[Chem. Pharm. Bull. 26(3) 864—873 (1978)]

UDC 547.943.057 : 547.836.3.04 : 581.192

Chelirubine[1]

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(Received August 9, 1977)

The structure of chelirubine (**1c**), one of the fully aromatized O_5-benzo[*c*]phenanthridine alkaloids, was unequivocally established by total synthesis using photocyclization of the enamide (**27**).

On this basis, the formulae (**36**), (**37**), and (**38**) were proposed for chelilutine, sanguirubine, and sanguilutine, respectively.

Keywords——chelirubine; structural establishment; photocyclization of enamide; other O_5-benzo[*c*]phenanthridine alkaloids; Schiff base

The natural occurrence of several fully aromatized O_5-benzo[*c*]phenanthridine alkaloids[3] in *Papaveraceous* plants is well known. Among them, chelirubine,[4] Base B isolated from *Macleaya cordata* (Willd.) R. Br. (*Bocconia cordata* Willd.),[5] and bocconine[6] were recognized as alkaloids having two methylenedioxy and one methoxy groups in their molecules. Although these three alkaloids were later proved to be identical,[6,7] two different names[8] [chelirubine and bocconine] and three tentative formulae (Ia, b, and c) have been proposed by Slavík,[9] Onda[10] and ourselves (H. I.).[11] In a preliminary communication,[12] we showed the validity of our formula (**1c**) for chelirubine by total synthesis using an enamide photocyclization. In this paper, we wish to give a full detail of the reason for our structural proposal and to show the experiments which have rigidly established its structure.

In 1955, Slavík *et al.*[4] isolated several fully aromatized benzo[*c*]phenanthridine alkaloids having five oxygen functions from *Chelidonium majus* L., and designated an alkaloid having two methylenedioxy and one methoxy groups as chelirubine. Then, in 1968, they[9] proposed

1) This forms Part XXXVII of "Studies on the Chemical Constituents of *Rutaceous* Plants" by H. Ishii and Part XII of "Photocyclization of Enamides" by I. Ninomiya. Part XXXVI (H. I.); H. Ishii, T. Ishikawa, and Y.-I. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **26**, 514 (1978). Part XI (I. N.); I. Ninomiya, A. Shinohara, T. Kiguchi, and T. Naito, *J.Chem.Soc. Perkin I*, **1976**, 1868.

2) Location: *a*) *1-33, Yayoi-cho, Chiba, 280, Japan*; *b*) *Motoyamakita, Higashinada, Kobe,* 658, *Japan*; *c*) The author to whom correspondence should be addressed.

3) F. Šantavý, "The Alkaloids," ed. by R.H. Manske, Academic Press, New York·London, 1970, Vol. 12, p. 333.

4) *a*) J. Slavík and L. Slavíková, *Coll. Czech. Chem. Commun.*, **20**, 21 (1955); J. Slavík, *ibid.*, **20**, 198 (1955); *b*) J. Slavík and L. Slavíková, *ibid.*, **25**, 1667 (1960).

5) C. Tani and N. Takao, *Yakugaku Zasshi*, **82**, 755 (1962).

6) M. Onda, K. Takiguchi, M. Hirakura, H. Fukushima, M. Akagawa, and F. Naoi, *Nippon Nogeikagaku Kaishi*, **39**, 168 (1965).

7) J. Slavík and F. Šantavý, *Coll. Czech. Chem. Commun.*, **37**, 2804 (1972).

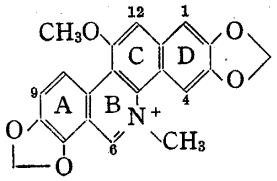
8) Since we recognize that the name "chelirubine" has a priority over "bocconine," this alkaloid is referred to as chelirubine in spite of the description in the original paper.[6,10]

9) J. Slavík, L. Dolejš, V. Hanuš, and A.D. Cross, *Coll. Czech. Chem. Commun.*, **33**, 1619 (1968).

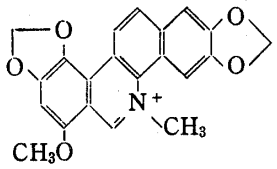
10) M. Onda, K. Abe, K. Yonezawa, N. Esumi, and T. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1435 (1970).

11) H. Ishii, T. Deushi, and K.-I. Harada, The 16th Symposium on the Chemistry of Natural Products, Osaka, Oct., 1972, Symposium Papers, p. 327.

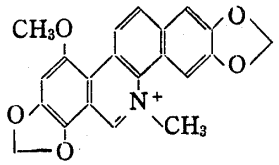
12) H. Ishii, K.-I. Harada, T. Ishida, E. Ueda, K. Nakajima, I. Ninomiya, T. Naito, and T. Kiguchi, *Tetrahedron Lett.*, **1975**, 319.



Slavík's formula **1a**



Onda's formula **1b**



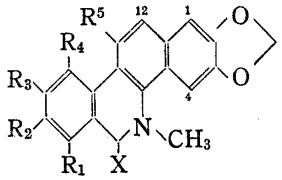
Ishii's formula **1c**

Chart 1

the tentative structure (**1a**), which has a methoxy group at C_{11} (ring C), for chelirubine on the basis of the following consideration: i) the fifth oxygen function appeared at the C_{11} position in the case of the known *Papaveraceous* benzo[*c*]phenanthridine alkaloids bearing a partially hydrogenated skeleton. This phenomenon has been clearly explained by biosynthetic experiments [for example chelidonine[3] (**2**)]; ii) in the nuclear magnetic resonance (NMR) spectrum of chelirubine, the signals due to aromatic protons would be assignable by supposing the formula (**1a**) as shown in Table I.

On the other hand, in 1962, Tani and Takao[5] reported the isolation of a fully aromatized O_5-benzo[*c*]phenanthridine alkaloid from *M. cordata* and tentatively called it Base B. Then,

Table I. Assignments of the Reported Data[9,10] of NMR Signals due to the Aromatic Protons of Sanguinarine and Chelirubine Derivatives



3: $R_1+R_2=OCH_2O$; $R_3=R_4=R_5=H$
4: $R_1+R_2=OCH_2O$; $R_3=R_4=H$; $R_5=OCH_3$
5: $R_1=OCH_3$; $R_2=R_5=H$; $R_3+R_4=OCH_2O$
6: $R_1+R_2=OCH_2O$; $R_3=R_5=H$; $R_4=OCH_3$

	X	Sanguinarine (**3**) derivatives	Chelirubine derivatives		
			by Slavík's formula (**4**)	by Onda's formula (**5**)	by Ishii's formula (**6**)
C_8-H	H			6.59(s)	
	CN			7.05(s)	
C_9-H	H	6.80 (d, J=8.6 Hz)	7.47 (d, J=9 Hz)		6.59(s)
	CN	7.14 (d, J=8 Hz)	7.64 (d, J=8 Hz)		7.05(s)
C_{10}-H	H	7.26 (d, J=8.6 Hz)	8.35 (d, J=9 Hz)		
	CN	7.58 (d, J=8 Hz)	8.33 (d, J=8 Hz)		
C_{11}-H	H	7.65 (d, J=8.6 Hz)		8.35 (d, J=9 Hz)	8.35 (d, J=9 Hz)
	CN	7.92 (d, J=9 Hz)		8.33 (d, J=8 Hz)	8.33 (d, J=8 Hz)
C_{12}-H	H	7.43 (d, J=8.6 Hz)	6.59(s)	7.47 (d, J=9 Hz)	7.47 (d, J=9 Hz)
	CN	7.68 (d, J=9 Hz)	7.05(s)	7.63 (d, J=8 Hz)	7.63 (d, J=8 Hz)
C_1-H	H	7.06(s)		7.11(s)	
	CN	7.39(s)		7.34(s)	
C_4-H	H	7.65(s)		7.72(s)	
	CN	7.58(s)		7.57(s)	

in 1965, Onda, *et al.*[6] examined the nematocidal principle of *M. cordata* and obtained an alkaloid which was identified with Takao's Base B and designated it bocconine. In 1970, Onda *et al.*[10] discussed the NMR spectra of bocconine derivatives in detail and proposed their formula (**1b**) for bocconine.

In the course of studies on the structural establishment of bocconoline[13] (**7**), we (H. I.) had a chance to analyse the NMR spectra of various types of benzo[*c*]phenanthridine alkaloids and their derivatives, and successfully assigned them. When we attempted to apply these assignments to the reported data of the NMR spectra of chelirubine and its derivatives, doubts were raised as to the validity of the previous proposals (**1a** and **1b**) for the structure of chelirubine. We came to the conclusion that the formula of chelirubine should be revised to a new one (**1c**) for the following reasons. Since all of the known benzo[*c*]phenanthridine alkaloids occurring in *Papaveraceous* plants carry their oxygen functions at C_2, C_3, C_7, and C_8 without exception, it seems reasonable to assume that four of the five oxygen functions in chelirubine would be at these positions. In this respect, we believe that Slavík's deduction is absolutely correct. However, when the NMR spectra of chelirubine derivatives were compared to that of the corresponding derivatives of sanguinarine (3), the down-field shift of the signal due to the C_9-proton remained unexplained (Table I).

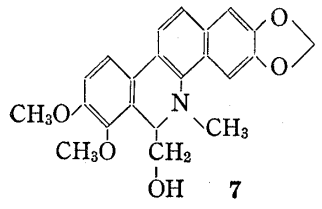


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Chart 2

On the other hand, in the last stages of the structural establishment of bocconine, Onda *et al.* were obliged to distinguish between the formulae (**1b**) and (**1c**), and adopted the former (**1b**) on the basis of the absence of a nuclear Overhauser effect (NOE) between the C_{11}-proton and the methoxy group in the NMR pectrum of dihydrobocconine. However, we would like to stress the importance of a statistical survey of the biogenetic pattern of the oxygen functions in the structural establishment of natural products. The result obtained on the NOE experiment by Onda could be accounted for by supposing that the methyl group of the methoxy group is located at the opposite side to the ring C in the preferred conformation of **1c**. Furthermore, the formula (**1c**) explains other variations of the chemical shift in the NMR spectra of chelirubine compared to the corresponding spectra of sanguinarine derivatives, as follows. The up-fields shift of the signal due to the C_9-proton of chelirubine derivative can be explained by the presence of the C_{10}-methoxy group, and the down-field shift of the C_{11}-proton by an anisotropic effect of the C_{10}-methoxy group. These considerations led us to propose the formula (**1c**) for chelirubine.

As a chemical proof to this proposal, the synthesis of chelirubine was undertaken. The initial plan was to synthesize the compound depicted by the formula (**1c**) using Robinson's synthetic sequence[14] but we[15] found that cyclization (Bischler-Napieralski reaction) of the key intermediate, the partially hydrogenated formamide (**8**), did not take place. In the second stage of our studies, we aimed at synthesizing the compound having the formula (**1b**) by photocyclization of the enamide[16]. During this experiment, however, photocyclization

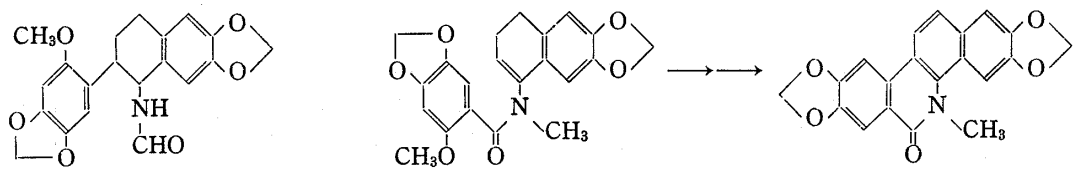
13) H. Ishii, K. Hosoya, and N. Takao, *Tetrahedron Lett.*, **1971**, 2429.

14) T. Richardson, R. Robinson, and E. Seijo, *J. Chem. Soc.*, **1927**, 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. Nagarakan, 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; K.W. Gopinath, T.R. Govindachari, and N. Viswanathan, *Tetrahedron*, **14**, 322 (1961); T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocyclic Chem.*, **10**, 31 (1973); K.Y. Zee-Cheng and C.C. Cheng, *ibid.*, **10**, 85, 867 (1973).

15) H. Ishii, T. Deushi, M. Sakamoto, T. Ishida, and K.-I. Harada, *Chem. Pharm. Bull.* (Tokyo), in preparation.

16) I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *J.Chem.Soc. Perkin I*, **1973**, 1696; I. Ninomiya, T. Kiguchi, and T. Naito, *J.Chem.Soc. Chem. Commun.*, **1974**, 81.

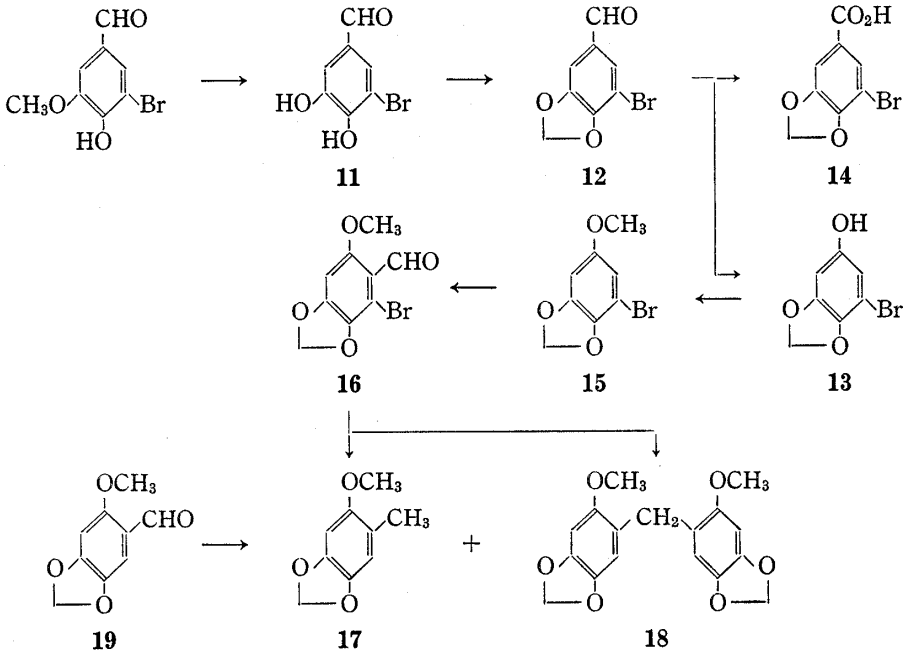
of an enamide having a methoxy group at an *ortho*-position has been shown to take place regiospecifically at the "root" of the *ortho*-methoxy group. For example, the enamide (**9**) provided oxyavicine (**10**). This fact means that we[17] could establish a useful procedure for the synthesis of the oxo derivatives of naturally occurring O_4-benzo[*c*]phenanthridine alkaloids in *Rutaceous* plants. We decided to apply this method to synthesis of the compound having the formula (**1c**). For this purpose, 2,3-dimethoxy-5,6-methylenedioxybenzoic acid (**24**) was required.



8 **9** **10**

Chart 3

The starting 5-bromoprotocatechualdehyde (**11**) was obtained from 5-bromovanillin[18] quantitatively by applying the method which Lange[19] reported for the cleavage of various alkyl *o*-hydroxyphenyl ethers. This bromoaldehyde (**11**) was treated with methylene iodide in dimethylsulfoxide (DMSO) in the presence of anhydrous potassium carbonate to give 5-bromopiperonal (**12**) in 68.8% yield. The Baeyer-Villiger oxidation of 5-bromopiperonal (**12**) with performic acid gave 5-bromosesamol (**13**), mp 102—104°, in 78.8% yield, accompanied by a small amount (0.6%) of 5-bromopiperonylic acid (**14**). Methylation of 5-bromosesamol (**13**) in the usual way gave 1-bromo-5-methoxy-2,3-methylenedioxybenzene (**15**), mp 49—51°, in 96.5% yield. Treatment of this methoxybenzene (**15**) with phosphorus oxychloride and dimethylformamide (DMF) gave 2-bromo-6-methoxy-3,4-methylenedioxybenzaldehyde (**16**), mp 208—209°, as the sole product in 91.5% yield. In order to establish the location of the inserted aldehyde group, debromination of the bromide (**16**) was attempted.



11 **12** **14** **16** **15** **13** **19** **17** **18**

Chart 4

17) I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Ueda, and K.-I. Harada, *J.Chem.Soc. Perkin I*, 1975, 762.
18) H.W. Dorn, W.H. Warren, and J.L. Bullock, *J. Am. Chem. Soc.*, **61**, 144 (1939).
19) R.G. Lange, *J. Org. Chem.*, **27**, 2037 (1962).

Catalytic hydrogenation of the bromoaldehyde (**16**) in acetic acid on 22% palladium-carbon in the presence of sodium acetate gave a mixture of 2-methoxy-4,5-methylenedioxy-toluene (**17**), mp 49—50°, and an unexpected compound (**18**), mp 138—140°, in 34.3 and 33.8% yields, respectively. The latter (**18**) gave elemental analysis in agreement with the molecular formula $C_{17}H_{16}O_6$ and showed a parent peak at *m/e* 316 as a base peak in the mass spectrum. In the NMR spectrum, it showed two methoxy and one methylene signal, attributable to that of the methylene of diphenylmethane, and two methylenedioxy groups. The signals due to aromatic protons appeared at 6.46 and 6.51 δ, each as 2H singlets. This evidence indicates that it could be bis(2-methoxy-4,5-methylenedioxyphenyl)methane (**18**). Formation of this dimeric product (**18**) could be explained by assuming the pathway in Chart 5. A similar product[20] was obtained in the catalytic reduction of 4-formyl-2-methylisocarbostyril. On the other hand, the same treatment of the known 2-methoxy-4,5-methylenedioxy-benzaldehyde[21] (**19**) gave a mixture of the same products [**17** and **18**] that was obtained in the case of the bromoaldehyde (**16**). This chemical evidence shows clearly that formylation of 1-bromo-5-methoxy-2,3-methylenedioxybenzene (**15**) took place at the C_6 position to give 2-bromo-6-methoxy-3,4-methylenedioxybenzaldehyde (**16**).

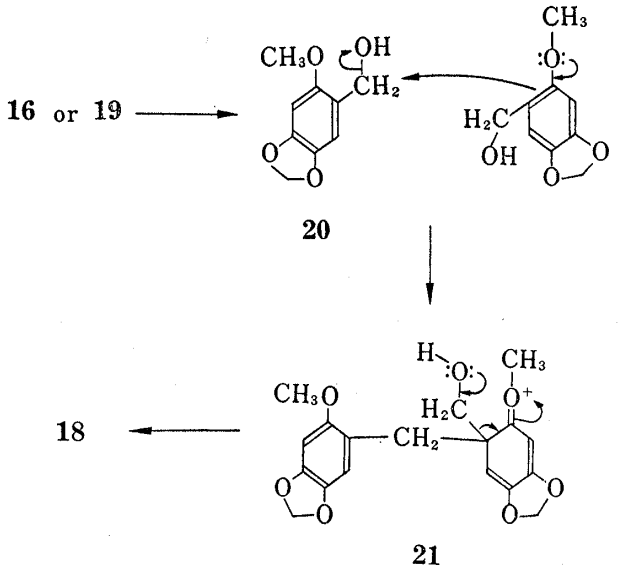


Chart 5

The Baeyer-Villiger oxidation of the aldehyde (**16**) with performic acid afforded 2-bromo-6-methoxy-3,4-methylenedioxyphenol (**22**), mp 128—129°, in 72.9% yield, which was converted to 1-bromo-2,3-dimethoxy-5,6-methylenedioxybenzene (**23**), mp 78—79°, by methylation with diazomethane in 97.9% yield or with dimethyl sulfate and 50% sodium hydroxide solution in methanol in 96.3% yield. Metalation of this bromide (**23**) with ethyl lithium followed by treatment with dry ice gave the desired 2,3-dimethoxy-5,6-methylenedioxybenzoic acid (**24**), mp 186—188°, in 93.2% yield.

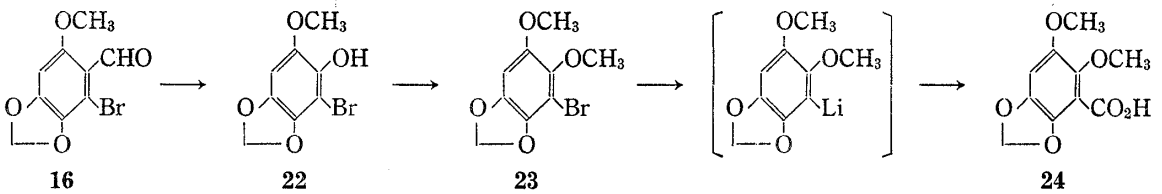


Chart 6

Treatment of the acid (**24**) with thionyl chloride gave the corresponding acid chloride (**25**), mp 66—68°, almost quantitatively, which was suitable for the following process without purification. N-Methyl-6,7-methylenedioxy-1-tetralonimine[17] (**26**) was acylated with the acid chloride (**25**) in the presence of triethylamine to give N-(3,4-dihydro-6,7-methylenedioxy-1-naphthyl)-2,3-dimethoxy-N-methyl-5,6-methylenedioxybenzamide (**27**), mp 120—123°, in

20) D.E. Horning, G. Lacasse, and J.M. Muchowski, *Can. J. Chem.*, **49**, 2785 (1971).
21) K. Fukui and M. Nakayama, *Nippon Kagaku Zasshi*, **84**, 606 (1963).

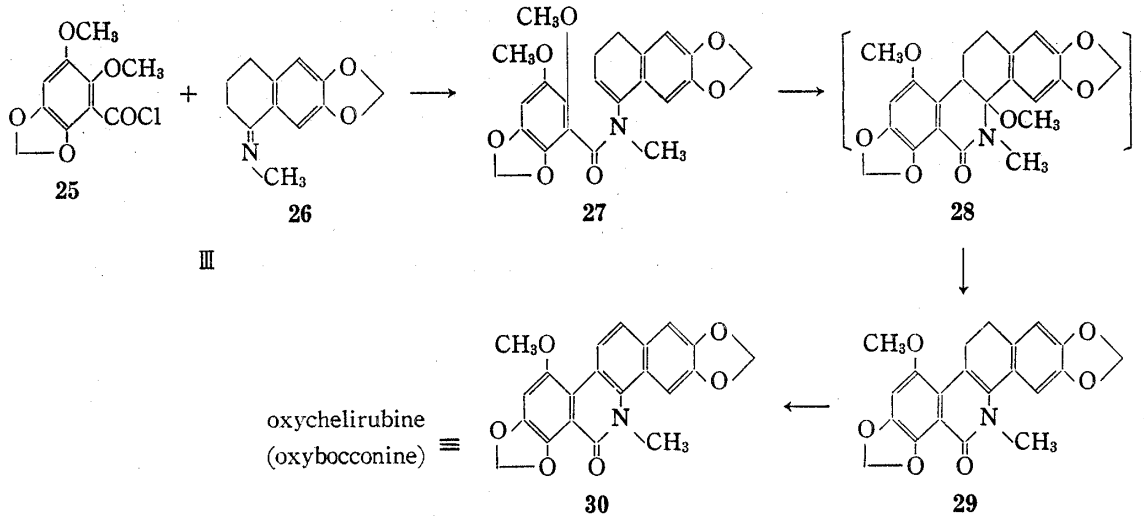


Chart 7

76.3% yield. Irradiation of a methanolic 0.005 M-solution of the enamide (**27**) with a low pressure mercury lamp for 5.5 hr afforded a labile photocyclized product (**28**), which was refluxed with a small amount of concentrated hydrochloric acid for 5 min to give 11,12-dihydro-5-methyl-2,3; 7,8-bismethylenedioxybenzo[*c*]phenanthridine-6(5H)-one (**29**), mp 253—256°, in 38.2% yield from the starting enamide (**27**). Dehydrogenation of the lactam (**29**) with 30% palladium-carbon in *p*-cymene gave 10-methoxy-5-methyl-2,3;7,8-bismethylenedioxybenzo[*c*]phenanthridin-6(5H)-one (**30**), mp 307—308° (lit.[10] mp 295—296°), in 70.4% yield. This fully aromatized lactam (**30**) was compeltely identical with an authentic sample of oxychelirubine (oxybocconine), kindly donated by Prof. Onda. This evidence indicates that chelirubine should be depicted by the formula (**1c**).

Reduction of oxychelirubine (**30**) with Vitride [a 70% benzene solution of sodium dihydrobis(2-methoxyethoxy) aluminate: $NaAlH_2$ $(OCH_2CH_2OCH_3)_2$] in xylene gave dihydrochelirubine (**31**), mp 205—207° (lit.[5] mp 201—202°; lit.[10] mp 206—207°), in 78.7% yield. Dehydrogenation of dihydrochelirubine (**31**) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) followed by treatment with concentrated hydrochloric acid afforded chelirubine (**1c**) chloride, as reddish-purple needles, mp 299—302° (dec.) (lit.[4b] mp 282—283°). This base was also characterized as the *ψ*-cyanide (**32**), mp 243—247° (lit.[4b] mp 273—274°).

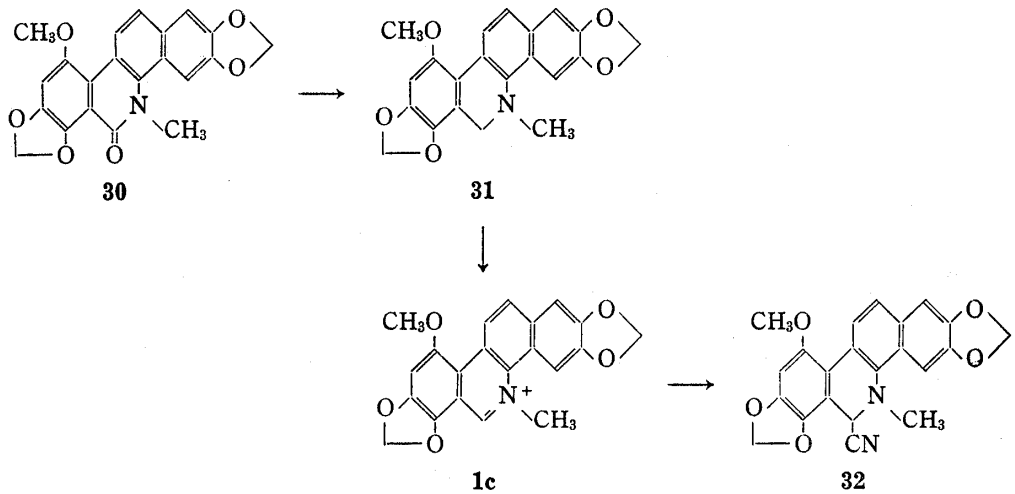
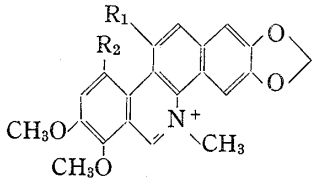
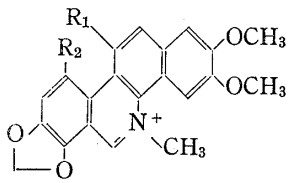


Chart 8

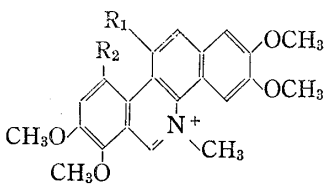
Finally, in connection with this study, we (H. I.) would like to propose the revised formulae (**33**), (**34**), and (**35**) for the structures of chelilutine, sanguirubine, and sanguilutine, respectively, for which Slavík[9] previously proposed the formulae (**36**), (**37**), and (**38**). It should be noted here that the positions of the methylenedioxy and the two methoxy groups at C_2, C_3, C_8, and C_9 in the formulae originally proposed for chelilutine (**33**) and sanguirubine (**34**) were assigned[9] arbitrarily, since the reported data for their NMR spectra gave no decisive answer on this matter. The work on structural establishment of these alkaloids by total synthesis is almost complete in our laboratory (H. I.) and will be reported in the near further.



33: R_1=H, R_2=OCH_3
36: R_1=OCH_3, R_2=H



34: R_1=H, R_2=OCH_3
37: R_1=OCH_3, R_2=H



35: R_1=H, R_2=OCH_3
38: R_1=OCH_3, R_2=H

Chart 9

Experimental[22]

5-Bromopiperonal (**12**)——A mixed solution of bromoprotocatechualdehyde[23] (**11**) (20.0 g; mp 225—230°), CH_2I_2 (49.7 g), and anhydrous K_2CO_3 (35.5 g) in DMSO (61.5 ml) was heated at 60° for 32 hr in a nitrogen stream, and poured into a large quantity of water. The precipitate was filtered off and purified by column chromatography on Al_2O_3 (Brockmann) using $CHCl_3$ as solvent to give colourless needles (14.5 g), mp 124—126° (lit.[24] mp 120°; lit.[25] mp 124—125°).

5-Bromosesamol (**13**)——To 85% HCOOH (80 ml) was added 35% H_2O_2 (24 g) under ice cooling. The mixture was stirred at room temperature for 1 hr. A solution of 5-bromopiperonal (**12**) (35.32 g) in 98% HCOOH (740 ml) was added to the solution of performic acid below 10° and stirred at 0° for 4 hr. After decomposition of the excess peracid by addition of Na_2SO_3 (35 g), the reaction mixture was poured into ice-water and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ aq., added to 5% NaOH aq. (500 ml) with vigorous stirring and stirred at room temperature for 30 min. The aqueous layer was made acidic with 10% HCl aq. and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. Recrystallization of the residue from benzene–hexane gave colourless needles (26.4 g), mp 102—104°. *Anal.* Calcd. for $C_7H_5BrO_3$: C, 38.74; H, 2.33. Found: C, 38.56; H, 2.31. IR ν_{max}^{Nujol} cm^{-1}: 3190 (OH), 937 (OCH_2O), C=O (nil). NMR ($CDCl_3$) δ: 4.72 (1H, s, OH), 5.97 (2H, s, OCH_2O), 6.34 (1H, d, J=2.5 Hz, arom. H), 6.41 (1H, d, J=2.5 Hz, arom. H). MS *m/e*: 218 (M^++2, 95.4%), 216 (M^+, base peak).

Acidification of the saturated $NaHCO_3$ solution gave 5-bromopiperonylic acid (**14**) (0.28 g), mp 250—252° (lit.[24] mp 253°).

1-Bromo-5-methoxy-2,3-methylenedioxybenzene (**15**)——To a solution of 5-bromosesamol (**13**) (6.00 g) in MeOH (16 ml) containing dimethyl sulfate (3.15 ml) was added 2 N NaOH aq. (52 ml) at room temperature. The mixture was kept at room temperature and addition of the same amounts of dimethyl sulfate and 2 N NaOH aq. was repeated three more times, monitoring by TLC. Finally, after further addition of 2 N NaOH aq. (50 ml), the mixture was refluxed for 30 min, cooled and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. Distillation of the residue at 109° (1.5 mmHg) gave an oily substance (6.17 g) which crystallized when kept in a refrigerator. Recrystallization of a portion

22) All melting points were measured on a micro-melting hot-stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were obtained with Hitachi EPI-G3 spectrometer. NMR spectra were obtained with JEOL JNM-MH-100 using tetramethylsilane as internal reference and the abbreviations of singlet, doublet, triplet, and multiplet are represented as s, d, t, and m, respectively. Mass spectra were measured with a Hitachi RMU-6E spectrometer at 70 eV chamber voltage on direct inlet system. For thin-layer chromatography (TLC) and preparative TLC, Kieselgel GF_{254} nach Stahl (Merck) was used. For column chromatography, Silicic acid, 100 mesh, Mallinckrodt Chemical Works was used.

23) Application of Lange's method[19] to the 5-bromovanillin gave this material (**11**) in excellent yield.

24) H. Kondo, H. Kataoka, G. Ito, K. Nakagawa, and M. Ikechi, *Itsuu Kenkyusho Nempo*, **1**, 54 (1950).

25) M. Erne and F. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950).

of the crystalline from hexane gave colourless needles, mp 49—51°. *Anal.* Calcd. for $C_8H_8BrO_3$: C, 41.59; H, 3.05. Found: C, 41.62; H, 2.99. NMR ($CDCl_3$) δ: 3.74 (3H, s, OCH_3), 5.97 (2H, s, OCH_2O), 6.39 (1H, d, J=2.0 Hz, arom. H), 6.44 (1H, d, J=2.0 Hz, arom. H). MS *m/e*: 232 (M^++2, 96.5%), 230 (M^+, base peak).

2-Bromo-6-methoxy-3,4-methylenedioxybenzaldehyde (16)——Phosphorus oxychloride (15 ml) was added over 1 hr to a solution of the methoxybenzene (**15**) (25.5 g) in dry DMF (25 ml) under ice cooling. After addition, the mixture was heated at 60° for 3 hr, poured into ice-water, made alkaline with 5% NaOH aq. and filtered. Recrystallization of the precipitate from EtOH or $CHCl_3$–hexane gave colourless needles (26.2 g), mp 208—209°. *Anal.* Calcd. for $C_9H_7BrO_4$: C, 41.72; H, 2.72. Found: C, 41.76; H, 2.65. IR ν_{max}^{Nujol} cm^{-1}: 1673 (CHO), 940 (OCH_2O). NMR ($CDCl_3$) δ: 3.90 (3H, s, OCH_3), 6.08 (2H, s, OCH_2O), 6.54 (1H, s, arom. H), 10.28 (1H, s, CHO). MS *m/e*: 260 (M^++2, 100%), 258 (M^+, base peak).

Catalytic Reduction of 2-Bromo-6-methoxy-3,4-methylenedioxybenzaldehyde (16)——A solution of the benzaldehyde (**16**) (300 mg) in AcOH (14.25 ml) containing AcONa (142.5 mg) was hydrogenated over 22% Pd–C prepared from 60 mg of $PdCl_2$ and 210 mg of Norit at atmospheric pressure and room temperature until absorption of hydrogen had ceased. After the catalyst had been removed by filtration, the filtrate was diluted with a large quantity of water and extracted with ether. The ethereal solution was washed with 2% $NaHCO_3$ aq., dried over anhydrous K_2CO_3 and evaporated to give a mixture showing two spots on TLC (benzene). The mixture was separated into each component by preparative TLC using benzene as solvent.

a) **2-Methoxy-4,5-methylenedioxytoluene (17)**——Recrystallization of the compound showing the upper spot on TLC from EtOH–H_2O gave colourless needles (66 mg), mp 49—50°. *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.76; H, 6.23. IR ν_{max}^{Nujol} cm^{-1}: 1630 (C=C), 940 (OCH_2O). NMR ($CDCl_3$) δ: 2.14 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 5.80 (2H, s, OCH_2O), 6.41 and 6.56 (each 1H, s, C_3 and C_6–H). MS *m/e*: 166 (M^+, 46.7%), 152 (base peak).

b) **Bis(2-methoxy-4,5-methylenedioxyphenyl)methane (18)**——Recrystallization of the compound showing the lower spot on TLC from $CHCl_3$–hexane gave colourless plates (62 mg), mp 138—140°. *Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.15; H, 4.99. IR ν_{max}^{Nujol} cm^{-1}: 1630, 1640 (C=C), 945, 925 (OCH_2O). NMR ($CDCl_3$) δ: 3.76 (8H, s, $OCH_3\times2$ and $\phi C\underline{H}_2\phi$),[26] 5.82 (4H, s, $OCH_2O\times2$), 6.46 and 6.51 (each 2H, s, arom. H). MS *m/e*: 316 (M^+, base peak).

Catalytic Reduction of 2-Methoxy-4,5-methylenedioxybenzaldehyde (19)——A solution of 2-methoxy-4,5-methylenedioxybenzaldehyde[21] (**19**) (208 mg) in AcOH (14.25 ml) containing AcONa (142.5 mg) was hydrogenated under the same conditions as described in the above experiment. The resulting mixture was treated according to the procedure described for the bromo-aldehyde (**16**) to give 2-methoxy-4,5-methylenedioxytoluene (**17**) (106 mg), mp 48—49°, and bis(2-methoxy-4,5-methylenedioxyphenyl)methane (**18**) (20 mg), mp 137—140°.

2-Bromo-6-methoxy-3,4-methylenedioxyphenol (22)——After addition of 35% H_2O_2 (5.7 g) to 85% HCOOH (19.4 ml) at 0°, the mixed solution was stirred at room temperature for 1 hr, and cooled again to 0°. A solution of 2-bromo-6-methoxy-3,4-methylenedioxybenzaldehyde (**16**) (7.7 g) in 98% HCOOH (310 ml) was gradually added to the cooled performic acid solution at 0—5° and then stirred at 0—5° for 5 hr. After decomposition of the excess peracid by addition of Na_2SO_3 (7.7 g), the reaction mixture was diluted with an equal volume of water and extracted with ether. The ethereal solution was washed with saturated NaCl aq. and then saturated $NaHCO_3$ aq. After addition of a 5% NaOH aq. to the ethereal solution, the two layers were vigorously stirred at room temperature for 1.5 hr. The ethereal solution was separated from the 5% NaOH aq. and washed with 5% NaOH aq. The original 5% NaOH aq. and washings were combined, made acidic with 17% HCl aq., and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to give colourless prisms (5.35 g), mp 128—129°, which were recrystallized from EtOH. *Anal.* Calcd. for $C_8H_7BrO_4$: C, 38.89; H, 2.86. Found: C, 39.03; H, 2.79. IR ν_{max}^{Nujol} cm^{-1}: 3410 (OH), 935 (OCH_2O). NMR ($CDCl_3$) δ: 3.81 (3H, s, OCH_3), 5.58 (1H, s, OH), 5.88 (2H, s, OCH_2O), 6.48 (1H, s, arom. H).

The ethereal solution separated from the 5% NaOH aq. was dried over anhydrous K_2CO_3 and evaporated to give unchanged starting aldehyde (**16**) (250 mg).

1-Bromo-2,3-dimethoxy-5,6-methylenedioxybenzene (23)——a) Using Diazomethane: A solution of CH_2N_2 (nitrosomethyl urea: 600 mg) in ether (5 ml) was added to a solution of the phenol (**22**) (164 mg) in MeOH (1 ml). The mixed solution was allowed to stand at room temperature for 30 min and evaporated to give colourless needles (175 mg), mp 78—79°, which were recrystallized from benzene–hexane. *Anal.* Calcd. for $C_9H_9BrO_4$: C, 41.51; H, 3.43. Found: C, 41.40; H, 3.47. IR ν_{max}^{Nujol} cm^{-1}: 935 (OCH_2O). NMR ($CDCl_3$) δ: 3.79 and 3.80 (each 3H, s, OCH_3), 5.93 (2H, s, OCH_2O), 6.49 (1H, s, arom. H).

b) Using Dimethyl Sulfate: To a solution of the phenol (**22**) (9.5 g) in MeOH (50 ml) containing dimethyl sulfate (16 ml) was added 50% NaOH aq. (10 ml). After the reaction mixture was heated under reflux for 1 hr, another 50% NaOH aq. (10 ml) was added. The mixture was allowed to stand at room temperature overnight, poured into a large quantity of water and extracted with ether. The ethereal solution

26) Addition of one drop of benzene-d_6 split this signal into 3.50 δ (6H, s, $OCH_3\times2$) and 3.86 δ (2H, s, $\phi C\underline{H}_2\phi$).

was washed with 5% NaOH aq., dried over anhydrous K_2CO_3 and evaporated. The residue (9.56 g), mp 78—79°, was identical with the sample prepared by treatment with CH_2N_2 and could be used for the following step without further purification.

2,3-Dimethoxy-5,6-methylenedioxybenzoic Acid (24)——To a stirred suspension of metal Li (9.75 g) in abs. ether (33 ml), a solution of EtBr (5.2 ml) in abs. ether (22 ml) was added dropwise at −20——−30° under argon. The mixture was stirred at the same temperature until all the Li was consumed. Then, a solution of the bromobenzene (23) (11.2 g) in abs. ether (65 ml) was added dropwise to the EtLi solution and stirred for further 15 min at −20——−30°. After an excess of dry ice was added, the reaction mixture was brought to room temperature. Then a suitable amount of water was added to the mixture. The separated ethereal solution was washed with water. The aqueous layer and washings were combined, made acidic with 17% HCl aq., and extracted with $CHCl_3$. The chloroform solution was dried over $MgSO_4$ and evaporated to give colourless needles (9.04 g), mp 186—188°, which were recrystallized from MeOH. *Anal.* Calcd. for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 52.93; H, 4.52. IR ν_{max}^{Nujol} cm^{-1}: 1738 (C=O), 924 (OCH_2O). NMR (DMSO-d_6) δ: 3.68 and 3.75 (each 3H, s, OCH_3), 5.95 (2H, s, OCH_2O), 6.88 (1H, s, arom. H).

2,3-Dimethoxy-5,6-methylenedioxybenzoyl Chloride (25)——A mixture of the benzoic acid (24) (4.4 g) and thionyl chloride (11.12 ml) was refluxed for 5 min and evaporated to dryness *in vacuo*. Recrystallization of a part of the residue from abs. hexane gave pale yellow rods, mp 66—68°. *Anal.* Calcd. for $C_{10}H_9ClO_5$: C, 49.10; H, 3.71. Found: C, 49.21; H, 3.67. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (COCl).

This material could be used for the following step without recrystallization.

N-(3,4-Dihydro-6,7-methylenedioxy-1-naphthyl)-2,3-dimethoxy-N-methyl-5,6-methylenedioxybenzamide (27)——Anhydrous methylamine gas was bubbled into a solution of 6,7-methylenedioxy-1-tetralone[17] (3 g) in dry $CHCl_3$ under ice-cooling. This mixed solution was added dropwise to a solution of $TiCl_4$ (3 ml) in dry $CHCl_3$ (35 ml). After stirring at room temperature for 30 min, the mixture was heated under reflux for 2 hr. The precipitate was filtered off and washed with $CHCl_3$. The filtrate and washings were combined and evaporated to dryness *in vacuo*. The residue [crude N-methyl-6,7-methylenedioxy-1-tetralonimine (26)] was dissolved in abs. benzene (51 ml) and filtered. After freshly distilled NEt_3 (19.8 ml) was added to the filtrate, a solution of the crude benzoyl chloride (25) [freshly prepared from 4.4 g of the benzoic acid (24)] in abs. benzene (4.5 ml) was added dropwise to the reaction mixture. The reaction mixture was then heated under reflux for 2.5 hr and evaporated to dryness *in vacuo*. A suitable amount of water and $CHCl_3$ was added to the residue and the mixture separated. The chloroform layer was washed with water, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on SiO_2. After discarding the benzene eluate, elution with benzene–AcOEt (10: 1) and with $CHCl_3$ gave colourless needles (4.95 g), mp 120—123°, which were recrystallized from $CHCl_3$–ether. *Anal.* Calcd. for $C_{22}H_{21}NO_7$: C, 64.22; H, 5.15; N, 3.40. Found: C, 64.18; H, 5.15; N, 3.38. IR ν_{max}^{Nujol} cm^{-1}: 1633 (C=O); $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630 (C=O). NMR[27] ($CDCl_3$) δ: 2.10 and 2.45 (each 2H, m, aliphatic H), 3.24 (3H, s, NCH_3), 3.76 and 3.85 (each 3H, diffused s, OCH_3), 5.34 (1H, m, olefinic H), 5.88 (4H, m, $OCH_2O \times 2$), 6.40, 6.54, and 6.80 (each 1H, s, arom. H).

11,12-Dihydro-10-methoxy-5-methyl-2,3;7,8-bismethylenedioxybenzo[*c*]phenanthridin-6(5H)-one (29)——A solution of the amide (27) (1.5 g) in abs. MeOH (700 ml) was irradiated with a low pressure mercury lamp in a nitrogen stream under ice-cooling until the starting material could no longer be observed on TLC (5.5 hr). The methanolic solution was evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ and chromatographed on Al_2O_3 [Woelm, acidic, grade II]. Elution with $CHCl_3$ gave a mixture[28] showing two spots on TLC [benzene–AcOEt (3: 2, v/v)] [*Rf*: 0.7 and 0.5]. The mixture was dissolved in MeOH (30 ml) containing one drop of conc. HCl and heated for 5 min to give a crystalline mass. After evaporation of MeOH under reduced pressure, the product was dissolved in $CHCl_3$. The chloroform solution was washed with 5% $NaHCO_3$ aq., dried over anhydrous K_2CO_3 and evaporated. Recrystallization of the residue from $CHCl_3$–MeOH gave yellow needles (528 mg), mp 253—256°. *Anal.* Calcd. for $C_{21}H_{17}NO_6$: C, 66.48; H, 4.52; N, 3.69. Found: C, 66.32; H, 4.46; N, 3.66. IR ν_{max}^{Nujol} cm^{-1}: 1640 (C=O), 940 (OCH_2O). NMR ($CDCl_3$) δ: 2.59 (2H, t, J=8.0 Hz, C_{12}–H), 3.10 (2H, t, J=8.0 Hz, C_{11}–H), 3.61 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 5.92 and 6.12 (each 2H, s, OCH_2O), 6.72 (1H, s, arom. H), 6.78 (2H, s, arom. H). MS *m/e*: 379 (M^+, 22.7%), 378 (M^+-1, base peak).

10-Methoxy-5-methyl-2,3; 7,8-bismethylenedioxybenzo[*c*]phenanthridin-6(5H)-one (Oxychelirubine) (30)——A mixture of the lactam (100 mg) and 30% Pd–C (50 mg) in *p*-cymene (3 ml) was refluxed for 6 hr in a nitrogen stream. After cooling, the reaction mixture was diluted with $CHCl_3$ and the catalyst was filtered off.

27) In the NMR spectrum of this compound (27) shows a small intensity of signals at 3.08, 6.42, 6.60, and 6.64 δ, and also some broadening of the signals due to the methoxy and the methylenedioxy groups. This phenomenon could be explained by the presence of the rotational isomers in a solution. [H. Ishii, Y. Watanabe, T. Ishida, E. Ueda, H. Ohida, and T. Ishikawa, *Chem. Pharm. Bull.*, in, preparation.

28) This mixture was confirmed to be composed of 4b,10b,11,12-tetrahydro-4b,10-dimethoxy-5-methyl-2,3; 7,8-bismethylenedioxybenzo[*c*]phenanthridin-6(5H)-one (28) and the desired dihydrobenzo[*c*]-phenanthridine (29) by the measurement of its NMR spectrum.

The filtrate was evaporated to dryness *in vacuo*. After washing with hexane, the residue was recrystallized from $CHCl_3$–MeOH or $CHCl_3$–acetone to give pale yellow needles (70 mg), mp 307—308°. *Anal.* Calcd. for $C_{21}H_{15}NO_6$: C, 66.84; H, 4.01; N, 3.71. Found: C, 66.75; H, 3.92; N, 3.58. IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O). NMR ($CDCl_3$) δ: 3.83 (3H, s, NCH_3), 3.98 (3H, s, OCH_3), 6.04 and 6.18 (each 2H, s, OCH_2O), 6.93 and 7.11 (each 1H, s, C_9 and C_1–H), 7.45 (1H, d, J=9.0 Hz, C_{12}–H), 7.46 (1H, s, C_4–H), 8.96 (1H, d, J=9.0 Hz, C_{11}–H).

This material was identical with an authentic sample of oxychelirubine (oxybocconine), mp 307—309° (lit.[10] mp 295—296°).

Dihydrochelirubine (31)——Vitride [a 70% benzene solution of $NaAlH_2$ $(OCH_2CH_2OCH_3)_2$; (Eastman Kodak)] (2 ml) was diluted with abs. xylene (20 ml). The diluted solution was added dropwise to a stirred solution of oxychelirubine (30) (1 g) in abs. xylene (280 ml), heated under reflux for 30 min, and poured into water. After separation of the organic layer, the aqueous layer was extracted with $CHCl_3$. The organic layer was combined with the chloroform solution, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on Al_2O_3 (Woelm, neutral, grade I) using $CHCl_3$ as solvent to give colourless prisms (757 mg), mp 205—207° (lit.[5] mp 201—202°; lit.[10] mp 206—207°), which were recrystallized from $CHCl_3$–MeOH. *Anal.* Calcd. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.19; H, 4.62; N, 3.81. IR ν_{max}^{Nujol} cm^{-1}: 1640, 1615 (C=C), 935 (OCH_2O). NMR ($CDCl_3$) δ: 2.57 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 4.09 (2H, s, C_6–H), 5.96 and 6.00 (each 2H, s, OCH_2O), 6.57 (1H, s, C_9–H), 7.08 (1H, s, C_1–H), 7.44 (1H, d, J=8.5 Hz, C_{12}–H), 7.68 (1H, s, C_4–H), 8.28 (1H, d, J=8.5 Hz, C_{11}–H).

Chelirubine (1c) Chloride——To an emulsion prepared by addition of 5% NaOH aq. (11 ml) to a solution of dihydrochelirubine (31) (565 mg) in benzene (22 ml), was added a solution of DDQ (550 mg) in benzene (22 ml). The mixture was stirred at room temperature for 1.5 hr. After the precipitate was filtered off, the organic layer was separated from the aqueous layer. The latter was extracted with AcOEt. The AcOEt extract was combined with the organic layer and evaporated to dryness *in vacuo*. The residue and the filtered precipitate were dissolved in acetone (50 ml) and a small amount of conc. HCl was added to this solution to give a precipitate. Recrystallization of the filtered precipitate from water or water–5% HCl aq. gave red purple needles (473 mg), mp 299—302° (dec.) (softened at around 150°) (lit.[4b] mp 282—283°). NMR (CF_3COOH) δ: 4.27 (3H, s, OCH_3), 4.96 (3H, s, N^+-CH_3), 6.24 and 6.44 (each 2H, s, OCH_2O), 7.48 (1H, s, C_1–H), 7.61 and 7.87 (each 1H, s, C_9 and C_4–H), 8.13 (1H, d, J=8.5 Hz, C_{12}–H), 9.49 (1H, s, C_6–H), 9.53 (1H, d, J=8.5 Hz, C_{11}–H).

Chelirubine ϕ-Cyanide (32)——To a stirred solution of chelirubine (1c) chloride (59.7 mg) in water (15 ml) was added KCN (14.7 mg) at room temperature. After the mixture had been stirred at room temperature for 30 min, the precipitate (51.3 mg) was filtered off. The filtrate was extracted with $CHCl_3$, dried over $MgSO_4$, evaporated to dryness *in vacuo*. The residue (9.9 mg) was combined with the precipitate. Recrystallization of the precipitate from $CHCl_3$–MeOH gave pale yellow fine prisms (45.8 mg), mp 243—247° (lit.[4b] mp 273—274°). *Anal.* Calcd. for $C_{22}H_{16}N_2O_5$: C, 68.03; H, 4.15; N, 7.21. Found: C, 68.06; H, 4.07; N, 7.10. NMR (DMSO-d_6) δ: 2.54 (3H, s, NCH_3), 3.83 (3H, s, OCH_3), 5.75 (1H, s, $ArC\underline{H}(CN)N$), 6.10 (3H, s, OCH_2O and $OC\underline{H}_AH_BO$), 6.15 (1H, d, J=1.0 Hz, $OCH_A\underline{H}_BO$), 6.99 (1H, s, C_9–H), 7.24 (1H, s, C_1–H), 7.50 (1H, s, C_4–H), 7.56 (1H, d, J=9.0 Hz, C_{12}–H), 8.25 (1H, d, J=9.0 Hz, C_{11}–H).