

Treatment of the norbase (**3**) with sodium borohydride in formic or in acetic acid gave the *N*-methyl- (**5**) or the *N*-ethyl- (**7**) dihydrobase, respectively, in good yield. The *N*-methyldihydrobase (**5**) could also be prepared by treatment of the norbase (**3**) with sodium borohydride and dimethyl sulfate in hexamethylphosphoric triamide. The dihydrobases (**5** and **7**) were readily convertible to the corresponding quaternary benzo[*c*]phenanthridine alkaloids by oxidation with Jones reagent or with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in good yields.

In addition, we found that the air-oxidation of the carbanions derived from the ψ-cyanides (**11**) of the quaternary bases (**1**) gave the corresponding oxybases (**10**) in excellent yields.

Keywords——quaternary benzo[*c*]phenanthridine alkaloid synthesis; *N*-alkyl-5,6-dihydrobenzo[*c*]phenanthridine; tertiary benzo[*c*]phenanthridine; *N*-alkylbenzo[*c*]phenanthridone; air-oxidation of ψ-cyanide carbanion; sodium borohydride–acetic acid; sodium borohydride–formic acid; sodium borohydride–dimethyl sulfate in hexamethylphosphoric triamide

It is well known that the quaternary bases of fully aromatized benzo[*c*]phenanthridine alkaloids[2] (**1**) occur naturally in Rutaceous plants, especially *Xanthoxylum* species. Among them, nitidine[3] (**1a**) and fagaronine[4] (**2**) are important because of strong antitumor activity against various types of experimental tumors (L1210, P388, S180A, *etc.*). These findings stimulated us to develop a preparative method for these alkaloids. Several synthetic sequences[4b,5] have been reported and some of them involve a direct quaternization step[3b,4b,5a] of a tertiary benzo[*c*]phenanthridine nucleus (the norbases) (**3**) with dimethyl sulfate in a mixed solvent of xylene and nitrobenzene at the last stage in the reaction sequences. Although this procedure was used as a general method for the quaternization of the norbases (**3**), Stermitz[4b] reported the formation of an inseparable mixture of the salt (**1**) of the desired quaternary base and the protic salt (**4**) of the starting norbase when this procedure was applied to the synthesis of fagaronine (**2**). Apart from their description,[4b] we have also experienced this problem, that is, when the norbases (**3**) were treated even with "magic methyl" (FSO_3CH_3), an inseparable mixture of almost equal amounts of the salts of quaternary and tertiary bases. Therefore, an improved method for the quaternization of the norbase (**3**) is desirable in the chemistry of benzo[*c*]phenanthridine alkaloids. In this report, we describe the establishment of a general procedure for this purpose.

Onda[5b,c] reported that dehydrogenation of *N*-methyl-5,6-dihydrobenzo[*c*]phenanthri-

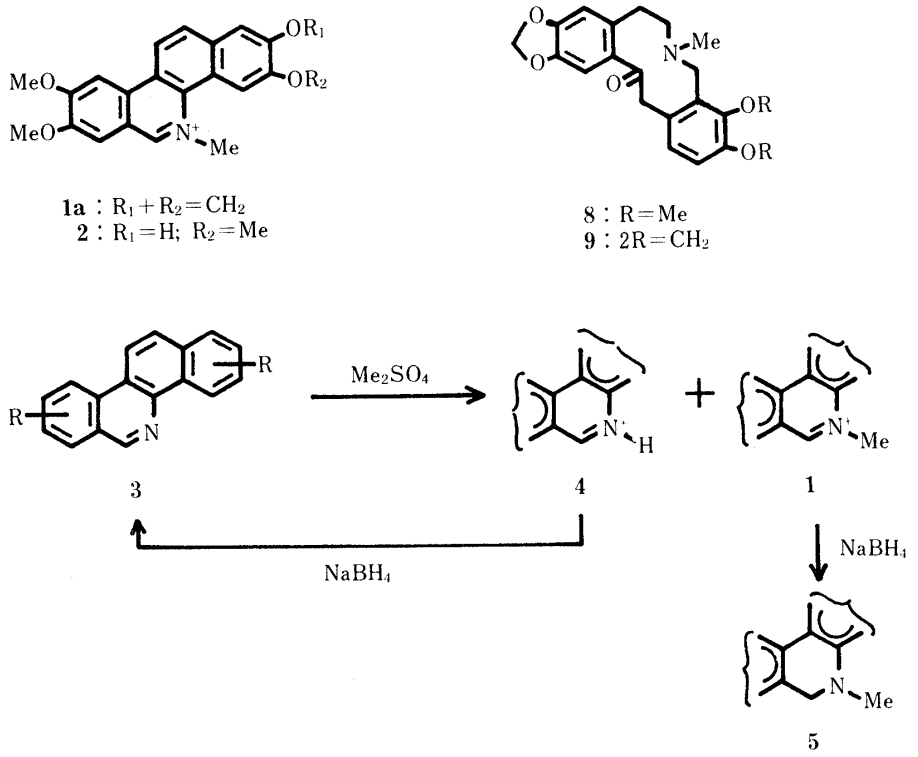
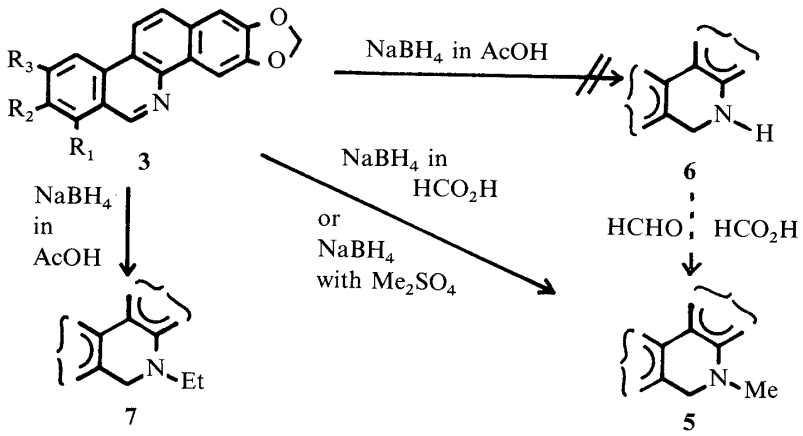


Chart 1

dine derivatives (the NMe-dihydrobases) (**5**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided the quaternary bases (**1**) in good yields. Therefore, we undertook to transform compounds having a tertiary benzo[*c*]phenanthridine skeleton [the norbases (**3**)] into the NMe-dihydrobases (**5**). As starting materials for our studies, two norbases (**3a** and **3b**) were prepared from naturally occurring benzo[*c*]phenanthridinium alkaloids [nitidine (**1a**) and chelerythrine (**1b**)] by thermal decomposition. Initially, we aimed at converting the norbases (**3**) into the NH-5,6-dihydrobenzo[*c*]phenanthridine derivatives (the NH-dihydrobases) (**6**), because Eschweiler–Clarke reaction[6] of the resulting NH-dihydrobases (**6**) would be expected to give the desired NMe-dihydrobases (**5**) in good yields. Actually, however, treatment of norchelerythrine (**3b**) with sodium borohydride in acetic acid gave an unexpected product (**7b**), almost quantitatively. The ultraviolet (UV) spectrum of the product (**7b**) was superimposable on that of dihydrochelerythrine[7] (**5b**). In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, it shows a 2H quartet ($J=7.0$ Hz) at δ 2.78 coupled with a 3H triplet ($J=7.0$ Hz) at δ 1.20, indicating the presence of an *N*-ethyl group in the molecule. These results led us to assign the product as *N*-ethyl-5,6-dihydronorchelerythrine (**7b**). Since *N*-alkylation of NH-compounds with sodium borohydride in carboxylic acids had already been reported,[8] this conclusion is reasonable. General applicability of this method for reductive *N*-ethylation of the norbases was confirmed by the preparation of three other *N*-ethyldihydrobases (**7a**, **7d**, and **7e**) from the corresponding norbases (**3a**, **3d**, and **3e**) (Table I).

This finding provided a hint for a direct preparative method for the NMe-dihydrobases (**5**) from the norbases (**3**). Treatment of norchelerythrine (**3b**) and *O*-ethyldecarine[5d] (**3d**) with sodium borohydride in formic acid produced the desired dihydrochelerythrine (**5b**) and *N*-methyl-5,6-dihydro-*O*-ethyldecarine (**5d**) in good yields, respectively. This method seems to have potential applicability to a phenolic norbase. This view is supported by the finding that treatment of decarine[5d,9] (**3f**), a naturally occurring phenolic base, with sodium borohydride in formic acid gave the desired *N*-methyl-5,6-dihydrodecarine (**5f**) in 79.3% yield. This

TABLE I. Yields of the Dihydrobases (**5** or **7**) from the Norbases (**3**)



No. of norbase (3)	Substituents			7	5	
	R_1	R_2	R_3	$NaBH_4$ in AcOH (%)	$NaBH_4$ in HCO_2H (%)	$NaBH_4$ with Me_2SO_4 (%)
a	H	OMe	OMe	62.4	—	79.7
b	OMe	OMe	H	85.2	88.8	80.3
c	H	OCH_2O		—	—	77.7
d	OMe	OEt	H	88.3	76.1	—
e	OEt	OMe	H	96.6	—	79.4
f[a]	OMe	OH	H	—	79.7	—
g	OMe	OMe	OMe	—	—	84.1

a) A naturally occurring base[2]: decarine.

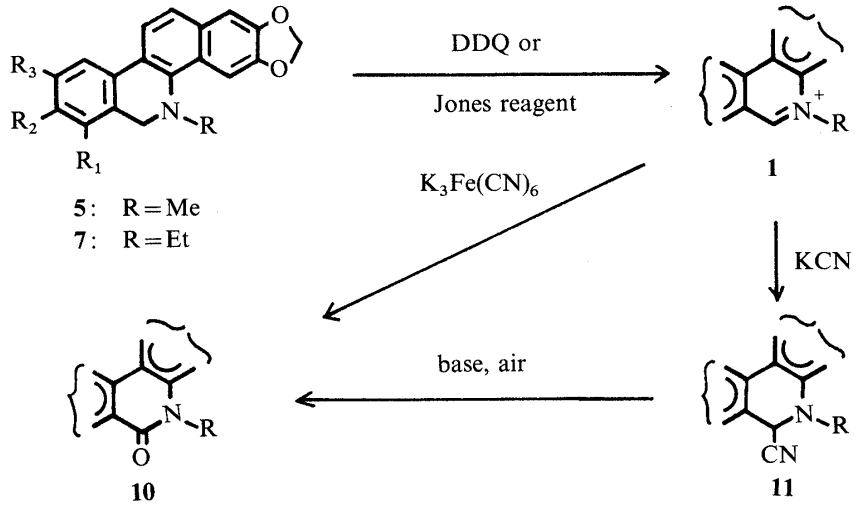
dihydrobase (**5f**) was used for structural establishment of the new quaternary phenolic base isolated from *Macleaya cordata* (WILLD.) R. Br. [*Bocconia cordata* WILLD.] (Papaveraceae: Japanese name "Takenigusa" or "Champagiku") by Takao *et al.*[10]

The above procedure is versatile in small-scale experiments but has the defect that a large amount of sodium borohydride is consumed. We, therefore, attempted to develop another procedure which is suitable for large-scale operation. When treated with an alkylating reagent, the norbase (**3**) was transformed into a mixture of the *N*-methylated quanternary salt (**1**) and the protic salt (**4**) of the starting norbase as stated above. Then, subsequent treatment of the reaction mixture with sodium borohydride resulted in formation of a mixture of the desired *N*-methylated dihydrobase (**5**) produced from the former salt (**1**) and the starting norbase (**3**) recovered from the latter one (**4**). Thus, taking into account the fact that dialkyl sulfate does not undergo reduction with sodium borohydride, when an adequate amount of the alkylating reagent is present in the reaction mixture, the recovered norbases (**3**) should be converted into a mixture of the *N*-methylated quaternary salt (**1**) and the protic salt (**4**) again. This consideration led us to conclude that such a pathway should operate when the norbases (**3**) are treated with an excess amount of sodium borohydride in the presence of an adequate amount of an alkylating reagent in a suitable solvent. In other words, we anticipated that the cyclic pathway would finally provide only the desired *N*-methylated dihydrobase (**5**) in good yield. In fact, treatment of a mixture of norchelerythrine (**3b**) and dimethyl sulfate in hexamethylphosphoric triamide (HMPA) with sodium borohydride afforded dihydrochelerythrine (**5b**) almost quantitatively. It should be noted here that similar treatment of the same norchelerythrine (**3b**) with diethyl sulfate, instead of dimethyl sulfate, resulted in recovery of the starting material (**3b**). This result reflects the difference of reactivity between these two

alkylating reagents in an S_N 2 type reaction. Five NMe-dihydrobases (**5**) were prepared from the corresponding norbases (**3**) by this procedure (Table I).

It is well known that separation of a mixture of quaternary benzo[*c*]phenanthridine alkaloids (**1**) is very difficult, so that, sometimes, the natural occurrence of these alkaloids has to be verified as the dihydrobases (**5**) after reduction of the crude mixture with sodium borohydride. As described above, in the course of transformation of α-allocryptopine (**8**) and protopine (**9**) into chelerythrine (**1b**) and sanguinarine (**1h**), Onda *et al.*[5b] succeeded in the dehydrogenation of dihydrochelerythrine (**5b**) and dihydrosanguinarine (**5h**) with DDQ to provide the corresponding quaternary bases (**1b** and **1h**) in good yields. Therefore, our seven dihydrobases (**5** and **7**) were converted to the desired quaternary bases (**1**) as shown in Table II according to their method.[5b,c] On the other hand, in the course of studies on oxidation of the dihydrobases (**5**) for another purpose, we occasionally found that oxidation with Jones reagent is also applicable to this conversion. This reagent was applied to nine dihydrobases[11] and gave the corresponding quaternary bases in fairly good yields as shown in Table II. Onda's method gave excellent results, but our method has the advantages of simple operation

TABLE II. Yields of the Quaternary Bases (**1**) from the Dihydrobases (**5** or **7**) and of the Oxybases (**10**) from the Quaternary Bases (**1**) by Various Methods



Substituents				No. of the dihydrobase	Yield of the quaternary base (**1**) chloride			Yield of the oxybase (**10**)		
R	R_1	R_2	R_3		No.	With DDQ (%)	With Jones reagent (%)	No.	With $K_3Fe(CN)_6$ (%)	*via* the ψ-cyanide (**11**) (%)
Me	H	OMe	OMe	**5a**	**a**[a]	—	92.3	**a**	76.3[18]	58.5
Me	OMe	OMe	H	**5b**	**b**[a]	—	79.7	**b**	—	61.9
Me	H	OCH_2O		**5c**	**c**[a]	—	81.7	**c**	—	56.9
Me	OMe	OEt	H	**5d**	**d**	67.5	—	**d**	34.3	—
Me	OEt	OMe	H	**5e**	**e**	87.2	78.3	**e**	—	69.3
Me	OMe	OMe	OMe	**5g**	**g**	87.5	85.4	**g**	—	—
Me	OCH_2O		H	**5h**	**h**[a]	54.9[b]	85.4	**h**	—	59.7
Et	H	OMe	OMe	**7a**	**i**	83.0	—	**i**	48.1	—
Et	OMe	OMe	H	**7b**	**j**	85.6	93.2	**j**	45.8	—
Et	OMe	OEt	H	**7d**	**k**	64.9	72.0	**k**	28.9	61.8
Et	OEt	OMe	H	**7e**	**l**	—	79.4	**l**	—	56.5

a) A naturally occurring base[2]: **a** (nitidine), **b** (chelerythrine), **c** (avicine), **h** (sanguinarine).
b) As the sulfate.

and a cheaper reagent.

Since, generally speaking, the quaternary bases (**1**) tended to bear undefined contents of water of crystallization, the derived quaternary bases were characterized as the oxybases (**10**) and/or the ψ-cyanides (**11**). In 1937, Späth[12] oxidized sanguinarine (**1h**) to oxysanguinarine (**10h**) by treatment with potassium ferricyanide in aqueous potassium hydroxide solution. This procedure is now a general method for this transformation. Therefore, five quaternary bases were derived to the corresponding oxybases (**10**) according to the general method. However, this method usually provided the desired oxybases in unsatisfactory yields. In the course of studies aimed at the preparation of a carbanion of the ψ-cyanide (**11**) of the quaternary bases, we occasionally found that the carbanion readily underwent air-oxidation to the corresponding oxybase (**10**) in good yield. We applied this method to seven quaternary bases (**1**) and obtained the corresponding oxybases (**10**) in fairly good yields. All of the oxybases[13] described in this report provided reasonable elemental analyses and spectral data, as described in Experimental. In conclusion, one of several restrictive steps in the Robinson synthetic sequence[5a,e,f] for benzo[*c*]phenanthridine alkaloids has been by-passed by the establishment of our general method for the preparation of the quaternary bases (**1**) from the norbases (**3**).

Experimental

Instruments, *etc.*, were as described in the preceding paper.[1b]

Nornitidine (3a)——Nitidine (**1a**) chloride (0.244 g) was heated at 110 °C for 10 h under reduced pressure (1 mmHg). Recrystallization of the residue from $CHCl_3$–MeOH gave yellow needles (0.152 g), mp 280—282 °C. *Anal.* Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 71.93; H, 4.46; N, 4.16. ^{1}H-NMR (CF_3CO_2H) δ: 4.23 and 4.37 (each 3H, s, OCH_3), 6.23 (2H, s, OCH_2O), 7.41 and 7.76 (each 1H, s, C_1– and C_7–H), 7.99 and 8.16 (each 1H, s, arom. H), 8.11 and 8.42 (each 1H, d, J=8.0 Hz, C_{12}– and C_{11}–H), 9.33[14] (1H, d, J=8.0 Hz, C_6–H).

General Procedure for Reductive *N*-Alkylation of the Norbases (3) with Sodium Borohydride in Acetic or Formic Acid [*N*-Alkyl-5,6-dihydrobenzo[*c*]phenanthridine Derivatives (The *N*-Alkyldihydrobases) (5 or 7)]——Sodium borohydride (100—200 mol) was added portionwise to a stirred solution of the norbase (**3**) (1 mol) in AcOH or HCO_2H at room temperature. The reaction proceeded exothermically with foaming. After being stirred at room temperature for 30 min, the reaction mixture was made weakly alkaline with 10% NaOH aq. and extracted with $CHCl_3$ or ethyl acetate. The organic layer was dried over K_2CO_3 and evaporated to dryness. The residue was purified by column chromatography on Al_2O_3 (neutral, grade III) with benzene, followed by recrystallization from a suitable solvent to give the desired *N*-alkyldihydrobase (**5** or **7**).

5-Ethyl-8,9-dimethoxy-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (*N*-Ethyl-5,6-dihydronornitidine) (7a)——Nornitidine (**3a**) (0.180 g), AcOH (20 ml), and $NaBH_4$ (3.00 g) gave colorless prisms (0.123 g), mp 174—177 °C (benzene–MeOH). *Anal.* Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.77; H, 5.90; N, 3.80. ^{1}H-NMR δ: 1.16 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.78 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 3.92 and 3.96 (each 3H, s, OCH_3), 4.15 (2H, s, $ArCH_2N$), 5.99 (2H, s, OCH_2O), 6.75, 7.08, 7.28, and 7.60 (each 1H, s, C_7–, C_1–, C_{10}–, and C_4–H), 7.45 and 7.67 (each 1H, d, J=8.5 Hz, C_{12}– and C_{11}–H).

5-Ethyl-7,8-dimethoxy-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (*N*-Ethyl-5,6-dihydronorchelerythrine) (7b)——Norchelerythrine[15] (**3b**) (0.093 g), AcOH (8 ml), and $NaBH_4$ (1.70 g) gave colorless fine needles (0.086 g), mp 147—148 °C (benzene–MeOH). *Anal.* Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.77; H, 5,84; N, 3.83. ^{1}H-NMR δ: 1.20 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.78 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 3.89 and 3.92 (each 3H, s, OCH_3), 4.34 (2H, s, $ArCH_2N$), 6.02 (2H, s, OCH_2O), 6.91 and 7.69 (each 1H, d, J=8.5 Hz, C_9– and C_{11}–H), 7.45 and 7.49 (each 1H, d, J=8.5 Hz, arom. H), 7.10 and 7.63 (each 1H, s, C_1– and C_4–H).

8-Ethoxy-5-ethyl-7-methoxy-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (*N*,*O*-Diethyl-5,6-dihydrodecarine) (7d)——*O*-Ethyldecarine[5d] (**3d**) (0.157 g), AcOH (20 ml), and $NaBH_4$ (1.70 g) gave colorless prisms (0.150 g), mp 162—164.5 °C (benzene–MeOH). *Anal.* Calcd for $C_{23}H_{23}NO_4 \cdot 1/4CH_3OH$: C, 72.45; H, 6.27; N, 3.63. Found: C, 72.24; H, 6.01; N, 3.62. ^{1}H-NMR δ: 1.19 and 1.49 (each 3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.78 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 3.91 (3H, s, OCH_3), 4.14 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 4.34 (2H, s, $ArCH_2N$), 6.02 (2H, s, OCH_2O), 6.90 and 7.69 (each 1H, d, J=8.5 Hz, C_9– and C_{11}–H), 7.09 and 7.62 (each 1H, s, C_1– and C_4–H), 7.45 (2H, d, J=8.5 Hz, C_{10}– and C_{12}–H).

7-Ethoxy-5-ethyl-8-methoxy-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (*N*,*O*-Diethyl-5,6-dihydroisodecarine) (7e)——*O*-Ethylisodecarine[5d] (**3e**) (0.298 g), AcOH (30 ml), and $NaBH_4$ (3.27 g) gave colorless prisms (0.313 g), mp 195—200 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C,

72.82; H, 6.10; N, 3.57. ^{1}H-NMR δ: 1.17 and 1.41 (each 3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.76 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 3.87 (3H, s, OCH_3), 4.06 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 4.32 (2H, s, $ArCH_2N$), 5.98 (2H, s, OCH_2O), 6.86 and 7.65 (each 1H, d, J=9.3 Hz, C_9– and C_{11}–H), 7.41 and 7.44 (each 1H, d, J=9.3 Hz, arom. H), 7.06 and 7.58 (each 1H, s, C_1– and C_4–H).

7,8-Dimethoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (Dihydrochelerythrine) (5b)——Norchelerythrine[15] (**3b**) (0.017 g), HCO_2H (2 ml), and $NaBH_4$ (0.189 g) gave colorless prisms (0.016 g), mp 166—168 °C ($CHCl_3$–MeOH) (lit.[9b] mp 167—170 °C).

8-Ethoxy-7-methoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (*O*-Ethyl-*N*-methyl-5,6-dihydrodecarine) (5d)——*O*-Ethyldecarine[5d] (**3d**) (0.054 g), HCO_2H (6 ml), and $NaBH_4$ (0.760 g) gave colorless prisms (0.043 g), mp 167—171 °C (benzene–MeOH). *Anal.* Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.90; H, 5.82; N, 3.78. ^{1}H-NMR δ: 1.48 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.57 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 4.13 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 4.27 (2H, s, $ArCH_2N$), 5.99 (2H, s, OCH_2O), 6.88 and 7.66 (each 1H, d, J=8.5 Hz, C_9– and C_{11}–H), 7.06 and 7.64 (each 1H, s, C_1– and C_4–H), 7.44 (2H, d, J=8.5 Hz, C_{10}– and C_{12}–H).

8-Hydroxy-7-methoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (*N*-Methyl-5,6-dihydrodecarine) (5f)——Decarine[9] (**3f**) (0.024 g), HCO_2H (3 ml), and $NaBH_4$ (0.281 g) gave colorless plates (0.020 g), mp 169—173 °C (EtOH). *Anal.* Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.47; H, 5.14; N, 3.92. IR ν_{max}^{KBr} cm^{-1}: 3430 (OH), ^{1}H-NMR δ: 2.57 (3H, s, NCH_3), 3.84 (3H, s, OCH_3), 4.26 (2H, s, $ArCH_2N$), 5.64 (1H, s, OH), 6.01 (2H, s, OCH_2O), 6.97 and 7.68 (each 1H, d, J=8.5 Hz, C_9– and C_{11}–H), 7.09 and 7.65 (each 1H, s, C_1– and C_4–H), 7.47 (2H, d, J=8.5 Hz, C_{10}– and C_{12}–H).

General Procedure for Reductive *N*-Alkylation of the Norbases (3) with Dimethyl Sulfate and Sodium Borohydride in Hexamethylphosphoric Triamide [The *N*-Methyldihydrobases (5)]——Sodium borohydride (5—15 mol) was added to a solution of the norbase (**3**) (1 mol) and dimethyl sulfate (18—35 mol) in HMPA at room temperature with stirring. The reaction mixture was heated at 50—60 °C (bath temperature). After 1 h, additional amounts of dimethyl sulfate (18—40 mol) and $NaBH_4$ (5—15 mol) were added. Then, the reaction mixture was heated at the same temperature for 0.5—1 h. The reaction mixture was made weakly basic with 5% NaOH aq. and extracted with ethyl acetate. The ethyl acetate solution was washed with water and sat. NaCl aq., dried over K_2CO_3, and evaporated to dryness. The residue was purified by column chromatography on Al_2O_3 (basic, grade II) with benzene or by preparative TLC on SiO_2 followed by recrystallization from a suitable solvent to give the desired *N*-methyldihydrobase (**5**).

8,9-Dimethoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (Dihydronitidine) (5a)——Nornitidine (**3a**) (0.102 g), Me_2SO_4 (0.5 ml), HMPA (5 ml), and $NaBH_4$ (0.060 g) were used. Additional Me_2SO_4 (1.5 ml) and $NaBH_4$ (0.180 g) were required. Colorless prisms (0.086 g), mp 220—224 °C ($CHCl_3$–MeOH) (lit.[16] mp 223.5—224 °C).

7,8-Dimethoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (Dihydrochelerythrine) (5b)——Norchelerythrine[15] (**3b**) (0.050 g), Me_2SO_4 (0.5 ml), HMPA (3 ml), and $NaBH_4$ (0.085 g) were used. Additional Me_2SO_4 (0.5 ml) and $NaBH_4$ (0.085 g) were required. Colorless prisms (0.042 g), mp 167—169 °C (benzene–MeOH) (lit.[9b] mp 167—170 °C).

5-Methyl-2,3;8,9-bismethylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (Dihydroavicine) (5c)——Noravicine[1b] (**3c**) (0.032 g), Me_2SO_4 (0.19 ml), HMPA (2 ml), and $NaBH_4$ (0.057 g) were used. Additional Me_2SO_4 (0.38 ml) and $NaBH_4$ (0.113 g) were required. Colorless prisms (0.026 g), mp 217—219 °C ($CHCl_3$–MeOH) (lit.[16] mp 223—224 °C).

7-Ethoxy-8-methoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (*O*-Ethyl-*N*-methyl-5,6-dihydroisodecarine) (5e)——*O*-Ethylisodecarine[5d] (**3e**) (0.104 g), Me_2SO_4 (0.5 ml), HMPA (3 ml), and $NaBH_4$ (0.056 g) were used. Additional Me_2SO_4 (0.5 ml) and $NaBH_4$ (0.056 g) were required. Colorless prisms (0.086 g), mp 198—205 °C (softened at 180—183 °C) (acetone). *Anal.* Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.88; H, 5.84; N, 3.74. ^{1}H-NMR δ: 1.40 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.56 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 4.06 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 4.27 (2H, s, $ArCH_2N$), 5.97 (2H, s, OCH_2O), 6.87 and 7.65 (each 1H, d, J=8.5 Hz, C_9– and C_{11}–H), 7.41 and 7.44 (each 1H, d, J=8.5 Hz, arom. H), 7.06 and 7.62 (each 1H, s, C_1– and C_4–H).

7,8,9-Trimethoxy-5-methyl-2,3-methylenedioxy-5,6-dihydrobenzo[*c*]phenanthridine (5g)——The norbase[1b] (**3g**) (0.525 g), Me_2SO_4 (2.7 ml), HMPA (15 ml), and $NaBH_4$ (0.263 g) were used. Additional Me_2SO_4 (5.3 ml) and $NaBH_4$ (0.256 g) were required. Pale yellow prisms (0.461 g), mp 163—165 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.63; H, 5.61; N, 3.63. ^{1}H-NMR δ: 2.56 (3H, s, NCH_3), 3.88, 3.89, and 3.93 (each 3H, s, OCH_3), 4.18 (2H, s, $ArCH_2N$), 6.00 (2H, s, OCH_2O), 7.04 (2H, s, C_1– and C_{10}–H), 7.44 and 7.61 (each 1H, d, J=9.0 Hz, C_{12}– and C_{11}–H), 7.62 (1H, s, C_4–H).

General Method[5b,c] for Oxidative Quaternization of the *N*-Alkyldihydrobases (5 or 7) with DDQ [*N*-Alkylbenzo[*c*]phenanthridinium (1) Salts]——A solution of DDQ (1.5—3 mol) in benzene was added dropwise to a stirred solution of the *N*-alkyldihydrobase (**5** or **7**) (1 mol) in benzene containing dil. NaOH aq. at room temperature. The reaction mixture was stirred at room temperature for several hours, then the solvent was distilled off under reduced pressure. The residue was diluted with water and extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and concentrated to *ca.* 1 ml. A large excess of 10% HCl aq. was dropped into the chloroform solution under ice-cooling. The resulting precipitates were collected by filtration and recrystallized from a suitable solvent to

give the desired quaternary base (**1**) salt.

8-Ethoxy-7-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium (*O*-Ethyl-*N*-methyldecarinium) (1d) Chloride——DDQ (0.068 g) in benzene (2 ml) was added to *O*-ethyl-*N*-methyl-5,6-dihydrodecarine (**5d**) (0.035 g) in benzene (2 ml) and 5% NaOH aq. (1 ml). The reaction time was 1 h. Yellow needles (0.026 g), mp 189—192 °C (dec.) (H_2O); ^{1}H-NMR[17] (CF_3CO_2H) δ: 1.64 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.44 (3H, s, OCH_3), 4.48 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.06 (3H, s, N^+CH_3), 6.24 (2H, s, OCH_2O), 7.52 and 8.04 (each 1H, s, C_1– and C_4–H), 8.12 and 8.21 (each 1H, d, J=8.5 Hz, C_9– and C_{12}–H), 8.56 and 8.60 (each 1H, d, J=8.5 Hz, arom. H), 9.78 (1H, s, C_6–H).

7-Ethoxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium (*O*-Ethyl-*N*-methylisodecarinium) (1e) Chloride——DDQ (0.095 g) in benzene (2 ml) was added to *O*-ethyl-*N*-methyl-5,6-dihydroisodecarine (**5e**) (0.099 g) in benzene (8 ml) and 5% NaOH aq. (1 ml). The reaction time was 0.5 h. Yellow fine needles (0.095 g), mp 181—185 °C (dec.) (MeOH–isoPrOH). This material was identical with the sample prepared by oxidation with Jones reagent described below.

7,8,9-Trimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium (1g) Chloride——DDQ (0.302 g) in benzene (12 ml) was added to the trimethoxy-dihydrobase (**5g**) (0.333 g) in benzene (15 ml) and 5% NaOH aq. (6.2 ml). The reaction time was 2 h. Pale yellow needles (0.318 g), mp 225—232 °C (softened at 190—195 °C) (dec.) (EtOH–MeOH). This material was identical with the sample prepared by oxidation with Jones reagent described below.

5-Methyl-2,3;7,8-bismethylenedioxybenzo[*c*]phenanthridinium (Sanguinarine) (1h) Sulfate——DDQ (0.136 g) in benzene (6 ml) was added to dihydrosanguinarine[11] (**5h**) (0.103 g) in benzene (4 ml) and 10% NaOH aq. (2 ml). Salt formation was carried out using 10% H_2SO_4 aq. instead of 10% HCl aq. The reaction time was 2 h. Orange fine needles (0.073 g), mp >300 °C (MeOH). This material was identical with the sample prepared by oxidation with Jones reagent described below.

5-Ethyl-8,9-dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridinium (*N*-Ethyl-*N*-nornitidine) (1i) Chloride——DDQ (0.103 g) in benzene (6 ml) was added to the dihydrobase (**7a**) (0.055 g) in benzene (3 ml) and 5% NaOH aq. (4 ml). The reaction time was 1 h. Yellow needles (0.050 g), mp 269—272 °C (dec.) (H_2O). ^{1}H-NMR (CF_3CO_2H) δ: 2.03 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.25 and 4.37 (each 3H, s, OCH_3), 5.33 (2H, q, J=7.0 Hz, $N^+C\underline{H}_2CH_3$), 6.25 (2H, s, OCH_2O), 7.54 and 7.77 (each 1H, s, C_1– and C_7–H), 7.92 and 8.22 (each 1H, s, arom. H), 8.18 and 8.54 (each 1H, d, J=8.5 Hz, C_{12}– and C_{11}–H), 9.41 (1H, s, C_6–H).

5-Ethyl-7,8-dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridinium (*N*-Ethyl-*N*-norchelerythrine) (1j) Chloride——DDQ (0.055 g) in benzene (4 ml) was added to the dihydrobase (**7b**) (0.035 g) in benzene (2 ml) and 5% NaOH aq. (1 ml). The reaction time was 1 h. Yellow needles (0.033 g), mp 160—164 °C (dec.) (dil. HCl aq.). This material was identical with the sample prepared by oxidation with Jones reagent described below.

8-Ethoxy-5-ethyl-7-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridinium (*N*,*O*-Diethyldecarinium) (1k) Chloride——DDQ (0.100 g) in benzene (5 ml) was added to the dihydrobase (**7d**) (0.069 g) in benzene (4 ml) and 5% NaOH aq. (2 ml). The reaction time was 2 h. Yellow fine needles (0.049 g), mp 174—178 °C (dec.) (MeOH–acetone). This material was identical with the sample prepared by oxidation with Jones reagent described below.

General Procedure for Oxidative Quaternization of the *N*-Alkyldihydrobases (5 or 7) with Jones Reagent [*N*-Alkylbenzo[*c*]phenanthridinium (1) Chloride]——Jones reagent[18] (1.1—1.5 mol) was added to an ice-cooled solution of the *N*-alkyldihydrobase (**5** or **7**) (1 mol) in acetone with stirring. The reaction mixture was stirred at the same temperature for 30 min, basified with 10% NaOH aq., and extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness. The residue was dissolved in a small amount of $CHCl_3$ or $CHCl_3$–MeOH. Dilute HCl aq. was added dropwise to the solution under ice-cooling. The resulting precipitates were collected by filtration and recrystallized from a suitable solvent.

8,9-Dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium (Nitidine) (1a) Chloride——Dihydronitidine (**5a**) (0.074 g), acetone (15 ml), and Jones reagent (0.18 ml) gave yellow needles (0.075 g), mp 286—292 °C (dec.) (H_2O). (lit.[9a] mp 278—283 °C).

7,8-Dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium (Chelerythrine) (1b) Chloride——Dihydrochelerythrine (**5b**) (0.500 g), acetone (50 ml), and Jones reagent (0.87 ml) gave yellow prisms (0.438 g), mp 192—193 °C (dec.) (MeOH–acetone) (lit.[9b] mp 203—206 °C).

5-Methyl-2,3;8,9-bismethylenedioxybenzo[*c*]phenanthridinium (Avicine) (1c) Chloride——Dihydroavicine (**5c**) (0.100 g), acetone (20 ml), and Jones reagent (0.18 ml) gave yellow prisms (0.090 g), mp >300 °C (MeOH). *Anal.* Calcd for $C_{20}H_{14}ClNO_4 \cdot 2H_2O$: C, 59.48; H, 4.49; N, 3.47. Found: C, 59.64; H, 4.18; N, 3.52. ^{1}H-NMR (CF_3CO_2H) δ: 4.96 (3H, s, N^+CH_3), 6.24 and 6.38 (each 2H, s, OCH_2O), 7.52 and 7.59 (each 1H, s, C_1– and C_7–H), 8.06 and 8.14 (each 1H, s, arom. H), 8.16 and 8.44 (each 1H, d, J=9.0 Hz, C_{12}– and C_{11}–H), 9.21 (1H, s, C_6–H).

7-Ethoxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium (*O*-Ethyl-*N*-methylisodecarinium) (1e) Chloride——The dihydrobase (**5e**) (0.220 g), acetone (20 ml), and Jones reagent (0.34 ml) gave yellow fine needles (0.188 g), mp 179—187 °C (dec.) (isoPrOH–MeOH). *Anal.* Calcd for $C_{22}H_{20}ClNO_4 \cdot 1/2H_2O$: C, 64.97; H, 5.20; N, 3.44. Found: C, 64.80; H, 4.99; N, 3.38. ^{1}H-NMR (CF_3CO_2H) δ: 1.60 (3H, dif. t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.20 (3H, s, OCH_3), 4.70 (2H, dif. q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.04 (3H, s, N^+CH_3), 6.22 (2H, s, OCH_2O), 7.48 (1H, s, C_1–H), 7.90—8.36 (3H, m, arom. H×3), 8.36—8.74 (2H, m, arom. H×2), 9.76 (1H, s, C_6–H).

7,8,9-Trimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium (1g) Chloride——The trimethoxydihydrobase (**5g**) (0.061 g), acetone (5 ml), and Jones reagent (0.14 ml) gave yellow needles (0.057 g), mp 225—232 °C (dec.) (EtOH–MeOH). ^{1}H-NMR (CD_3OD) δ: 4.02, 4.27, and 4.35 (each 3H, s, OCH_3), 4.88 (3H, s, N^+CH_3), 6.22 (2H, s, OCH_2O), 7.44 (1H, s, C_1–H), 7.93 (1H, dif. s, arom. H), 8.05 (2H, dif. s, arom. H × 2), 8.48—8.72 (1H, m, arom. H), 9.64 (1H, s, C_6–H).

5-Methyl-2,3;7,8-bismethylenedioxybenzo[*c*]phenanthridinium (Sanguinarine) (1h) Chloride——Dihydrosanguinarine[11] (**5h**) (1.042 g), acetone (100 ml), and Jones reagent (1.88 ml) gave orange fine needles (0.982 g), mp 285—287 °C (dec.) (isoPrOH–MeOH) (lit.[5c] mp 286—288 °C).

5-Ethyl-7,8-Dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridinium (*N*-Ethyl-*N*-norchelerythrine) (1j) Chloride——The dihydrobase (**7b**) (0.019 g), acetone (0.4 ml), and Jones reagent (0.04 ml) gave yellow prisms (0.020 g), mp 160—164 °C (dec.) (isoPrOH–MeOH). ^{1}H-NMR[17] (CF_3CO_2H) δ: 2.01 (3H, t, J=7.0 Hz, $CH_2\underline{CH}_3$), 4.22 and 4.42 (each 3H, s, OCH_3), 5.38 (2H, dif. q, J=7.0 Hz, $N^+\underline{CH}_2CH_3$), 6.24 (2H, s, OCH_2O), 7.52 and 7.90 (each 1H, s, C_1– and C_4–H), 8.14 and 8.22 (each 1H, d, J=8.5 Hz, C_9– and C_{12}–H), 8.54 and 8.63 (each 1H, d, J=8.5 Hz, arom. H), 9.84 (1H, s, C_6–H).

8-Ethoxy-5-ethyl-7-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridinium (*N*,*O*-Diethyldecarinium) (1k) Chloride——The dihydrobase (**7d**) (0.150 g), acetone (15 ml), and Jones reagent (0.24 ml) gave yellow fine needles (0.118 g), mp 174—177 °C (dec.) (MeOH–acetone). ^{1}H-NMR (CD_3OD) δ: 1.56 and 1.80 (each 3H, t, J=7.0 Hz, $CH_2\underline{CH}_3$), 4.34 (3H, s, OCH_3), 4.41 (2H, m, $OC\underline{H}_2CH_3$), 5.37 (2H, q, J=7.0 Hz, $N^+C\underline{H}_2CH_3$), 6.26 (2H, s, OCH_2O), 7.51 and 7.94 (each 1H, s, C_1– and C_4–H), 8.16 and 8.58 (each 2H, d, J=9.0 Hz, C_9–, C_{12}–, C_{10}–, and C_{11}–H), 9.97 (1H, s, C_6–H).

7-Ethoxy-5-ethyl-8-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridinium (*N*,*O*-Diethylisodecarinium) (11) Chloride——The dihydrobase (**7e**) (0.273 g), acetone (50 ml), and Jones reagent (0.6 ml) gave yellow prisms (0.237 g), mp 164—167 °C (dec.) (isoPrOH–MeOH). *Anal.* Calcd for $C_{23}H_{22}ClNO_4 \cdot 1/2H_2O$: C, 65.63; H, 5.51; N, 3.33. Found: C, 65.38; H, 5.29; N, 3.34. ^{1}H-NMR[17] (CF_3CO_2H) δ: 1.62 and 2.01 (each 3H, t, J=7.0 Hz, $CH_2\underline{CH}_3$), 4.21 (3H, s, OCH_3), 4.71 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.38 (2H, q, J=7.0 Hz, $N^+C\underline{H}_2CH_3$), 6.24 (2H, s, OCH_2O), 7.51 and 7.87 (each 1H, s, C_1– and C_4–H), 8.14, 8.19, 8.55, and 8.60 (each 1H, d, J=9.5 Hz, arom. H), 9.83 (1H, s, C_6–H).

General Procedure for Syntheses of 5-Alkylbenzo[*c*]phenanthridin-6(5*H*)-ones (The Oxybases) (10) by Oxidation of the Quaternary Base (1) Salts with Potassium Ferricyanide——The quaternary base (**1**) salt (1 mol) was dissolved in a solution of KOH (*ca.* 25 mol) in aqueous THF. An aqueous solution of $K_3Fe(CN)_6$ (5.5—10 mol) was dropped into the above solution with stirring under reflux. Refluxing was continued for several hours, then the reaction mixture was extracted with benzene or $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Purification of the residue by preparative thin layer chromatography (p-TLC) followed by recrystallization from a suitable solvent gave the desired oxybase (**10**).

8-Ethoxy-7-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (10d)——$K_3Fe(CN)_6$ (0.200 g) in H_2O (4 ml) was added to the quaternary base (**1d**) chloride (0.033 g) in THF (5 ml), H_2O (10 ml), and KOH (0.103 g). The reaction time was 0.5 h. Colorless fine needles (0.011 g), mp 209—211 °C (benzene–MeOH). *Anal.* Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 69.84; H, 5.07; N, 3.72. IR ν_{max}^{KBr} cm^{-1}: 1650 (CO). ^{1}H-NMR δ: 1.49 (3H, t, J=7.0 Hz, $CH_2\underline{CH}_3$), 3.88 (3H, s, OCH_3), 4.10 (3H, s, NCH_3), 4.21 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.02 (2H, s, OCH_2O), 7.12 and 7.52 (each 1H, s, C_1– and C_4–H), 7.35 and 7.48 (each 1H, d, J=8.5 Hz, C_9– and C_{12}–H), 7.93 and 7.94 (each 1H, d, J=8.5 Hz, arom. H).

5-Ethyl-8,9-dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (10i)——$K_3Fe(CN)_6$ (0.202 g) in H_2O (4 ml) was added to the quaternary base (**1i**) chloride (0.022 g) in THF (4 ml), H_2O (8 ml), and KOH (0.112 g). The reaction time was 0.5 h. Colorless prisms (0.010 g), mp 222—223.5 °C (benzene–MeOH). *Anal.* Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71.Found: C, 69.78; H, 5.02; N, 3.55. IR ν_{max}^{KBr} cm^{-1}: 1634 (CO). ^{1}H-NMR δ: 1.52 (3H, t, J=7.0 Hz, $CH_2\underline{CH}_3$), 4.05 and 4.09 (each 3H, s, OCH_3), 4.51 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 6.07 (2H, s, OCH_2O), 7.13 and 7.89 (each 1H, s, C_1– and C_7–H), 7.50 and 7.92 (each 1H, d, J=8.5 Hz, C_{12}– and C_{11}–H), 7.53 and 7.55 (each 1H, s, arom. H).

5-Ethyl-7,8-Dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (10j)——$K_3Fe(CN)_6$ (0.203 g) in H_2O (4 ml) was added to the quaternary base (**1j**) chloride (0.040 g) in THF (10 ml), H_2O (12 ml), and KOH (0.098 g). The reaction time was 0.5 h. Colorless prisms (0.018 g), mp 185—188 °C (benzene–MeOH). *Anal.* Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.24; H, 5.03; N, 3.75. IR ν_{max}^{KBr} cm^{-1}: 1642 (CO). ^{1}H-NMR δ: 1.46 (3H, t, J=7.0 Hz, $CH_2\underline{CH}_3$), 3.96 and 4.08 (each 3H, s, OCH_3), 4.43 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 6.04 (2H, s, OCH_2O), 7.11 and 7.46 (each 1H, s, C_1– and C_4–H), 7.33 and 7.90 (each 1H, d, J=9.0 Hz, C_9– and C_{10}–H), 7.47 and 7.92 (each 1H, d, J=8.5 Hz, C_{12}– and C_{11}–H).

8-Ethoxy-5-ethyl-7-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (10k)——$K_3Fe(CN)_6$ (0.329 g) in H_2O (5 ml) was added to the quaternary base (**1k**) chloride (0.043 g) in THF (5 ml), H_2O (10 ml), and KOH (0.212 g). The reaction time was 3.5 h. Colorless fine needles (0.012 g), mp 177—179 °C ($CHCl_3$–MeOH). This material was identical with the sample prepared by air-oxidation of the ψ-cyanide (**11k**).

General Procedure for Syntheses of the Oxybases (10) by Air-Oxidation of the Carbanions Prepared from 5-Alkyl-6-cyano-5,6-dihydrobenzo[*c*]phenanthridine (The ψ-Cyanides) (11)——i) The ψ-Cyanides (**11**): Potassium cyanide

(1—2 mol) was added to a stirred solution of the quaternary base (1) salt (1 mol) in H_2O or aqueous MeOH at room temperature. Stirring was continued at room temperature or at 50—60 °C, if required, for *ca.* 1 h. The resulting precipitates were collected by filtration, then recrystallized from a suitable solvent to give the desired ψ-cyanide (**11**).

ii) The Oxybases (**10**) from the ψ-Cyanides (**11**): Sodium hydride[19] (1.5—3 mol) was added to a stirred solution of the ψ-cyanide (**11**) (1 mol) in HMPA at room temperature. The reaction mixture was stirred at room temperature for several hours. After addition of sat. NaCl aq., the reaction mixture was extracted with ethyl acetate. The organic layer was washed with sat. NaCl aq. several times, dried over K_2CO_3, and evaporated to dryness *in vacuo*. Recrystallization of the residue from a suitable solvent gave the desired oxybase (**10**).

8,9-Dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (Oxynitidine) (10a)——i) Nitidine ψ-Cyanide (**11a**): Nitidine (**1a**) chloride (0.209 g), H_2O (50 ml), and KCN (0.041 g) were heated for 0.5 h. Colorless prisms (0.140 g), mp 223—230 °C (softened at 210 °C) ($CHCl_3$–MeOH) [lit.[20] mp 234 °C (softened at 215—216 °C)]. *Anal.* Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.58; H, 4.80; N, 7.20. ^{1}H-NMR δ: 2.58 (3H, s, NCH_3), 3.92 and 3.96 (each 3H, s, OCH_3), 5.06 (1H, s, ArCHN), 6.02 (2H, s, OCH_2O), 6.92 and 7.08 (each 1H, s, arom. H), 7.30 and 7.62 (each 1H, s, C_{10}– and C_4–H), 7.51 and 7.63 (each 1H, d, J=9.0 Hz, C_{12}– and C_{11}–H).

ii) Oxynitidine (**10a**): Nitidine ψ-cyanide (**11a**) (0.095 g), HMPA (3.0 ml), and NaH (0.034 g) were used. The reaction time was 1 h. Colorless prisms (0.078 g), mp 286—288 °C ($CHCl_3$–MeOH) (lit.[16] mp 285—286 °C).

This material was identical with an authentic sample of oxynitidine.[16]

7,8-Dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (Oxychelerythrine) (10b)——i) Chelerythrine ψ-Cyanide (**11b**): Chelerythrine (**1b**) chloride (0.514 g), H_2O (15 ml), and KCN (0.098 g) were heated for 1 h. Colorless prisms (0.371 g), mp 226—231 °C (acetone) (lit. mp 240—245 °C[16]; mp 229—233 °C[21]; mp 260—261 °C[22]). This material was identical with an authentic sample[16] of chelerythrine ψ-cyanide (**11b**).

ii) Oxychelerythrine (**10b**): The ψ-cyanide (**11b**) (0.046 g), HMPA (2 ml), and NaH (0.008 g) were used. The reaction time was 3.5 h. Colorless fine needles (0.037 g), mp 199—203 °C ($CHCl_3$–MeOH) (lit.[9b] mp 200—203 °C). This material was identical with an authentic sample of oxychelerythrine.[9b]

5-Methyl-2,3;8,9-bismethylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (Oxyavicine) (10c)——i) Avicine ψ-Cyanide (**11c**): Avicine (**1c**) sulfate[23] (0.043 g), aqueous MeOH [MeOH (5 ml) and H_2O (15 ml)], and KCN (0.010 g) were heated for 0.5 h. Colorless prisms (0.026 g), mp >300 °C (softened at 220 °C) ($CHCl_3$–MeOH) (lit.[24] mp >340 °C). *Anal.* Calcd for $C_{21}H_{14}N_2O_4$: C, 70.38; H, 3.94; N, 7.82. Found: C, 69.90; H, 3.94; N, 7.32. ^{1}H-NMR (DMSO-d_6) δ: 2.52 (3H, s, NCH_3), 5.68 (1H, s, ArCHN), 6.06 and 6.09 (each 2H, s, OCH_2O), 7.09, 7.30, 7.47, and 7.55 (each 1H, s, arom. H), 7.59 and 7.80 (each 1H, d, J=8.0 Hz, C_{12}– and C_{11}–H).

ii) Oxyavicine (**10c**): Avicine ψ-cyanide (**11c**) (0.060 g), HMPA (2.0 ml), and NaH (0.012 g) were used. The reaction time was 4.5 h. Colorless prisms (0.046 g), mp 281.5—282 °C (softened at 263—264 °C) ($CHCl_3$–EtOH) (lit. mp 276—277 °C[5f]; mp 278—283 °C[5g]). This material was identical with an authentic sample of oxyavicine.[5g]

7-Ethoxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (10e)——i) The ψ-Cyanide (**11e**): The quaternary base (**1e**) chloride (0.176 g), H_2O (10 ml), and KCN (0.038 g) were heated for 1 h. Colorless prisms (0.138 g), mp 241—249 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 70.91; H, 5.09; N, 7.02. ^{1}H-NMR δ: 1.46 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.60 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 4.24 (2H, m, $OC\underline{H}_2CH_3$), 5.61 (1H, s, ArCHN), 6.01 (2H, s, OCH_2O), 7.02, 7.49, 7.51, and 7.68 (each 1H, d, J=9.0 Hz, C_9–, C_{12}–, C_{10}–, and C_{11}–H), 7.09 and 7.61 (each 1H, s, C_1– and C_4–H).

ii) The Oxybase (**10e**): The ψ-cyanide (**11e**) (0.052 g), HMPA (2.5 ml), and NaH (0.010 g) were used. The reaction time was 2 h. Colorless prisms (0.044 g), mp 163—164.5 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 69.83; H, 4.98; N, 3.71. IR ν_{max}^{KBr} cm^{-1}: 1653 (CO). ^{1}H-NMR δ: 1.52 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.85 (3H, s, NCH_3), 3.94 (3H, s, OCH_3), 4.25 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.02 (2H, s, OCH_2O), 7.07 and 7.47 (each 1H, s, C_1– and C_4–H), 7.30 and 7.43 (each 1H, d, J=9.5 Hz, C_9– and C_{12}–H), 7.85 (2H, d, J=9.5 Hz, C_{10}– and C_{11}–H).

5-Methyl-2,3;7,8-bismethylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (Oxysanguinarine) (10h)——i) Sanguinarine ψ-Cyanide (**11h**): Sanguinarine (**1h**) sulfate (0.043 g), H_2O (10 ml), and KCN (0.010 g) were heated for 0.5 h. Colorless prisms (0.028 g), mp 235—239 °C ($CHCl_3$–MeOH) (lit.[22] mp 242—243 °C). *Anal.* Calcd for $C_{21}H_{14}N_2O_4$: C, 70.38; H, 3.94; N, 7.82. Found: C, 70.39; H, 3.86; N, 7.80. ^{1}H-NMR δ: 2.64 (3H, s, NCH_3), 5.29 (1H, s, ArCHN), 6.00—6.16 (2H, m, OCH_2O), 6.02 (2H, s, OCH_2O), 6.93, 7.36, 7.53, and 7.70 (each 1H, d, J=8.0 Hz, C_9–, C_{12}–, C_{10}–, and C_{11}–H), 7.10 and 7.64 (each 1H, s, C_1– and C_4–H).

ii) Oxysanguinarine (**10h**): Sanguinarine ψ-cyanide (**11h**) (0.040 g), HMPA (1.5 ml), and NaH (0.015 g) were used. The reaction time was 2 h. Colorless fine needles (0.031 g), mp >300 °C ($CHCl_3$–MeOH) (lit. mp 356—358 °C[22]; mp 360 °C[7b]). *Anal.* Calcd for $C_{20}H_{13}NO_5$: C, 69.16; H, 3.77; N, 4.03. Found: C, 69.03; H, 3.72; N, 4.05. IR ν_{max}^{KBr} cm^{-1}: 1660 (CO). ^{1}H-NMR δ: 3.91 (3H, s, NCH_3), 6.07 and 6.26 (each 2H, s, OCH_2O), 7.16 and 7.58 (each 1H, s, C_1– and C_4–H), 7.22, 7.53, 7.76, and 7.98 (each 1H, d, J=8.5 Hz, C_9–, C_{12}–, C_{10}–, and C_{11}–H).

8-Ethoxy-5-ethyl-7-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (10k)——i) The ψ-Cyanide (**11k**): The quaternary base (**1k**) chloride (0.087 g), aqueous MeOH [MeOH (2 ml) and H_2O (6 ml)], and KCN (0.021 g) were heated for 1 h. Colorless prisms (0.066 g), mp 207—210 °C (MeOH–$CHCl_3$). *Anal.* Calcd for $C_{24}H_{22}N_2O_4$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.53; H, 5.65; N, 7.22. ^{1}H-NMR δ: 1.16 and 1.49 (each 3H, t, J=

7.0 Hz, $CH_2C\underline{H}_3$), 2.86 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 4.04 (3H, s, OCH_3), 4.16 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.84 (1H, s, ArCHN), 6.04 (2H, s, OCH_2O), 7.02 and 7.71 (each 1H, d, J=8.5 Hz, C_9– and C_{11}–H), 7.12 and 7.61 (each 1H, s, C_1– and C_4–H), 7.53 (2H, d, J=8.5 Hz, C_{10}– and C_{12}–H).

ii) The Oxybase (**10k**): The ψ-cyanide (**11k**) (0.074 g), HPMA (1 ml), and NaH (0.013 g) were used. The reaction time was 2.5 h. Colorless fine needles (0.057 g), mp 177—179 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{23}H_{21}NO_5$: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.57; H, 5.51; N, 3.89. IR ν_{max}^{KBr} cm^{-1}: 1650 (CO). ^{1}H-NMR δ: 1.45 and 1.47 (each 3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.09 (3H, s, OCH_3), 4.18 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 4.42 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 6.03 (2H, s, OCH_2O), 7.09 and 7.44 (each 1H, s, C_1– and C_4–H), 7.30 and 7.43 (each 1H, d, J=9.0 Hz, C_9– and C_{12}–H), 7.86 and 7.90 (each 1H, d, J=9.0 Hz, arom. H).

7-Ethoxy-5-ethyl-8-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (10l)——i) The ψ-Cyanide (**11l**): The quaternary base (**1l**) chloride (0.103 g), H_2O (5 ml), and KCN (0.023 g) were heated for 1 h. Colorless prisms (0.073 g), mp 215—225 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{24}H_{22}N_2O_4$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.97; H, 5.70; N, 7.08. ^{1}H-NMR δ: 1.13 and 1.45 (each 3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.83 (2H, dif. q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 3.87 (3H, s, OCH_3), 4.22 (2H, m, $OC\underline{H}_2CH_3$), 5.78 (1H, s, ArCHN), 5.98 (2H, s, OCH_2O), 6.97 and 7.65 (each 1H, d, J=9.0 Hz, C_9– and C_{11}–H), 7.06 and 7.54 (each 1H, s, C_1– and C_4–H), 7.46 and 7.48 (each 1H, d, J=9.0 Hz, arom. H).

ii) The Oxybase (**10l**): The ψ-cyanide (**11l**) (0.053 g), HMPA (2.5 ml), and NaH (0.010 g) were used. The reaction time was 4 h. Slightly brown needles (0.040 g), mp 162—164 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{23}H_{21}NO_5$: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.30; H, 5.38; N, 3.61. IR ν_{max}^{KBr} cm^{-1}: 1650 (CO). ^{1}H-NMR δ: 1.37 and 1.50 (each 3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.92 (3H, s, OCH_3), 4.25 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 4.43 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 6.01 (2H, s, OCH_2O), 7.08 and 7.41 (each 1H, s, C_1– and C_4–H), 7.29 and 7.42 (each 1H, d, J=9.0 Hz, C_9– and C_{12}–H), 7.85 and 7.88 (each 1H, d, J=9.0 Hz, arom. H).

References and Notes

1) *a*) This work was presented in part at the 20th Symposium on the Chemistry of Natural Products, Sendai, October 1976 [T. Ishikawa and H. Ishii, Symposium Papers, p. 380]; *b*) Part LIV: H. Ishii, K.-I. Harada, T. Ishida, T. Deushi, T. Masuda, M. Sakamoto, Y.-I. Ichikawa, T. Takahashi, M. Ishikawa, and T. Ishikawa, *Chem. Pharm. Bull.*, **32**, 2971 (1984).

2) For a review of the chemistry of these alkaloids see, *a*) R. H. F. Manske, "The Alkaloids," ed. by R. H. F. Manske, Academic Press, New York, London, Vol. 4, 1954, p. 253; *idem*, *ibid.*, Vol. 7, 1959, p. 430; *idem*, *ibid.*, Vol. 10, 1968, p. 485; F. Šantavý, *ibid.*, Vol. 12, 1970, p. 417; V. Preininger, *ibid.*, Vol. 15, 1975, p. 241; F. Šantavý, *ibid.*, Vol. 17, 1979, p 493; *b*) H. Ishii and T. Ishikawa, *Yakugaku Zasshi*, **101**, 663 (1981).

3) *a*) M. E. Wall, M. C. Wani, and Y. L. Taylor, Abstracts of Papers, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept. 1971, MEDI 34; Abstracts of the Third International Congress of Heterocyclic Chemistry: B, Sendai, 1971, p. 29; *b*) R. K.-Y. Zee-Cheng and C. C. Cheng, *J. Med. Chem.*, **18**, 66 (1975).

4) *a*) W. M. Messmer, M. Tin-Wa, H. H. S. Fong, C. Bevelle, N. R. Farnsworth, D. J. Abraham, and J. Trojánek, *J. Pharm. Sci.*, **61**, 1858 (1972); M. Tin-Wa, C. L. Bell, C. Bevelle, H. H. S. Fong, and N. R. Farnsworth, *ibid.*, **63**, 1476 (1974); *b*) J. P. Gillespie, L. G. Amoros, and F. R. Stermitz, *J. Org. Chem.*, **39**, 3239 (1974); F. R. Stermitz, J. P. Gillespie, L. G. Amoros, R. Romero, T. A. Stermitz, K. A. Larson, S. Earl, and J. E. Ogg, *J. Med. Chem.*, **18**, 708 (1975).

5) *a*) A. S. Bailey, R. Robinson, and R. S. Staunton, *J. Chem. Soc.*, **1950**, 2277; K.-Y. Zee-Cheng and C. C. Cheng, *J. Heterocycl. Chem.*, **10**, 85, 867 (1973); *b*) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.*, **19**, 31 (1971); *c*) M. Onda and K. Kawakami, *ibid.*, **20**, 1484 (1972); *d*) H. Ishii, T. Ishikawa, and Y.-I. Ichikawa, *ibid.*, **26**, 514 (1978); *e*) T. Richardson, R. Robinson, and E. Seijo, *J. Chem. Soc.*, **1937**, 835; A. S. Bailey and R. Robinson, *ibid.*, **1950**, 1375; A. S. Bailey and C. R. Worthing, *ibid.*, **1956**, 4535; K. W. Gopinath, T. R. Govindachari, K. Nagarajan, and N. Viswanathan, *ibid.*, **1957**, 4760; H. R. Arthur and Y. L. Ng, *ibid.*, **1959**, 4010; K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy, and N. Viswanathan, *ibid.*, **1959**, 4012; *f*) K. W. Gopinath, T. R. Govindachari, and N. Viswanathan, *Tetrahedron*, **14**, 322 (1961); *g*) I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Ueda, and K.-I. Harada, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 762; *h*) R. A. Abramovitch and G. Tertzakian, *Can. J. Chem.*, **41**, 2265 (1963); R. A. Abramovitch, D. Newman, and G. Tertzakian, *ibid.*, **41**, 2390 (1963); S. F. Dyke and M. Sainsbury, *Tetrahedron*, **23**, 3161 (1967); S. F. Dyke, M. Sainsbury, and B. J. Moon, *ibid.*, **24**, 1467 (1968); S. F. Dyke, B. J. Moon, and M. Sainsbury, *Tetrahedron Lett.*, **1968**, 3933; I. Ninomiya, T. Naito, and T. Mori, *ibid.*, **1969**, 3643; M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.*, **17**, 404 (1969); M. Sainsbury, S. F. Dyke, and B. J. Moon, *J. Chem. Soc.* (*C*), **1970**, 1797; T. Kametani, K. Kigasawa, M. Hiiragi, O. Kusama, E. Hayashi, and H. Ishimaru, *Chem. Pharm. Bull.*, **19**, 1150 (1971); T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocycl. Chem.*, **10**, 31 (1973); I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1696; S. V. Kessar, G. Singh, and P. Balakrishnan, *Tetrahedron Lett.*, **1974**, 2269; H. Ishii, K.-I. Harada, T. Ishida, E. Ueda, K. Nakajima, I.

Ninomiya, T. Naito, and T. Kiguchi, *ibid.*, **1975**, 319; I. Ninomiya, T. Naito, and H. Ishii, *Heterocycles*, **3**, 307 (1975); W. J. Begley and J. Grimshaw, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2324; S. V. Kessar, Y. P. Gupta, K. Dhingra, G. S. Sharma, and S. Narula, *Tetrahedron Lett.*, **1977**, 1459; I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, **7**, 137 (1977); H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K.-I. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Pharm. Bull.*, **26**, 864 (1978); M. Cushman and L. Cheng, *J. Org. Chem.*, **43**, 286 (1978); S. V. Kessar, *Acc. Chem. Res.*, **11**, 283 (1978) and references therein; N. Takao, M. Kamigauchi, M. Sugiura, I. Ninomiya, O. Miyata, and T. Naito, *Heterocycles*, **16**, 221 (1981); M. J. Hearn and S. L. Swanson, *J. Heterocycl. Chem.*, **18**, 207 (1981) and references therein; S. D. Phillips and R. N. Castle, *ibid.*, **18**, 223 (1981) and references therein.

6) M. L. Moore, "Organic Reactions," Vol. 5, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1949, p. 301.
7) *a*) H. Ishii, K. Hosoya, and N. Takao, *Tetrahedron Lett.*, **1971**, 2429; *b*) C. Tani and N. Takao, *Yakugaku Zasshi*, **82**, 755 (1962).
8) N. Aimi, E. Yamanaka, J. Endo, S. Sakai, and J. Haginiwa, *Tetrahedron*, **29**, 2015 (1973); G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974); T. Iwakuma, N. Umino, and N. Itoh, *Yuki Gosei Kagaku Kyokai Shi*, **35**, 300 (1977); N. Umino, T. Iwakuma, M. Ikezaki, and N. Itoh, *Chem. Pharm. Bull.*, **26**, 2897 (1978).
9) *a*) H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Yakugaku Zasshi*, **96**, 1458 (1976); *b*) H. Ishii, T. Ishikawa, and J. Haginiwa, *ibid.*, **97**, 890 (1977); *c*) J. Vaquette, J.-L. Pousset, R.-R. Paris, and A. Cavé, *Phytochemistry*, **13**, 1257 (1974).
10) *a*) Takao *et al.* (private communication: May 24, 1977) reduced a mixture of the crude isolated quaternary bases with sodium borohydride and obtained a new phenolic tertiary base from the resulting products. The tertiary base was identical with a sample of our dihydrobase (**5f**), suggesting that the natural occurrence of *N*-methyldecarinium base (**1f**); *b*) N. Takao, M. Kamigauchi, K. Iwasa, and H. Ishii, Abstracts of Papers, The 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980, p. 231.
11) Since our supply of commercial sanguinarine (P. & B. Research Chemicals) contained protopine (**9**) and chelerythrine (**1b**) as contaminants, we carried out $NaBH_4$ reduction of the commercial sanguinarine followed by chromatography on silica gel (Merck, Art. 7734) with chloroform as the solvent to obtain pure dihydrosanguinarine (**5h**) in 33.2% yield.
12) E. Späth, F. Schlemmer, G. Schenck, and A. Gempp, *Chem. Ber.*, **70**, 1677 (1937).
13) These oxybases were employed as samples for the measurement of the ^{1}H-NMR spectra in the presence of $Eu(dpm)_3$.[2b]
14) Since the ^{1}H-NMR spectrum was measured in CF_3CO_2H, the counterpart of this signal, the N^+H proton, could not be observed.
15) H. Ishii, K. Hosoya, T. Ishikawa, and J. Haginiwa, *Yakugaku Zasshi*, **94**, 309 (1974).
16) H. Ishii, H. Ohida, and J. Haginiwa, *Yakugaku Zasshi*, **92**, 118 (1972).
17) The NMR spectrum of this material was measured on the hydroxide, instead of the chloride, because of insolubility of the chloride in various solvents.
18) J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Synth.*, **45**, 77 (1965).
19) A commercial 52.9% suspension of NaH in mineral oil was used without any treatment.
20) H. R. Arthur, W. H. Hui, and Y. L. Ng, *J. Chem. Soc.*, **1959**, 1840.
21) P. J. Scheuer, M. Y. Chang, and C. E. Swanholm, *J. Org. Chem.*, **27**, 1472 (1962).
22) J. Slavík and L. Slavíková, *Coll. Czech. Chem. Commun.*, **25**, 1667 (1960).
23) In this case, the general procedure was applied to avicine (**1c**) sulfate. Avicine (**1c**) sulfate was prepared by a method similar to that employed for its chloride using 10% H_2SO_4 aq. instead of dilute HCl aq.
24) H. R. Arthur, W. H. Hui, and Y. L. Ng, *J. Chem. Soc.*, **1959**, 4007.