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Studies on the Chemical Constituents of Rutaceous Plants. LIV.[1] The Development of a Versatile Method for the Synthesis of Antitumor-Active Benzo[*c*]phenanthridine Alkaloids. (4).[1b] Limitation of Bischler–Napieralski Cyclization and Detailed Examination of the Dehydrogenation of the Bischler–Napieralski Products in the Robinson Synthetic Pathway for Benzo[*c*]phenanthridine Alkaloids

HISASHI ISHII,* KEN-ICHI HARADA, TOSHIAKI ISHIDA, TAKEO DEUSHI, TAKESHI MASUDA, MITSUGI SAKAMOTO, YUH-ICHIRO ICHIKAWA, TSUTOMU TAKAHASHI (deceased), MUNEKAZU ISHIKAWA, and TSUTOMU ISHIKAWA

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

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In order to establish a versatile method for the preparation of antitumor benzo[*c*]phenanthridine alkaloids, the reaction steps from the 2-aryl-1-formamido-1,2,3,4-tetrahydronaphthalenes (**2**) to the fully aromatized benzo[*c*]phenanthridine derivatives (**5**) *via* the 4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridines (**4**) in the Robinson preparative sequence were examined in detail.

Bischler–Napieralski reaction of the formamide (**2**) having an alkoxy group at the *para* position to the cyclizing point of the 2-phenyl ring substituent gave a mixture of the *trans*- and *cis*-tetrahydrobenzo[*c*]phenanthridines (**4**) with or without formation of the 2-aryl-3,4-dihydronaphthalene derivative (**6**). There is a limitation in that the presence of the alkoxy group at the *para* position is required for success in cyclizing the formamide derivative (**2**). Otherwise, the 2-aryl-3,4-dihydronaphthalene derivative (**6**) is the sole product.

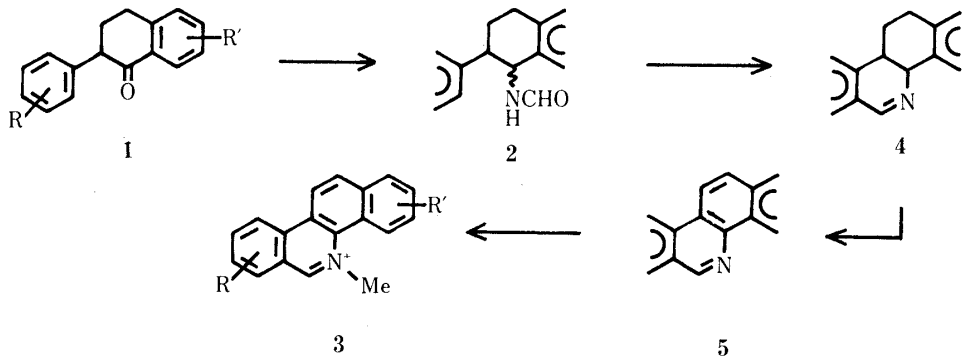
For the dehydrogenation of the resulting *trans*- and *cis*-tetrahydrobenzo[*c*]phenanthridines (*trans*- and *cis*-**4**) into the fully aromatized product (**5**), catalytic dehydrogenation with 30% palladium–charcoal in *p*-cymene and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation in the presence of or in the absence of 5% sodium hydroxide aqueous solution were investigated. The catalytic dehydrogenation provided either the desired fully aromatized product (**5**) or the dihydrobenzo[*c*]phenanthridine (**8**). The species of the product depends upon the species of the starting material (**4**).

The DDQ-oxidation gave a variety of results. The mode of product formation seems to be regulated by various factors, including the reaction conditions, the species of substituents of the starting material (**4**), and the stereochemistry of the starting material (**4**). The mechanisms of formation of various products are discussed.

Keywords——benzo[*c*]phenanthridine alkaloid synthesis; Bischler–Napieralski cyclization limitation; hydroaromatic compound dehydrogenation; DDQ oxidation stereochemistry; 2-aryl-1-formamido-1,2,3,4-tetrahydronaphthalene derivative; tetrahydrobenzo[*c*]phenanthridine derivative; dihydrobenzo[*c*]phenanthridine derivative; fully aromatized benzo[*c*]phenanthridine derivative

In the previous paper,[1b] we reported on a detailed examination of synthetic procedures from 2-aryl-1-tetralones (tetralones) (**1**) to the corresponding 1-formamido-1,2,3,4-tetrahydronaphthalenes (formamides) (**2**), which are key intermediates in the Robinson synthetic sequence[2] for benzo[*c*]phenanthridine alkaloids[3] (**3**) having antileukemic activity.[4]

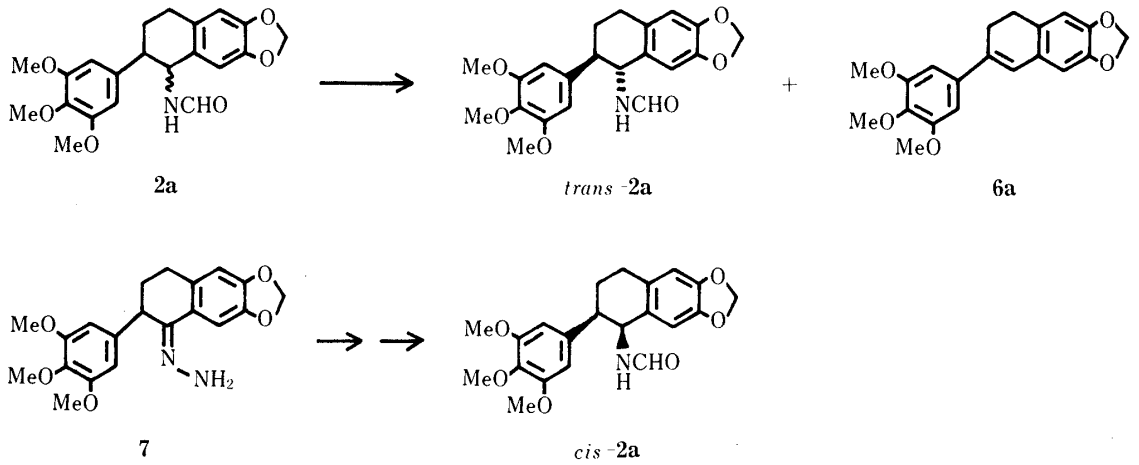
In this paper, we describe a limitation of the Bischler–Napieralski reaction of the formamide derivatives (**2**) and some problems in the dehydrogenation of the resulting 4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridines (2*H*-isoquinolines) (**4**) to the fully aromatized benzo[*c*]-phenanthridine derivatives (norbases) (**5**).



1 2 4 3 5

Chart 1

As described in the previous paper,[1b] the formamide (**2**) was obtained as a mixture of diastereomeric isomers from the tetralone (**1**) by various methods. However, in the case of the trimethoxy-formamide (**2a**), we succeeded in separation of the pure *trans*-isomer (*trans*-**2a**) from the diastereomeric reaction mixture (**2a**) by fractional recrystallization or by treatment of the mixture (**2a**) with formic acid. The latter method depends upon the fact that the *cis*-formamide (*cis*-**2a**) is more easily subject to β-elimination than the *trans*-formamide (*trans*-**2a**) to give the 2-aryl-3,4-dihydronaphthalene derivative (stilbene) (**6a**). On the other hand, the pure *cis*-isomer (*cis*-**2a**) could be prepared by catalytic hydrogenation of the tetralone hydrazone (**7**) followed by formylation with formamide ($HCONH_2$).



2a *trans*-2a 6a

7 *cis*-2a

Chart 2

Treatment of the pure *trans*-trimethoxy-formamide (*trans*-**2a**) with phosphorus oxychloride in toluene gave the corresponding 2*H*-isoquinoline (*trans*-**4a**) in 89.4% yield as the sole product.

Before the attempt at Bischler–Napieralski reaction of the *cis*-trimethoxy-formamide (*cis*-**2a**) was made, we had expected that the β-elimination of a formamide molecule might take place in preference to cyclization to give the trimethoxy-stilbene (**6a**). However, the

treatment of the *cis*-isomer (*cis*-**2a**) with phosphorus oxychloride in toluene gave the desired cyclized product (*cis*-**4a**) in 73.9% yield along with small amounts of two by-products (**6a** and **8a**). One of these by-products was recognized to be the expected trimethoxy-stilbene (**6a**). The molecular formula of the other was found to be $C_{21}H_{19}NO_5$ on the basis of elemental analysis. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, it shows only a 4H signal at δ 3.03 as a multiplet in the aliphatic proton region. These data indicated that the second by-product was 7,8,9-trimethoxy-2,3-methylenedioxy-11,12-dihydrobenzo[*c*]phenanthridine (trimethoxy-isoquinoline) (**8a**) formed by air-oxidation of the desired cyclized product (*cis*-**4a**).

Practically, however, the *cis*-isomer (*cis*-**2a**) is available for the Bischler–Napieralski reaction. In other words, separation of the diastereomeric mixture of the formamide products (**2**) obtained by Leuckart reaction is unnecessary before the Bischler–Napieralski reaction. In fact, the Bischler–Napieralski reaction of the diastereomeric mixture of the trimethoxy-formamide (**2a**) provided the 2*H*-isoquinoline product (**4a**) in a reasonable yield. It should be added here that, in general, isolation of each component from the diastereomeric mixture by column chromatography was quite easy with the resulting 2*H*-isoquinoline products (*trans*- and *cis*-**4**), compared with the starting formamides (**2**) or the corresponding amine derivatives[1b] (**9**). Furthermore, it is of interest that, in the ^{1}H-NMR spectrum, long-range coupling (J=3.0 Hz) between the protons at C_{4b} and at C_6 was observed in both epimers (*trans*- and *cis*-**4a**).

In connection with our studies on the structure–activity relationship for the antileukemic activity of benzo[*c*]phenanthridine alkaloids and on the structural establishment[5] of chelirubine (**3d**), we examined the Bischler–Napieralski reaction of three other formamides, avicine-formamide (**2b**), the formamide of the 5-methoxy-2,3-methylenedioxy compound (**2c**), and chelirubine-formamide (**2d**) (Chart 3).

In 1961, Gopinath *et al.*[2b] reported the synthesis of oxyavicine (**10**). In their report,[2b] they claimed that the desired avicine-2*H*-isoquinoline (**4b**), mp 235—236 °C, was the sole product (possibly a diastereomeric mixture) of Bischler–Napieralski reaction of the avicine-formamide (**2b**). In our experiment, Bischler–Napieralski reaction of the avicine-formamide (**2b**), which was obtained by Leuckart reaction[1b] of the avicine-tetralone (**1b**), in toluene as a solvent provided three products (**6b**, *trans*-**4b**, and *cis*-**4b**) in 14.2, 38.9, and 34.2% yields, respectively, while when acetonitrile was used as a solvent, an additional product (**8b**) was obtained in 3.6% yield along with the above three compounds (**6b**, *trans*-**4b**, and *cis*-**4b**) in 20.8, 25.9, and 38.4% yields, respectively.

The first product was confirmed to be the avicine-stilbene[1b] (**6b**), the β-elimination product derived from the starting material (**2b**) as described above. It should be noted here that the yield of the β-elimination product (**6**) varied with the structure of the starting formamide derivative (**2**). Moreover, the reaction conditions, especially the species of solvent, are important determinants of the yield of the β-elimination product (**6**).

The second and third products were diastereomeric isomers of the desired avicine-2*H*-isoquinoline (*trans*- and *cis*-**4b**). The assignment of stereochemistry was based on a comparison of J values of the signals due to their C_{4b}-protons. In the ^{1}H-NMR spectrum, the signal of the former (*trans*-**4b**) was observed at δ 4.14 as a double doublet having J values of 16.0 and 4.0 Hz, while the latter (*cis*-**4b**) appeared at δ 4.49 as a double doublet having J values of 6.0 and 4.0 Hz. Decoupling of the double doublet signal in the latter (*cis*-**4b**) disclosed that the J value of 4.0 Hz could be assigned to a long-range coupling between C_{4b}–H and C_6–H, while the J value of 6.0 Hz was ascribable to the coupling between C_{4b}–H and C_{10b}–H. Thus, we could conclude that the former (*trans*-**4b**) has a *trans* ring juncture of rings B and C, and the latter (*cis*-**4b**) a *cis* one. The fourth product which was obtained in the Bischler–Napieralski reaction in acetonitrile was the air-oxidation product, the avicine-isoquinoline derivative (**8b**).

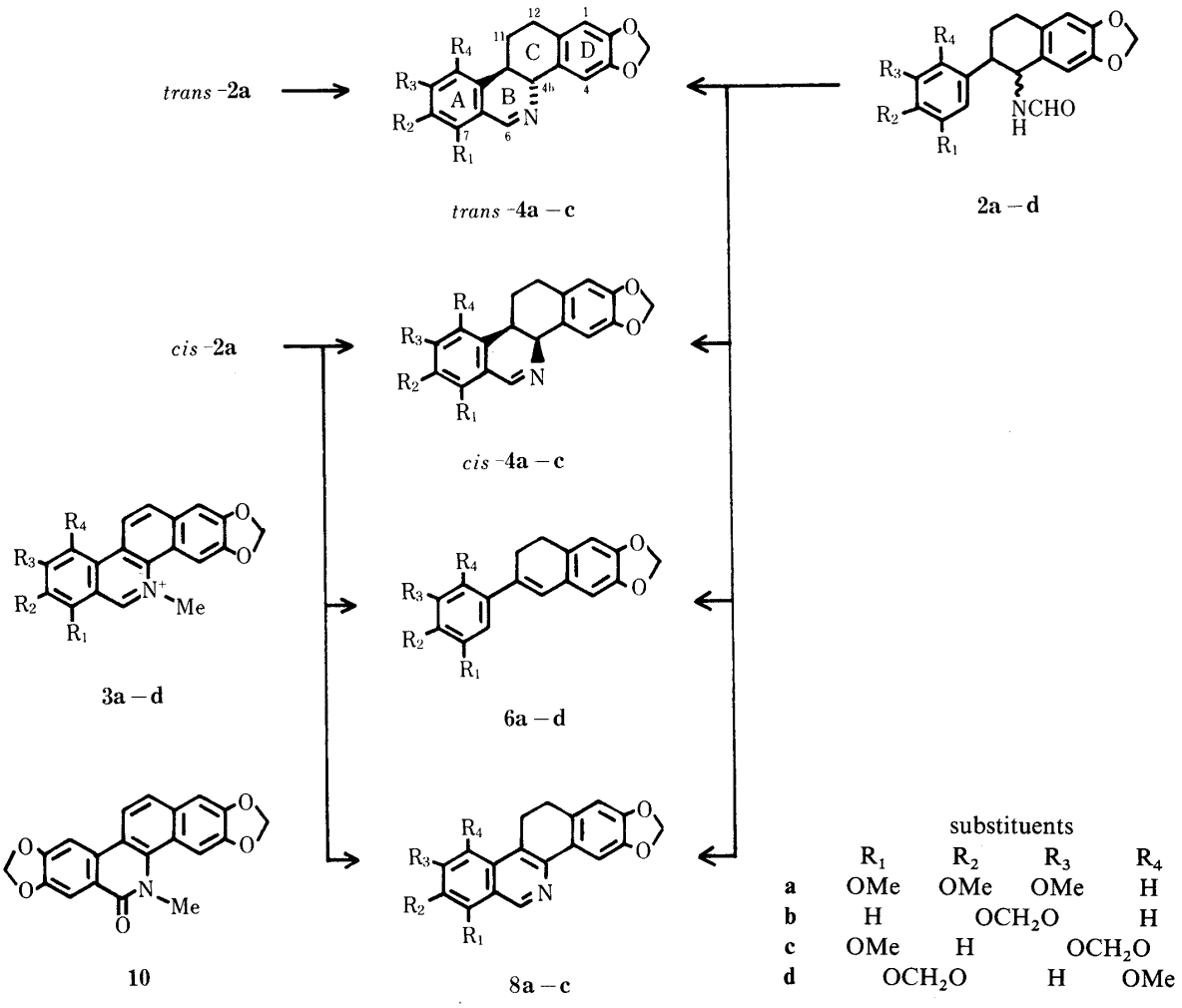


Chart 3

In the case of the 5-methoxy-2,3-methylenedioxy-formamide (**2c**), we isolated only the desired *trans*- and *cis*-2*H*-isoquinoline derivatives (*trans*- and *cis*-**4c**) in 32.2 and 26.8% yields, respectively. The structural assignment of these compounds was also based upon the observation of the *J* values of their C_{4b}-protons in the ^{1}H-NMR spectrum.

Finally, in the case of the chelirubine-formamide (**2d**), we could not obtain any cyclized product (**4d** or **8d**) but only the corresponding stilbene (**6d**). From this result we may conclude that, for successful cyclization in the Bischler–Napieralski reaction of the formamide derivative (**2**), the presence of an alkoxy group at the *para* position to the cyclizing point is required in the starting formamide derivative (**2**) at least. In the previous paper,[1b] we pointed out that the synthesis of the formamide derivative (**2**) from the tetralone (**1**) was one of the problem steps in the Robinson synthetic sequence. Further, it should be added here that Bischler–Napieralski reaction of the formamide derivative (**2**) is also a difficult step in this reaction sequence.

Subsequently, we also investigated the Pictet–Spengler reaction of the *trans*- and the *cis*-trimethoxy-amines (*trans*- and *cis*-**9a**). Treatment of these amine (*trans*- and *cis*-**9a**) hydrochlorides with formalin in ethanolic hydrogen chloride gave the corresponding 1,2,3,4-tetrahydroisoquinoline derivatives (*trans*- and *cis*-**11**) in 44.9 and 60.7% yields, respectively.

In order to prepare the norbases (**5**), dehydrogenation of the cyclized products (**4**) was needed. Initially, we examined catalytic dehydrogenation with 30% palladium–charcoal in *p*-

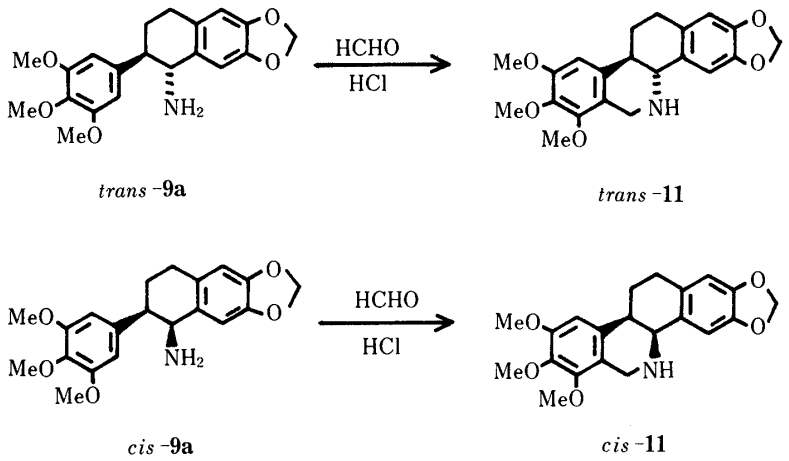


Chart 4

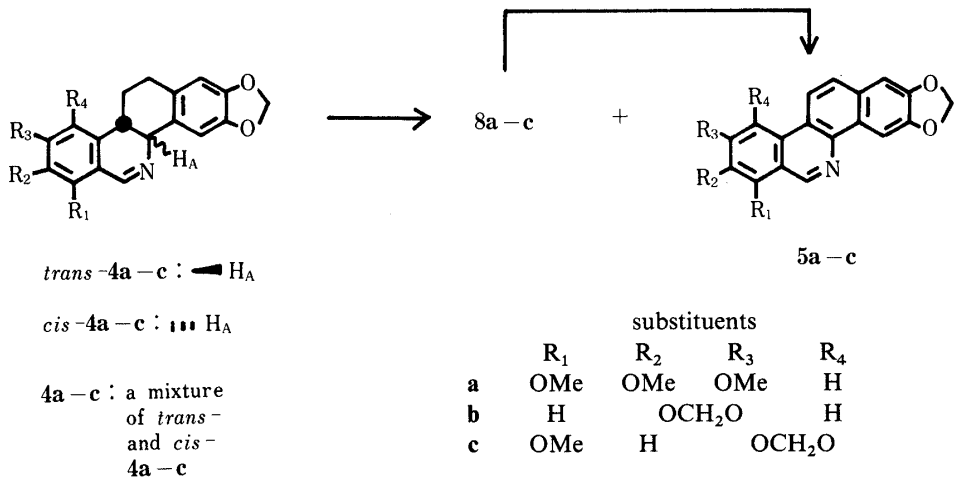


Chart 5

cymene. The cyclized trimethoxy derivatives [the *trans*- and the *cis*-trimethoxy-2*H*-isoquinolines (*trans*- and *cis*-**4a**), the diastereomeric mixture (**4a**), and the trimethoxy-isoquinoline (**8a**)] were subjected to dehydrogenation under the above conditions to give the benzo[*c*]phenanthridine derivatives (trimethoxy-norbase) (**5a**) in relatively good yields regardless of the stereochemistry of the starting materials. The corresponding cyclized derivatives (*trans*- and *cis*-**4b**, **4b**, and **8b**) related to avicine (**3b**) were also subjected to dehydrogenation. These experiments indicated that the diastereomeric mixture (**4**) obtained by Bischler–Napieralski reaction of the Leuckart mixture (**2**) can be used in the subsequent dehydrogenation without purification.

However, in the case of the 5-methoxy-2,3-methylenedioxy-2*H*-isoquinoline (**4c**), the dehydrogenation stopped at the stage of the isoquinoline derivative (**8**) to give the 5-methoxy-2,3-methylenedioxy-isoquinoline (**8c**) as a sole product. Moreover, all attempts, including dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[6] (DDQ) (*vide infra*), at further dehydrogenation of the isoquinoline (**8c**) under various conditions resulted in recovery of the starting material (**8c**).

Thus, we also examined other dehydrogenations of the cyclized trimethoxy products (**4a**, *trans*- and *cis*-**4a**, and **8a**). Initially, the *trans*- and the *cis*-trimethoxy-2*H*-isoquinolines (*trans*- and *cis*-**4a**) were treated with DDQ in benzene. In the case of the *trans*-isomer (*trans*-**4a**), the

TABLE I. Product Ratio in the Oxidation of the Cyclized Trimethoxy Derivatives with DDQ in Benzene

Starting material	Product and recovered starting material		
	2*H*-Isoquinoline derivative (**4a**)	Isoquinoline derivative (**8a**)	Norbase derivative (**5a**)
trans-2*H*-Isoquinoline derivative (*trans*-**4a**)	2[a]	9	2
cis-2*H*-Isoquinoline derivative (*cis*-**4a**)	2[a]	2	7
Isoquinoline derivative (**8a**)		1[a]	1

a) Recovered starting material.

reaction mixture contained the starting material (*trans*-**4a**), the isoquinoline (**8a**), and the norbase (**5a**) in the ratio[7] of 2 : 9 : 2, while in the case of the *cis*-isomer (*cis*-**4a**), the product mixture contained the starting *cis*-isomer (*cis*-**4a**), the isoquinoline (**8a**), and the norbase (**5a**) in the ratio[7] of 2 : 2 : 7. These results could be explained by assuming that parts of the starting base (*trans*- or *cis*-**4a**) and the resulting isoquinoline (**8a**) were removed from the reaction system as precipitates by the salt-formation[8] with the hydroquinone derivative produced from DDQ during dehydrogenation.

The difference of the product-ratio between the *trans*- and the *cis*-2*H*-isoquinolines (*trans*- and *cis*-**4a**) can be interpreted as follows. Many research groups[9] have studied in detail the dehydrogenation of hydroaromatic compounds by allylic (benzylic) oxidation with high potential quinones (DDQ, chloranil, *etc.*). The rate-determining step of the oxidation is a formation of the allylic (benzylic) cation formed by subtraction of an allylic (benzylic) hydrogen as a hydride. The stereoelectronic effects[9a] are also well-established. The subtraction takes place predominantly on an allylic (benzylic) hydrogen parallel to the π-electrons of the allyl (benzyl) group. In other words, a hydrogen perpendicular to a benzene ring would be favorable as regards formation of the allylic (benzylic) cation. In the case of the *trans*-2*H*-isoquinoline (*trans*-**4**), there are three quasi-axial protons situated perpendicular to a benzene ring (ring A or D), at C_{4b}, C_{10b}, and C_{12}. This consideration leaves three possible pathways (A, B, and C in Chart 6) for DDQ oxidation of the *trans*-isomer (*trans*-**4**). Since, however, loss of the C_{4b}-hydrogen was expected to predominate because it results in formation of the most stable benzyl cation (**12**), providing the isoquinoline (**8**), we could exclude two other pathways (B and C) as main pathways in this reaction. Slight resistance of the trimethoxy-isoquinoline (**8a**) to DDQ-oxidation has been shown by an experiment in which similar treatment of the isoquinoline (**8a**) with DDQ gave a reaction mixture containing equal amounts of the starting isoquinoline (**8a**) and the norbase (**5a**). Therefore, the formation of the large amount of the isoquinoline (**8a**) in the DDQ-oxidation of the *trans*-trimethoxy-2*H*-isoquinoline (*trans*-**4a**) seems reasonable.

On the other hand, it should be pointed out that two conformers, a nonsteroidal-like form (**15**) and a steroidal-like one (**16**), might be expected for the *cis*-isomer (*cis*-**4a**). However, since a detailed examination of the Dreiding models disclosed that the nonsteroidal-like form (**15**) is so puckered that the two benzene rings of the *cis*-isomer (*cis*-**4a**) stand perpendicular to each other, we may exclude the nonsteroidal-like form (**15**) as a reaction species. This consideration allows us to exclude two possible pathways (D and E) as major

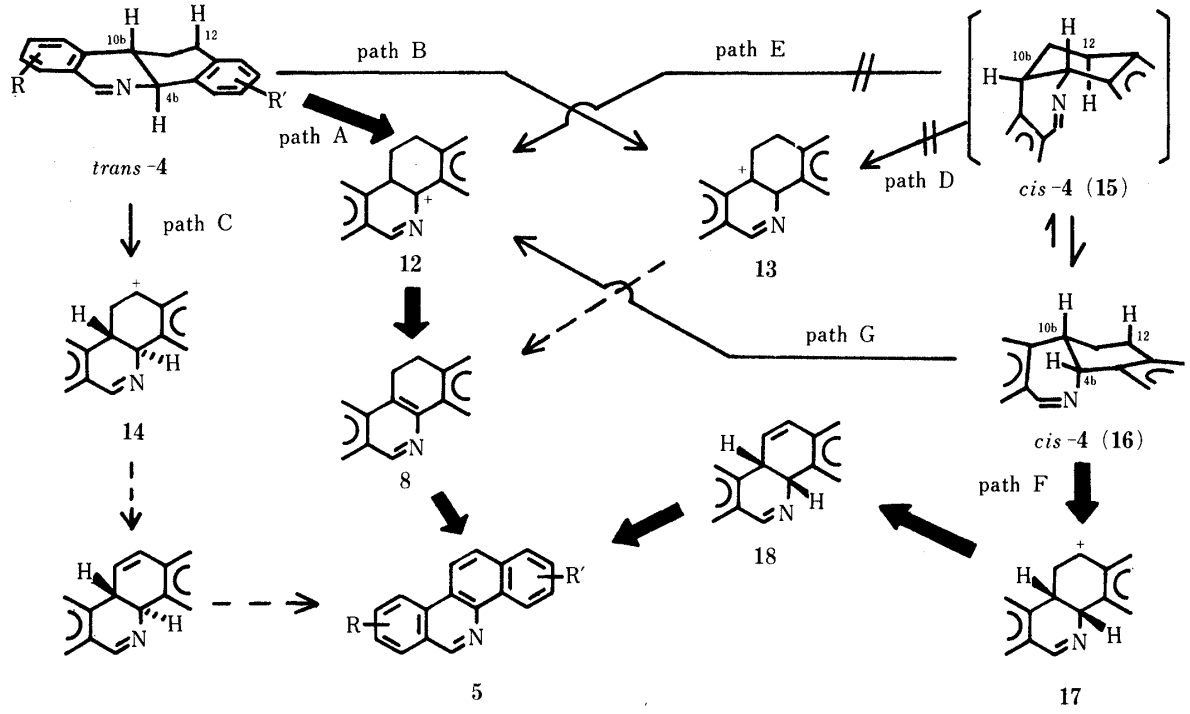


Chart 6

pathways.

The more planar steroidal-like form (**16**) has only one quasi-axial proton at C_{12}. Removal of the C_{12}-hydrogen as a hydride affords the benzyl cation (**17**) which gives the 4b,10b-2*H*-isoquinoline (**18**) (path F in Chart 6). The resulting 2*H*-isoquinoline (**18**) may be expected to be susceptible to DDQ-oxidation to yield the norbase (**5**). The formation of the isoquinoline derivative (**8a**) from the *cis*-isomer (*cis*-**4a**) indicates that the C_{4b}-proton parallel to the π-electrons of the C–N double bond in the steroidal-like form (**16**) is lost to some extent (path G).

In 1971, Onda *et al.*[10] reported the oxidation method with DDQ in the presence of 5% sodium hydroxide aqueous solution. In order to check our assumption regarding the formation of a mixture of the starting material (**4**) and the resulting dehydrogenated products (**5** and **8**), we carried out the oxidation of the cyclized trimethoxy products (*trans*- and *cis*-**4a**, and **8a**) and avicine derivatives (*trans*- and *cis*-**4b**, and **8b**) with DDQ under their conditions. The experimental results are shown in Table II. The *trans*-2*H*-isoquinoline derivatives (*trans*-**4a** and **-4b**) gave only the isoquinoline derivatives (**8a** and **8b**) in good yields. The *cis*-2*H*-isoquinoline derivatives (*cis*-**4a** and **-4b**) also gave only the corresponding isoquinoline products (**8a** and **8b**) with some recovery of the starting materials (*cis*-**4a** and **-4b**), although the *cis*-trimethoxy-2*H*-isoquinoline (*cis*-**4a**) gave a relatively large amount of the corresponding norbase (**5a**) in the absence of 5% sodium hydroxide aqueous solution as described above. These experimental results may be rationalized by assuming that dehydrogenation of the 2*H*-isoquinoline derivatives (**4**) or the resulting isoquinoline derivatives (**8**) by DDQ competes with the decomposition of DDQ in the presence of sodium hydroxide aqueous solution, because it is well known that DDQ[9b] is easily decomposed by treatment with aqueous solvent. However, it is not clear why the *cis*-2*H*-isoquinoline (*cis*-**4a** and **-4b**) did not give the desired norbase (**5a** and **5b**) through path F in the presence of 5% sodium hydroxide aqueous solution in view of the formation of the desired product (**5a** and **5b**) in the absence of the sodium hydroxide.

TABLE II. Yields or Product Ratios in the Oxidation of the Cyclized Products with DDQ in Benzene in the Presence of 5% Sodium Hydroxide Aqueous Solution

	Starting material	Product and recovered starting material		
		cis-2*H*-Isoquinoline derivative (*cis*-**4**)	Isoquinoline derivative (**8**)	Norbase derivative (**5**)
Trimethoxy series	*trans*-Trimethoxy-2*H*-isoquinoline derivative (*trans*-**4a**)		72.6%[a]	—
	cis-Trimethoxy-2*H*-isoquinoline derivative (*cis*-**4a**)	46.6%[b]	34.0%	—
	Trimethoxy-isoquinoline derivative (**8a**)		1[b]	1
Avicine series	*trans*-Avicine-2*H*-isoquinoline derivative (*trans*-**4b**)		84.3%[a]	—
	cis-Avicine-2*H*-isoquinoline derivative (*cis*-**4b**)	5[b]	5	1
	Avicine-isoquinoline derivative (**8b**)		7[b]	2

a) Practically the sole product.
b) Recovered starting material.

It should be added here that the rate of oxidation of the *trans*-isomer (*trans*-**4**) should be faster than that of the *cis*-isomer (*cis*-**4**) because the resonance stabilization of the intermediate cation (**12**) is expected to be larger than that of the cation (**17**). This expectation was supported by the finding that treatment of an equimolar mixture of the *trans*- and the *cis*-trimethoxy-2*H*-isoquinolines (*trans*- and *cis*-**4a**) with DDQ in benzene in the presence of 5% sodium hydroxide aqueous solution resulted in recovery of 72.7% of the *cis*-isomer (*cis*-**4a**) and complete consumption of the starting *trans*-isomer (*trans*-**4a**) with the formation of the isoquinoline (**8a**) in 48.6% yield.

Furthermore, it is of interest that, on oxidation of the isoquinoline derivatives (**8**) with DDQ, the avicine-isoquinoline (**8b**) provided a mixture of the starting avicine-isoquinoline (**8b**) and the norbase product (**5b**) in the ratio[7] of 7 : 2, while the trimethoxy-isoquinoline (**8a**) afforded a similar mixture of the starting material (**8a**) and the corresponding norbase (**5a**) in the ratio[7] of 1 : 1, demonstrating that the former (**8b**) resists DDQ-oxidation more than the trimethoxy-isoquinoline (**8a**) does.

In conclusion, the Robinson sequence for synthesis of benzo[*c*]phenanthridine alkaloids has a limitation in the Bischler–Napieralski reaction step. Moreover, the success of dehydrogenation of the resulting 2*H*-isoquinoline product (**4**) to the desired norbase (**5**) depends upon the structure of the starting materials. Since we wish to synthesize various types of benzo[*c*]phenanthridine alkaloids for studies of the structure–activity relationship, we hope to achieve further improvements in the Robinson sequence for its application as a general method.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) and ultraviolet (UV) spectra were recorded on a Hitachi EPI-G3 spectrometer (in Nujol) and on a Hitachi EPS-3T spectrophotometer (as solution in 95% ethanol), respectively. ^{1}H-NMR spectra were recorded on a JEOL JNM-4H-100 spectrometer in deuteriochloroform, with tetramethylsilane as an internal reference. Mass spectra (MS) were measured on a Hitachi RMU-6E spectrometer at 70 eV chamber voltage with a direct

inlet system. For chromatography (column), silicic acid (100 mesh), Mallinckrodt Chemical Works, Silica gel 60 (70—230 mesh ASTM), Merck, and aluminum oxide (neutral, grade I), Woelm, 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 by mixed melting point determination. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad. The assignment of NH or OH signals was confirmed by disappearance of the signals after addition of deuterium oxide.

General Procedure for Bischler–Napieralski Reaction of the Formamide (2)——A solution of the starting formamide (**2**) in toluene or acetonitrile containing $POCl_3$ was refluxed under argon. The mixture was diluted with water, made alkaline with 10% NaOH aq. or 5% NH_4OH aq., and then extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. If required, separation of each component was carried out by column chromatography or by preparative TLC.

7,8,9-Trimethoxy-2,3-methylenedioxy-*trans*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *trans*-Trimethoxy-2*H*-isoquinoline) (*trans*-4a)——The *trans*-trimethoxy-formamide[1b] (*trans*-**2a**) (0.300 g), toluene (3 ml), and $POCl_3$ (0.6 ml) were refluxed for 15 min. Colorless pillars (0.256 g), mp 152—154 °C (benzene–hexane). *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.58; H, 5.77; N, 3.69. ^{1}H-NMR δ: 1.50—3.05 (5H, m, C_{10b}–H, C_{11}–H_2, and C_{12}–H_2), 3.87, 3.93, and 3.99 (each 3H, s, OCH_3), 4.00[11] (1H, m, C_{4b}–H), 5.89 (2H, s, OCH_2O), 6.57 (1H, s, C_1–H), 6.69 (1H, s, C_{10}–H), 7.50 (1H, s, C_4–H), 8.67[11] (1H, d, J=3.0 Hz, C_6–H).

On the *cis*-Trimethoxy-formamide (*cis*-2a)——The *cis*-trimethoxy-formamide[1b] (*cis*-**2a**) (0.602 g), toluene (5.6 ml), and $POCl_3$ (1.2 ml) were refluxed for 20 min.

i) 7,8,9-Trimethoxy-2,3-methylenedioxy-*cis*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *cis*-Trimethoxy-2*H*-isoquinoline) (*cis*-**4a**): Recrystallization of the crude reaction mixture from benzene–hexane ($CHCl_3$–hexane or EtOH–Et_2O) gave colorless needles (0.212 g), mp 119—122 °C. *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.52; H, 5.75; N, 3.77. ^{1}H-NMR δ: 1.50—2.00 (2H, m, C_{11}–H_2), 2.65—3.10 (3H, m, C_{10b}–H and C_{12}–H_2), 3.88, 3.94, and 3.99 (each 3H, s, OCH_3), 4.44[11] (1H, dd, J=6.0 and 3.0 Hz, C_{4b}–H), 5.89 (2H, m, OCH_2O), 6.52 and 6.55 (each 1H, s, arom. H), 6.98 (1H, s, C_4–H), 8.53[11] (1H, d, J=3.0 Hz, C_6–H).

An additional crop of this material (0.212 g; total yield, 0.424 g) was isolated from the third fraction of the following column chromatography.

ii) 6,7-Methylenedioxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalene (The Trimethoxy-stilbene) (**6a**): The crude material obtained from the mother liquor of the above material (*cis*-**4a**) was chromatographed on SiO_2 with benzene–AcOEt (30 : 1, v/v). The first eluate gave colorless needles (0.006 g), mp 116—121 °C (lit.[1b] mp 120—121 °C), which were recrystallized from cyclohexane. This material was identical with a sample of the trimethoxy-stilbene[1b] (**6a**).

iii) 7,8,9-Trimethoxy-2,3-methylenedioxy-11,12-dihydrobenzo[*c*]phenanthridine (The Trimethoxy-isoquinoline) (**8a**): The second eluate gave colorless needles (0.011 g), mp 160.5—162 °C, which were recrystallized from MeOH. *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.85; H, 5.26; N, 3.97. IR ν_{max} cm^{-1}: 1620, 1585 (C=N, C=C). ^{1}H-NMR δ: 3.03 (4H, m, C_{11}– and C_{12}–H_2), 3.96, 4.00, and 4.10 (each 3H, s, OCH_3), 5.96 (2H, s, OCH_2O), 6.70 (1H, s, C_1–H), 6.97 (1H, s, C_{10}–H), 7.92 (1H, s, C_4–H), 9.28 (1H, s, C_6–H).

The third eluate gave the desired cyclized product (*cis*-**4a**) (0.212 g).

On the Leuckart Mixture of the Trimethoxy-formamide (2a)——The formamide[12] (**2a**) (1.006 g), toluene (9.4 ml), and $POCl_3$ (1.9 ml) were refluxed for 10 min. The crude reaction mixture was chromatographed on SiO_2 with benzene–AcOEt.

i) 7,8,9-Trimethoxy-2,3-methylenedioxy-*trans*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *trans*-Trimethoxy-2*H*-isoquinoline) (*trans*-**4a**): The first eluate with benzene–AcOEt (20 : 1—10 : 1, v/v) gave colorless prisms (0.497 g), mp 149—152 °C, which were recrystallized from EtOH. This material was identical with a sample of the *trans*-trimethoxy-2*H*-isoquinoline (*trans*-**4a**).

ii) 7,8,9-Trimethoxy-2,3-methylenedioxy-*cis*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *cis*-Trimethoxy-2*H*-isoquinoline) (*cis*-**4a**): The second eluate with benzene–AcOEt (10 : 1, v/v) followed by AcOEt gave colorless prisms (0.244 g), mp 120—124 °C, which were recrystallized from MeOH–Et_2O. This material was identical with a sample of the *cis*-trimethoxy-2*H*-isoquinoline (*cis*-**4a**).

On the Leuckart Mixture of the Avicine-formamide (2b) in Toluene——The avicine-formamide[1b] (**2b**) (0.303 g), $POCl_3$ (0.9 ml), and toluene (3 ml) were refluxed for 1 min. Column chromatography of the reaction mixture on SiO_2 with benzene–AcOEt gave three fractions [fr. 1: benzene–AcOEt (20 : 1, v/v), fr. 2: benzene–AcOEt (10 : 1, v/v), and fr. 3: AcOEt followed by MeOH].

i) 6,7-Methylenedioxy-2-(3,4-methylenedioxyphenyl)-3,4-dihydronaphthalene (The Avicine-stilbene) (**6b**): Recrystallization of fr. 1 from $CHCl_3$–MeOH (or benzene–hexane) gave colorless prisms (0.037 g), mp 161—162 °C (lit.[2b] mp 155 °C). *Anal.* Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.80. Found: C, 73.46; H, 4.81. ^{1}H-NMR δ: 2.40—3.10 (4H, m, C_3– and C_4–H_2), 5.88 and 5.93 (each 2H, s, OCH_2O), 6.50—7.20 (6H, m, arom. H and C_1–H).

ii) 2,3;8,9-Bismethylenedioxy-*trans*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *trans*-Avicine-2*H*-isoquinoline) (*trans*-**4b**): Recrystallization of fr. 2 from $CHCl_3$–benzene (or $CHCl_3$) gave colorless prisms (0.112 g), mp >300 °C.[13] *Anal.* Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.09; H, 4.75; N, 4.31. ^{1}H-

NMR ($CDCl_3+CD_3OD$) δ: 1.60—1.94 (1H, m, aliph. H), 2.46—2.70 and 2.80—3.02 (each 2H, m, aliph. H), 4.14[11] (1H, dd, $J=16.0$ and 4.0 Hz, C_{4b}–H), 5.88 and 6.00 (each 2H, s, OCH_2O), 6.60 (1H, s, C_1–H), 6.88 and 6.92 (each 1H, s, arom. H), 7.38 (1H, s, C_4–H), 8.26[11] (1H, d, $J=4.0$ Hz, C_6–H).

iii) 2,3;8,9-Bismethylenedioxy-*cis*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *cis*-Avicine-2*H*-isoquinoline) (*cis*-**4b**): Recrystallization of fr. 3 from EtOH gave colorless prisms (0.098 g), mp >300 °C.[14] *Anal.* Calcd for $C_{19}H_{14}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.96; H, 4.74; N, 4.27. ^{1}H-NMR δ: 1.56—1.98 (2H, m, C_{11}–H_2), 2.68—3.00 (3H, m, C_{10b}–H and C_{12}–H_2), 4.49[11] (1H, dd, $J=6.0$ and 4.0 Hz, C_{4b}–H), 5.88 and 5.96 (each 2H, s, OCH_2O), 6.53 (1H, s, C_1–H), 6.70 and 6.76 (each 1H, s, arom. H), 6.98 (1H, s, C_4–H), 8.12[11] (1H, d, $J=4.0$ Hz, C_6–H).

On the Leuckart Mixture of the Avicine-formamide (2b) in Acetonitrile——The general procedure was applied to a solution of the avicine-formamide[1b] (**2b**) (2.00 g) and $POCl_3$ (3.6 ml) in acetonitrile (40 ml). Refluxing was required for 15 min. The residue was chromatographed on SiO_2 with $CHCl_3$ and fractionated into four fractions (fr. 1—fr. 4) in the order of elution.

i) 6,7-Methylenedioxy-2-(3,4-methylenedioxyphenyl)-3,4-dihydronaphthalene (The Avicine-stilbene) (**6b**): Recrystallization of fr. 1 from benzene–hexane gave colorless needles (0.360 g), mp 152—160 °C (lit.[2b] mp 155 °C).

ii) 2,3;8,9-Bismethylenedioxy-11,12-dihydrobenzo[*c*]phenanthridine (The Avicine-isoquinoline) (**8b**): Recrystallization of fr. 2 from $CHCl_3$ gave colorless needles (0.067 g), mp >300 °C. This material was identical with the avicine-2*H*-isoquinoline (**8b**) described below.

iii) 2,3;8,9-Bismethylenedioxy-*trans*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *trans*-Avicine-2*H*-isoquinoline) (*trans*-**4b**): Recrystallization of fr. 3 from $CHCl_3$ gave colorless prisms (0.490 g), mp >300 °C,[13] which were identical with the sample of the *trans*-avicine-2*H*-isoquinoline (*trans*-**4b**) mentioned above.

iv) 2,3;8,9-Bismethylenedioxy-*cis*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *cis*-Avicine-2*H*-isoquinoline) (*cis*-**4b**): Recrystallization of fr. 4 from EtOH gave colorless prisms (0.728 g), mp >300 °C,[14] which were identical with the sample of the *cis*-avicine-2*H*-isoquinoline (*cis*-**4b**) mentioned above.

On the Methoxy-bismethylenedioxy-formamide (2c)——The methoxy-bismethylenedioxy-formamide[1b] (**2c**) (0.098 g), toluene (1 ml), and $POCl_3$ (0.25 ml) were refluxed for 15 min. Preparative TLC of the residue on SiO_2 with $CHCl_3$–Et_2O (1 : 1, v/v) gave two fractions showing *Rf* 0.61 and 0.28.

i) 7-Methoxy-2,3;9,10-bismethylenedioxy-*trans*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *trans*-Methoxy-bismethylenedioxy-2*H*-isoquinoline) (*trans*-**4c**): Recrystallization of the fraction showing *Rf* 0.61 from benzene gave colorless needles (0.030 g), mp 211—214 °C. *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.34; H, 4.84; N, 4.02. IR ν_{max} cm^{-1}: 1632 (C=N). ^{1}H-NMR δ: 1.74—2.18 (1H, m, C_{11}–H_A), 2.56—3.18 (4H, m, C_{10b}–H, C_{11}–H_B, and C_{12}–H_2), 3.82 (3H, s, OCH_3), 4.04 (1H, br d, $J=14.0$ Hz, C_{4b}–H), 5.89 and 5.94 (each 2H, s, OCH_2O), 6.46 and 6.56 (1H, s, arom. H), 7.50 (1H, s, C_4–H), 8.68 (1H, d, $J=3.0$ Hz, C_6–H).

ii) 7-Methoxy-2,3;9,10-bismethylenedioxy-*cis*-4b,10b,11,12-tetrahydrobenzo[*c*]phenanthridine (The *cis*-Methoxy-bismethylenedioxy-2*H*-isoquinoline) (*cis*-**4c**): Recrystallization of the fraction showing *Rf* 0.28 from benzene–cyclohexane gave colorless prisms (0.025 g), mp 185—188 °C. *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.64; H, 4.88; N, 4.00. IR ν_{max} cm^{-1}: 1637 (C=N). ^{1}H-NMR δ: 1.63—2.01 (2H, m, C_{11}–H_2), 2.69—2.91 (2H, m, C_{12}–H_2), 2.99—3.25 (1H, m, C_{10b}–H), 3.81 (3H, s, OCH_3), 4.36[11] (1H, dd, $J=7.0$ and 3.5 Hz, C_{4b}–H), 5.88 and 5.91[15] (each 1H, s, OCH_2O), 5.97 and 6.01[15] (each 1H, s, OCH_2O), 6.42 and 6.55 (each 1H, s, arom. H), 6.99 (1H, s, C_4–H), 8.59[11] (1H, d, $J=3.5$ Hz, C_6–H).

Attempted Bischler–Napieralski Reaction of the Chelirubine-formamide (2d)——The general procedure was applied to a solution of the chelirubine-formamide (**2d**) (0.060 g) in $CHCl_3$ (2 ml) with $POCl_3$ (0.2 ml). Refluxing was required for 65 h. The temperature was gradually raised from room temperature to reflux temperature with monitoring of formation of the product by TLC during the reaction. After evaporation of the mixture under reduced pressure, the residue was washed with hexane, dissolved in H_2O, basified with NH_4OH aq., and extracted with Et_2O. The ethereal solution was dried over K_2CO_3 and evaporated to dryness to give a black residue, which was negative in the test with Meyer reagent.

The hexane washing was dried over K_2CO_3 and evaporated to dryness. Recrystallization of the residue from benzene–cyclohexane afforded colorless needles (0.005 g), mp 119—200 °C. This material was identical with 2-(2-methoxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalene[1b] (the chelirubine-stilbene) (**6d**).

Pictet–Spengler Reaction of the *trans*-Trimethoxy-amine (*trans*-9a) [7,8,9-Trimethoxy-2,3-methylenedioxy-*trans*-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (*trans*-11)]——A mixture of 37% HCHO aq. (0.5 ml) and conc. HCl (0.1 ml) was added to a solution of the *trans*-trimethoxy-amine (*trans*-**9a**) HCl salt[1b] (0.102 g) in aqueous EtOH [2.6 ml; EtOH–H_2O (1 : 1, v/v)]. The mixture was refluxed for 2 h, basified with 10% NaOH aq., and extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Recrystallization of the residue from $CHCl_3$ gave colorless pillars[16] (0.043 g), mp 239—244 °C. *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.21; H, 6.14; N, 3.62. IR ν_{max} cm^{-1}: 3390 (NH).

Pictet–Spengler Reaction of the *cis*-Trimethoxy-amine (*cis*-9a) [7,8,9-Trimethoxy-2,3-methylenedioxy-*cis*-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (*cis*-11)]——A mixture of 37% HCHO aq. (1 ml) and conc. HCl (0.2 ml) was added to a solution of the *cis*-amine (*cis*-**9a**) HCl salt[1b] (0.100 g) in aqueous EtOH [6 ml; EtOH–H_2O

(1 : 1, v/v)]. The mixture was refluxed for 2 h, diluted with water, and extracted with Et_2O. The aqueous solution was basified with 10% NaOH aq. and extracted with $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. Recrystallization of the residue from $CHCl_3$–cyclohexane gave slightly brown needles[16] (0.057 g), mp 170 °C. *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.10; H, 6.16; N, 3.66. IR ν_{max} cm^{-1}: 3400 (NH).

General Procedure for Dehydrogenation of the Cyclized Products with 30% Palladium–Charcoal in *p*-Cymene——A solution of the starting cyclized product in *p*-cymene containing 30% Pd–C was refluxed for several hours under a nitrogen stream. When the reaction was over, the reaction mixture was diluted with $CHCl_3$ and then the catalyst was removed by filtration. If required, the catalyst was washed with a hot mixed solution of $CHCl_3$ and MeOH. The filtrate (and washings) was evaporated to dryness *in vacuo*. Addition of hexane to the residue gave precipitates which were collected by filtration. If required, column chromatography or preparative TLC of the resulting product was carried out. Recrystallization of the crude material from a suitable solvent gave the desired product.

On the *trans*-Trimethoxy-2*H*-isoquinoline (*trans*-4a) [7,8,9-Trimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (The Trimethoxy-norbase) (5a)]——The *trans*-trimethoxy-2*H*-isoquinoline (*trans*-**4a**) (0.304 g), *p*-cymene (7.5 ml), and 30% Pd–C (0.10 g) were refluxed for 2 h. Colorless needles (0.262 g), mp 196—198 °C ($CHCl_3$–MeOH) (or benzene–hexane). *Anal.* Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.86. Found: C, 68.90; H, 4.70; N, 3.79. IR ν_{max} cm^{-1}: 1610, 1580 (C=N, C=C). ^{1}H-NMR δ: 3.99, 4.05, and 4.14 (each 3H, s, OCH_3), 6.08 (2H, s, OCH_2O), 7.17 (1H, s, C_1–H), 7.59 (1H, s, C_{10}–H), 7.71 (1H, d, J=8.0 Hz, C_{12}–H), 8.16 (1H, d, J=8.0 Hz, C_{11}–H), 8.70 (1H, s, C_4–H), 9.54 (1H, s, C_6–H).

On the *cis*-Trimethoxy-2*H*-isoquinoline (*cis*-4a) [The Trimethoxy-norbase (5a)]——The *cis*-trimethoxy-2*H*-isoquinoline (*cis*-**4a**) (0.102 g), *p*-cymene (2.5 ml), and 30% Pd–C (0.033 g) were refluxed for 2.5 h. Colorless needles (0.081 g), mp 195—197 °C ($CHCl_3$–MeOH) (or benzene–hexane). This material was identical with a sample of the above trimethoxy-norbase (**5a**).

On a Diastereomeric Mixture of the Trimethoxy-2*H*-isoquinoline (4a) [The Trimethoxy-norbase (5a)]——A diastereomeric mixture of the trimethoxy-2*H*-isoquinoline (**4a**) (0.500 g) [prepared from a Leuckart mixture[1b] of the trimethoxy-formamide (**2a**)], *p*-cymene (10 ml), and 30% Pd–C (0.100 g) were refluxed for 2 h. Colorless needles (0.370 g), mp 195—197 °C ($CHCl_3$–MeOH) (or benzene–hexane). This material was identical with a sample of the above trimethoxy-norbase (**5a**).

On the Trimethoxy-isoquinoline (8a) [The Trimethoxy-norbase (5a)]——The trimethoxy-isoquinoline (**8a**) (0.080 g), *p*-cymene (2.5 ml), and 30% Pd–C (0.026 g) were refluxed for 1 h. Colorless needles (0.065 g), mp 197—198 °C ($CHCl_3$–MeOH). This material was identical with a sample of the above trimethoxy-norbase (**5a**).

On the *trans*-Avicine-2*H*-isoquinoline (*trans*-4b) [2,3;8,9-Bismethylenedioxybenzo[*c*]phenanthridine (Noravicine) (5b)]——The *trans*-avicine-2*H*-isoquinoline (*trans*-**4b**) (0.101 g), *p*-cymene (15 ml), and 30% Pd–C (0.20 g) were refluxed for 2 h. The filtered catalyst was washed with $CHCl_3$–MeOH. Colorless needles (0.074 g), mp >300 °C ($CHCl_3$–benzene). *Anal.* Calcd for $C_{19}H_{11}NO_4$: C, 71.92; H, 3.49; N, 4.41. Found: C, 71.67; H, 3.47; N, 4.41. ^{1}H-NMR (CF_3CO_2H) δ: 6.19 and 6.35 (each 2H, s, OCH_2O), 7.37 (1H, s, C_1–H), 7.59 (1H, s, C_7–H), 7.93 (1H, s, C_{10}–H), 8.04 (1H, d, J=8.5 Hz, C_{12}–H), 8.08 (1H, s, C_4–H), 8.31 (1H, d, J=8.5 Hz, C_{11}–H), 9.14 (1H, d, J=8.0 Hz,[17] C_6–H).

On the *cis*-Avicine-2*H*-isoquinoline (*cis*-4b) [Noravicine (5b)]——The *cis*-avicine-2*H*-isoquinoline (*cis*-**4b**) (0.081 g), *p*-cymene (12 ml), and 30% Pd–C (0.16 g) were refluxed for 2 h. Colorless prisms (0.050 g), mp >300 °C ($CHCl_3$–benzene). This material was identical with a sample of noravicine (**5b**).

On a Diastereomeric Mixture of the Avicine-2*H*-isoquinoline (4b) [Noravicine (5b)]——A diastereomeric mixture of the avicine-2*H*-isoquinoline (**4b**) (0.100 g), *p*-cymene (15 ml), and 30% Pd–C (0.20 g) were refluxed for 2 h. Colorless prisms (0.064 g), mp >300 °C ($CHCl_3$–benzene). This material was identical with a sample of noravicine (**5b**).

On the Avicine-isoquinoline (8b) [Noravicine (5b)]——The avicine-isoquinoline (**8b**) (0.103 g), *p*-cymene (15 ml), and 30% Pd–C (0.20 g) were refluxed for 2 h. Colorless prisms (0.078 g), mp >300 °C ($CHCl_3$–benzene). This material was identical with a sample of noravicine (**5b**).

On the *cis*-Methoxy-bismethylenedioxy-2*H*-isoquinoline (*cis*-4c) [7-Methoxy-2,3;9,10-bismethylenedioxy-11,12-dihydrobenzo[*c*]phenanthridine (The Methoxy-bismethylenedioxy-isoquinoline) (8c)]——The *cis*-methoxy-bismethylenedioxy-2*H*-isoquinoline (*cis*-**4c**) (0.100 g), *p*-cymene (2.0 ml), and 30% Pd–C (0.020 g) were refluxed for 2 h. Slightly red needles[18] (0.075 g), mp 299—302 °C (softened at 285 °C) (benzene). *Anal.* Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found: C, 68.94; H, 4.25; N, 3.85. IR ν_{max} cm^{-1}: 1636 (C=N). UV λ_{max} nm (log ε): 211 (4.37), 230 (4.36), 240 (4.35), 250 (4.35), 297 (4.19), 323 (4.23), 370 (4.10), 384 (4.12). ^{1}H-NMR (CF_3CO_2H) δ: 3.02 (2H, t, J=8.0 Hz, C_{12}–H_2), 3.62 (2H, t, J=8.0 Hz, C_{11}–H_2), 4.17 (3H, s, OCH_3), 6.05 and 6.32 (each 2H, s, OCH_2O), 6.92, 6.98, and 7.32 (each 1H, s, arom. H), 9.24[17] (1H, d, J=8.0 Hz, C_6–H).

General Procedure for Dehydrogenation of the Cyclized Trimethoxy-Products with DDQ in Benzene——A solution of the cyclized product [the *trans*-trimethoxy-2*H*-isoquinoline (*trans*-**4a**), the *cis*-trimethoxy-2*H*-isoquinoline (*cis*-**4a**), or the trimethoxy-isoquinoline (**8a**)] and DDQ in abs. benzene was refluxed for several hours under Ar. The resulting precipitates were collected by filtration. The precipitates were added to 10% NaOH aq. and extracted with

$CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to dryness *in vacuo*. The ratio of products [the starting material, the trimethoxy-isoquinoline (**8a**), and/or the trimethoxy-norbase (**5a**)] was estimated by ^{1}H-NMR measurement of the crude reaction mixture.

On the *trans*-Trimethoxy-2*H*-isoquinoline (*trans*-4a)——The *trans*-trimethoxy-2*H*-isoquinoline (*trans*-**4a**) (0.231 g), DDQ (0.302 g), and abs. benzene (6.5 ml) were refluxed for 2 h. The ratio of the starting material (*trans*-**4a**), the trimethoxy-isoquinoline (**8a**), and the trimethoxy-norbase (**5a**) in the reaction mixture (0.202 g) was 2 : 9 : 2.

On the *cis*-Trimethoxy-2*H*-isoquinoline (*cis*-4a)——The *cis*-trimethoxy-2*H*-isoquinoline (*cis*-**4a**) (0.237 g), DDQ (0.307 g), and abs. benzene (6.0 ml) were refluxed for 2 h. The ratio of the starting material (*cis*-**4a**), the trimethoxy-isoquinoline (**8a**), and the trimethoxy-norbase (**5a**) in the reaction mixture (0.216 g) was 2 : 2 : 7.

On the Trimethoxy-isoquinoline (8a)——The trimethoxy-isoquinoline (**8a**) (0.101 g), DDQ (0.069 g), and abs. benzene (3 ml) were refluxed for 2 h. The ratio of the starting trimethoxy-isoquinoline (**8a**) and the trimethoxy-norbase (**5a**) in the reaction mixture (0.090 g) was 1 : 1.

General Procedure for Dehydrogenation of the Cyclized Products with DDQ in Benzene in the Presence of 5% Sodium Hydroxide Aqueous Solution——A solution of DDQ in benzene was added portionwise to a stirred solution of the starting cyclized compound in benzene in the presence of 5% NaOH aq. at room temperature over several hours. After being stirred for a further period, the reaction mixture was diluted with benzene. The benzene layer was separated and the aqueous layer was extracted with benzene or $CHCl_3$, if required. The organic layer was washed with 5% NaOH aq., dried over K_2CO_3, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on SiO_2 followed by recrystallization from a suitable solvent, or the ratio of starting material and products was determined by ^{1}H-NMR spectroscopy.

On the *trans*-Trimethoxy-2*H*-isoquinoline (*trans*-4a) [The Trimethoxy-isoquinoline (8a)]——DDQ (0.412 g) in benzene (18 ml) was added over a period of 2 h to the *trans*-trimethoxy-2*H*-isoquinoline (*trans*-**4a**) (0.203 g) in benzene (20 ml) and 5% NaOH aq. (5.4 ml). Stirring was continued for a further 0.5 h. The crude reaction mixture was chromatographed on SiO_2 with benzene–AcOEt (10 : 1, v/v). The first eluate gave colorless prisms (0.147 g), mp 158.5—161.5 °C (EtOH). This material was identical with the sample of the trimethoxy-isoquinoline (**8a**) obtained as an air-oxidation product in the Bischler–Napieralski reaction of the *cis*-trimethoxy-formamide (*cis*-**2a**).

The second eluate (more polar fraction) gave a mixture (0.030 g) of the starting material (*trans*-**4a**) and the trimethoxy-isoquinoline (**8a**).

On the *cis*-Trimethoxy-2*H*-isoquinoline (*cis*-4a)——DDQ (0.615 g) in benzene (26.3 ml) was added over a period of 6 h to the *cis*-trimethoxy-2*H*-isoquinoline (*cis*-**4a**) (0.301 g) in benzene (30 ml) and 5% NaOH aq. (8.1 ml). The crude reaction mixture was chromatographed on SiO_2 with benzene–AcOEt (30 : 1, v/v). The first eluate gave colorless prisms (0.102 g), mp 156—159.5 °C (EtOH). This material was identical with the sample of the trimethoxy-isoquinoline (**8a**).

The second eluate with benzene–AcOEt (10 : 1, v/v) gave colorless prisms (0.140 g), mp 119.5—121.5 °C (benzene–hexane). This material was identical with the starting material (*cis*-**4a**).

On an Equimolar Mixture of the *cis*- (*cis*-4a) and the *trans*-(*trans*-4a) Trimethoxy-2*H*-isoquinoline—DDQ (0.187 g) in benzene (8.0 ml) was added over a period of 0.5 h to a mixture of the *cis*- and the *trans*-trimethoxy-2*H*-isoquinoline [*cis*-**4a** (0.151 g) and *trans*-**4a** (0.151 g)] in benzene (30 ml) and 5% NaOH aq. (8.2 ml). The stirring was continued for a further 1 h. The reaction mixture was chromatographed on SiO_2 with benzene–AcOEt (30 : 1, v/v). The first eluate gave colorless prisms (0.146 g), mp 156—159 °C (EtOH). This material was identical with a sample of the trimethoxy-isoquinoline (**8a**).

The second eluate with benzene–AcOEt (1 : 1, v/v) gave colorless prisms (0.110 g), mp 118—121 °C (benzene–hexane). This material was identical with the starting *cis*-trimethoxy-2*H*-isoquinoline (*cis*-**4a**).

On the Trimethoxy-isoquinoline (8a)——DDQ (0.212 g) in benzene (9 ml) was added over a period of 2.5 h to the trimethoxy-isoquinoline (**8a**) (0.104 g) in benzene (10 ml) and 5% NaOH aq. (3 ml). Stirring was continued for a further 0.5 h. The ratio of the starting trimethoxy-isoquinoline (**8a**) and the trimethoxy-norbase (**5a**) in the reaction mixture (0.105 g) was 1 : 1.

On the *trans*-Avicine-2*H*-isoquinoline (*trans*-4b) [2,3;8,9-Bismethylenedioxy-11,12-dihydrobenzo[*c*]phenanthridine (The Avicine-isoquinoline) (8b)]——DDQ (0.200 g) in benzene (8.2 ml) was added over a period of 80 min to the *trans*-avicine-2*H*-isoquinoline (*trans*-**4b**) (0.070 g) in benzene (12 ml) and 5% NaOH aq. (2.1 ml). Stirring was continued for a further 40 min. Colorless needles (0.054 g), mp > 300 °C ($CHCl_3$). *Anal.* Calcd for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found: C, 71.28; H, 4.10; N, 4.33. ^{1}H-NMR (CF_3CO_2H) δ: 2.98—3.25 (2H, m, C_{12}–H_2), 3.25—3.50 (2H, m, C_{11}–H_2), 6.06 and 6.29 (each 2H, s, OCH_2O), 6.94 (1H, s, C_1–H), 7.34 (1H, s, C_7–H), 7.42 (1H, s, C_{10}–H), 7.54 (1H, s, C_4–H), 8.84 (1H, d, J = 8.0 Hz,[17] C_6–H). MS *m/z*: 319 (M^+, base peak).

On the *cis*-Avicine-2*H*-isoquinoline (*cis*-4b)——DDQ (0.291 g) in benzene (12 ml) was added over a period of 80 min to the *cis*-avicine-2*H*-isoquinoline (*cis*-**4b**) (0.101 g) in benzene (17 ml) and 5% NaOH aq. (3.0 ml). Stirring was continued for a further 65 min. The ratio of the starting material (*cis*-**4b**), the avicine-isoquinoline (**8b**), and noravicine (**5b**) in the reaction mixture (0.096 g) was 5 : 5 : 1.

On the Avicine-isoquinoline (8b)——DDQ (0.289 g) in benzene (5 ml) was added over period of 80 min to the avicine-isoquinoline (**8b**) (0.102 g) in benzene (180 ml) and 5% NaOH aq. (3 ml). Stirring was continued for a further

2 h. The ratio of the starting avicine-isoquinoline (**8b**) and noravicine (**5b**) in the reaction mixture (0.101 g) was 7 : 2.

References and Notes

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13) The crystal form changed from prisms to needles at 230—235°C.
14) The crystal form changed from prisms to needles at 160°C.
15) These signals were practically observed as a pair of two 1H singlets rather than the expected AB quartet. This may be caused by the fact that the chemical shifts of these two protons are close to each other.
16) This material was not sufficiently soluble in various solvents for measurement of the ^{1}H-NMR spectrum to be possible.
17) This coupling was observed as a vicinal coupling between C_6-H and NH which was formed by protonation of the nitrogen atom in this compound with CF_3CO_2H.
18) The crystals melted at 218—223°C and gave plates, mp 299—302°C (softened at 285 °C).