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Utilization of Protopine and Related Alkaloids. XII.[1] An Improved Route to an Analog of the Alkaloid Corynoline

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Photolysis of dihydroisoquinoline (**2**) in the presence of nitrosobenzene gives the epoxyimine (**10**), sodium borohydride reduction of which affords the aniline (**14**). Reaction of the dehydro compound (**17**) derived from **14** with performic acid followed by hydrolysis provides the diol (**20**). Hydrogenolysis of **20** over a palladium catalyst affords the corynoline analog (**7**). All compounds are formed under strictly stereoselective control.

Keywords——benzo[*c*]phenanthridines; photolysis; Diels-Alder addition; epoxidation; Bohlmann band; nuclear magnetic resonance

We previously reported the synthesis of an analog of corynoline, *trans*-11-hydroxy-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine (**7**), from α-allocryptopine and berberinium chloride.[3] The first key step in this procedure is the isolation of the *pseudo*-cyanide (**3**) in moderate yield from the photolysate of the dihydroisoquinoline (**2**) derived from these alkaloids *via* the methosulfate (**1**). The second is the insertion of a double bond in the C ring, and it was found that DDQ[4] oxidation of the lactam (**4**) was best for this. The third is stereoselective hydroxylation at the 11-position in the lactam (**5**). Thus, since this procedure consists of many rather complicated steps, we have attempted to simplify it. Very recently, we reported that the photocycloaddition of the isocarbostyril (**8**) to nitrosobenzene gave the epoxyimine (**9**) as a sole product in good yield.[1] This paper describes the successful application of this type of reaction to the synthesis of **7**.

Photolysis of **2** in the presence of nitrosobenzene stereoselectively gave the epoxyimine (**10**) (40%). In the nuclear magnetic resonance (NMR) spectrum, the 10b-Me group resonates at higher field (δ 0.68) than in related compounds,[3,5] and this suggests the 10b-Me group to be *cis* to the D ring, *i.e.*, the *trans* B/C ring fusion, with shielding due to the anisotropic effect of the D ring.[6] Since the steric surroundings of C-4b and C-12 on both faces in the initial photo-product (**11**) from **8** are nearly the same, the Diels-Alder addition of **11** to nitrosobenzene stereoselectively gives **9** having the *cis* B/C ring fusion, which is considered to be more stable than the *trans* isomer.[1] In the case of the initial photo-product (**12**) formed from **2**, it is thought that the 10b-Me group sterically prevents the approach of nitrosobenzene from the same side, giving the *trans* B/C isomer (**10**) ("steric approach control"). The regioisomer (**13**) is sterically excluded in that the N-phenyl group enters over the molecular framework of **12**, causing large steric congestion. In fact, the regioselectivity of this reaction is clearly illustrated by the structure of the compound obtained in the next reaction.

Although **10** resisted catalytic hydrogenation under neutral or acidic conditions, it was reduced with sodium borohydride to give the aniline (**14**) stereoselectively in quantitative yield. The B/C ring fusion in **14** is confirmed to be steroidal-*cis* by comparison of its NMR

1) Part XI: M. Onda and H. Yamaguchi, *Chem. Pharm. Bull.*, **27**, 2076 (1979).
2) Location: *Minato-ku, Tokyo 108, Japan.*
3) *a*) M. Onda, K. Yuasa, J. Okada, K. Kataoka, (née Yonezawa), and K. Abe, *Chem. Pharm. Bull.*, **21**, 1333 (1973); *b*) M. Onda, K. Yuasa, and J. Okada, *ibid.*, **22**, 2365 (1974).
4) 2,3-Dichloro-5,6-dicyanobenzoquinone.
5) M. Onda, Y. Harigaya, and J. Horie, *Chem. Pharm. Bull.*, **26**, 3330 (1978).
6) H. Hart, S.K. Ramaswami, and R. Willer, *J. Org. Chem.*, **44**, 1 (1979).

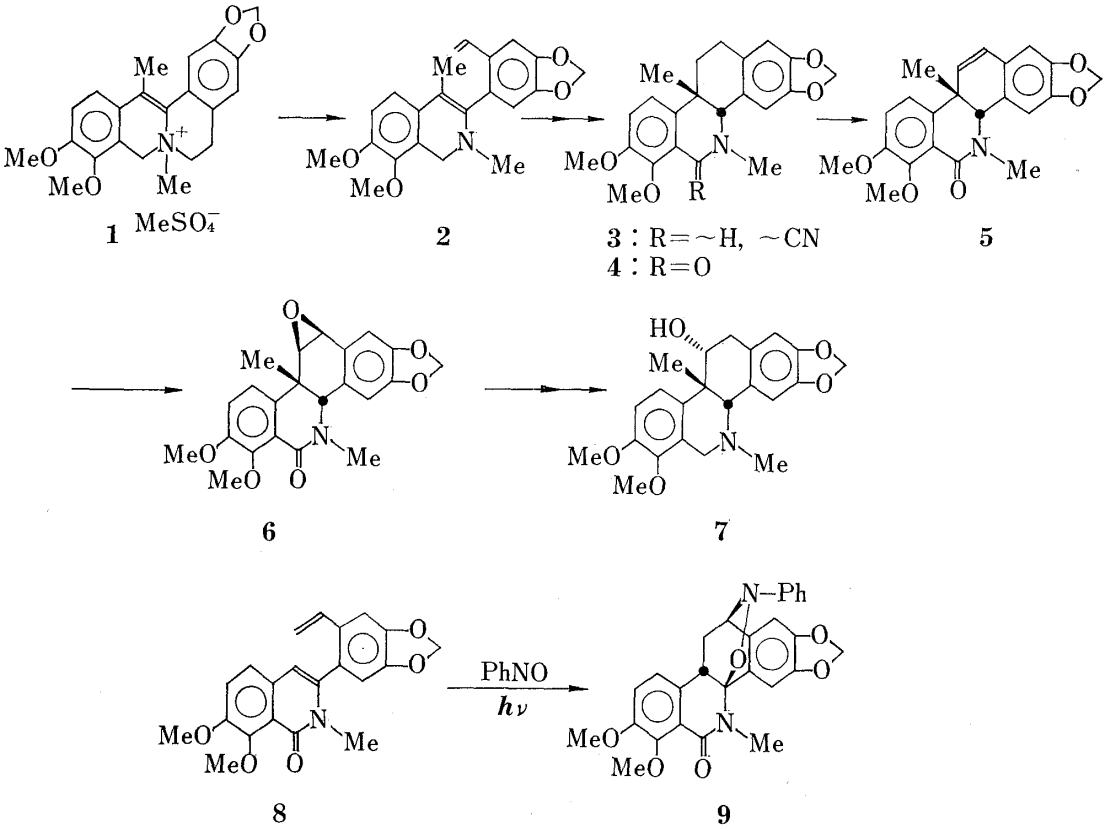
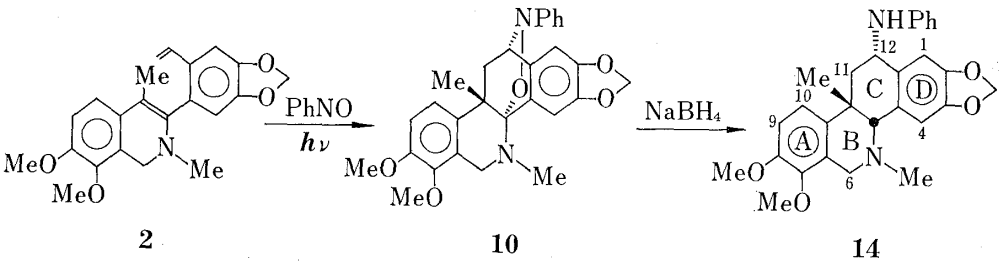


Chart 1



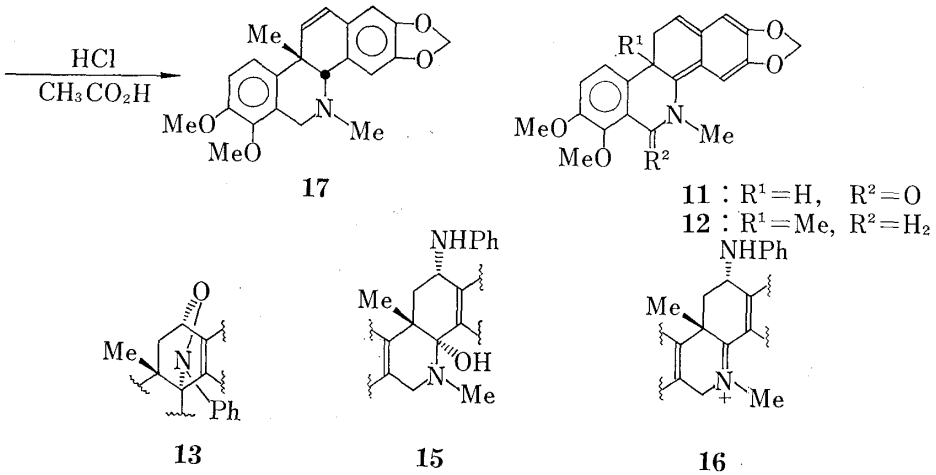


Chart 2

signals for the 4-H, 4b-H and 5-Me group (see "Experimental"), which are characteristic for distinguishing the *cis* B/C ring fusion from the *trans* fusion, with those of related compounds[5] and by its infrared (IR) spectrum, which shows the Bohlmann bands at 2775 and 2755 cm^{-1}.[7] The multiplicity of the 12-H is observed as a triplet with J 8 Hz in the NMR spectrum of **14**. This may be ascribed to a slightly flattened chair conformation of the C ring in **14** due to steric interaction between the 12-NHPh (eq) group and the D ring. The positions of the nitrogen and oxygen atoms in **10** at this stage are thus determined. The stereoselective formation of **14** can be explained as follows. The carbinolamine (**15**) obtained by reductive cleavage of the N-O bond in **10** directly affords **14** by the back-side attack of the hydride ion at C-4b, or the iminium salt (**16**), which is formed from **15**, is attacked by the hydride ion from the *syn* side with respect to the 10b-Me group to yield the stable *cis* isomer (**14**).

Treatment of **14** under acidic conditions afforded the dehydro compound (**17**) (43%) with the loss of aniline. The presence of a newly introduced double bond in **17** is clear from its NMR spectrum [δ 6.24 (d, J 10 Hz) and 5.83 (dd, J 10 and 2 Hz)].

Oxidation of **17** with performic acid stereoselectively gave the diol monoester (**19**) (85%), hydrolysis of which provided the diol (**20**) in quantitative yield. A "one-pot" procedure increased the yield of **20** from **17** (91%). The 12-OCHO group in **19** is thought to be *trans* to the 11-OH group on the basis that epoxides are opened at the more reactive center by the

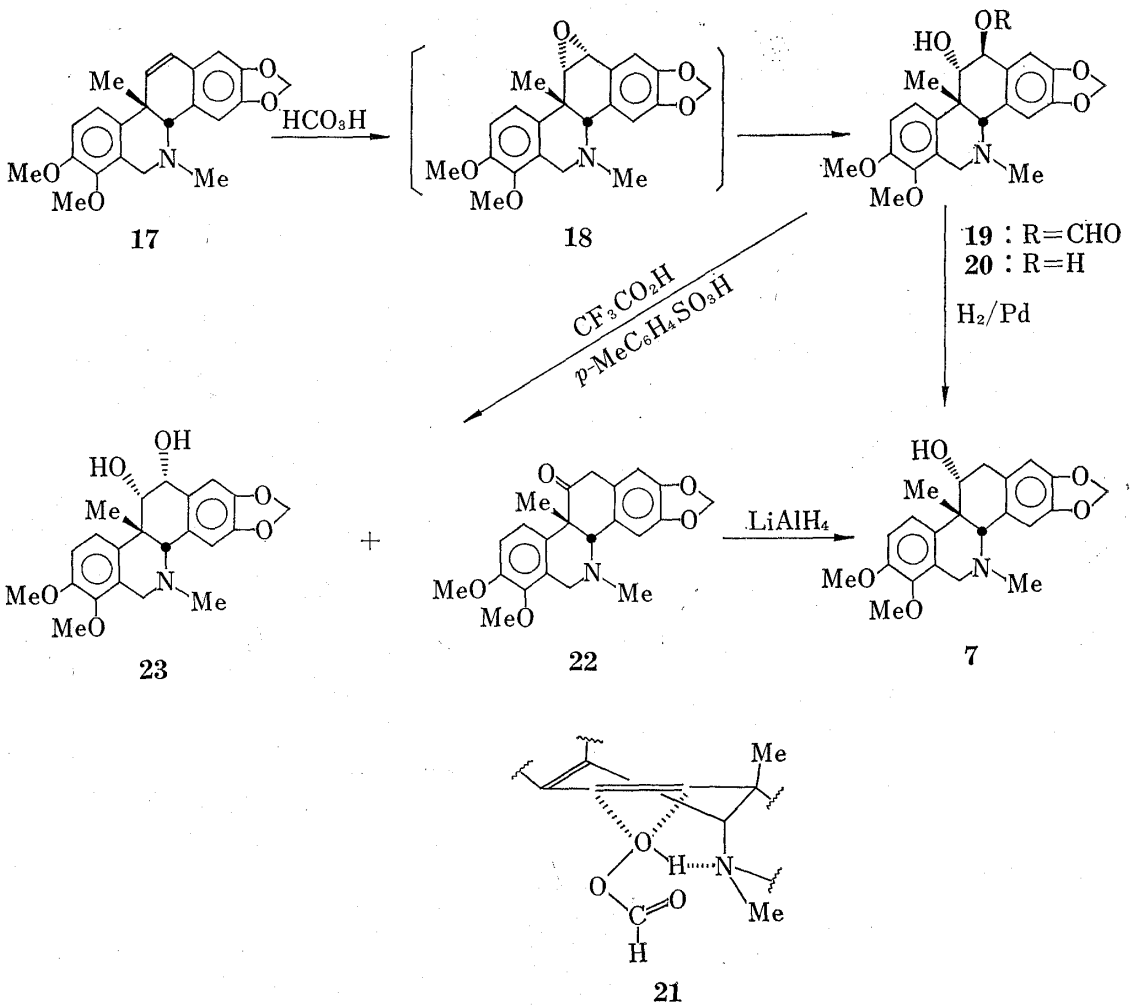


Chart 3

7) N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.*, **26**, 1880 (1978).

attack of organic acids to yield *trans*-diol monoesters. In general, W-path coupling between the 4b-H and 11-H is characteristically observed in the NMR spectra of corynoline and its analogs. Since the 4b-H's in **19** and **20** appear as doublets with J 2 Hz, the 11-OH groups are *trans* (axial) to the 10b-Me groups. Epoxidation of **5** with *m*-chloroperbenzoic acid stereoselectively gave the epoxide (**6**) by the attack of the reagent from the less hindered side *syn* to the 10b-Me group.[3b] Owing to the lower bulkiness of performic acid and the presence of the basic nitrogen atom in this case, **17** probably affords the expoxide (**18**) *via* the transition state (**21**) and subsequently, formic acid attacks at the more reactive position, C-12, from the back-side to give **19**.

Catalytic hydrogenation of **20** gave **7** (67%), which was identical with an authentic sample[3b] by comparison of spectral data and mixed melting point determination.

Dehydration of **20** under acidic conditions afforded the ketone (**22**) (44%)[3b] and diol (**23**) (20%). It has already been reported that on reduction with lithium aluminium hydride **22** stereoselectively gave **7**.[3b] The NMR spectrum of **23** indicates the coupling constant of the 4b-H to be 2 Hz, establishing that the 11-OH group is *trans* (axial) to the 10b-Me group. Accordingly, **23** is considered to result from epimerization at C-12 in **20**.

Thus, we have been able to improve the synthesis of **7**. Applications of this procedure to the syntheses of chelidonine, homochelidonine and their analogs are now in progress.

Experimental

Melting points were determined on a micro hot-stage apparatus and are not corrected. IR spectra were recorded on a JASCO IR-G spectrometer in chloroform. NMR spectra were taken on a JEOL JNM PS-100 (100 MHz) spectrometer in deuterochloroform.[8] Mass spectra (MS) were measured with a JEOL JMS-OIS spectrometer. Preparative thin-layer chromatographies (prep. TLC) were performed on silica gel plates using benzene/ethyl acetate=3/1 (v/v) as a solvent unless otherwise noted.

***trans*-4b,12-N-Phenylepoxyimino-10b-methyl-*trans*-4b,5,6,10b,11,12-hexahydrochelerythrine (10)**——A solution of **1**[3a] (150 mg) in 25% methanolic KOH solution (0.8 ml) was heated at 80° for 3 min. The reaction mixture was poured onto ice-water, and the precipitate was collected by filtration and dissolved in benzene (30 ml). The benzene solution was washed with water and then dried over Na_2SO_4 for 30 min. A solution of nitrosobenzene (27 mg) in anhyd. benzene (20 ml) was added to the filtered benzene solution, and the mixture was irradiated with a 100 W medium pressure mercury lamp under N_2 for 6 min. Work-up gave an oil, and prep. TLC afforded **10** (59 mg, 40%), *Rf* 0.45, as colorless needles of mp 188.5—189.5° (from methanol). NMR δ: 7.14—6.69 (8H, m, aromatic H's), 6.58 (1H, s, 1-H),[9] 5.88 and 5.85 (1H each, d, J 1 Hz, 2,3-OCH_2O–), 4.75 (1H, dd, J 4 and 2.5 Hz, 12-H), 4.38 and 4.10 (1H each, d, J 16 Hz, 6-H_2), 3.89 (3H, s, 7-OMe), 3.84 (3H, s, 8-OMe), 3.03 (3H, s, 5-Me), 2.93 (1H, dd, J 14 and 2.5 Hz, 11-H),[10] 1.99 (1H, dd, J 14 and 4 Hz, 11-H),[11] 0.68 (3H, s, 10b-Me). *Anal.* Calcd for $C_{28}H_{28}N_2O_5$: C, 71.17; H, 5.97; N, 5.93. Found: C, 71.12; H, 5.97; N, 5.77. MS *m/e*: M^+, 472.200 (M, 472.200).

***trans*-12-Anilino-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine (14)**——$NaBH_4$ (40 mg) was added to a solution of **10** (77 mg) in methanol (30 ml) and stirring was continued at room temperature for 15 min. After concentration *in vacuo*, the residue was extracted with benzene. Work-up gave an oil, and prep. TLC afforded **14** (73 mg, 98%), *Rf* 0.53, as light yellow crystals of mp 139—140.5° (from hexane). IR ν_{max} cm^{-1}: 3400 (NH), 2775 and 2755 (Bohlmann bands). NMR δ: 7.18—7.10 (4H, m, aromatic H's), 6.96—6.70 (5H, m, aromatic H's), 5.96 (2H, s, 2,3-OCH_2O–), 5.09 (1H, br s, 12-NH),[12] 4.90 (1H, t, J 8 Hz, 12-H), 4.24 and 3.49 (1H each, d, J 16 Hz, 6-H_2), 3.83 (3H, s, 7-OMe), 3.81 (3H, s, 8-OMe), 3.03 (1H, s, 4b-H), 2.46 and 1.75 (1H each, dd, J 14 and 8 Hz, 11-H_2), 2.26 (3H, s, 5-Me), 1.13 (3H, s, 10b-Me). *Anal.* Calcd for $C_{28}H_{30}N_2O_4 \cdot 3/4H_2O$: C, 71.17; H, 6.73; N, 5.93. Found: C, 71.02; H, 6.60; N, 5.62. MS *m/e*: 456.204 (50%) (M–H_2, 456.205), 365.162 (100%) (M–$C_6H_5NH_2$, 365.163).

10b-Methyl-*cis*-4b,5,6,10b-tetrahydrochelerythrine (17)——A solution of **14** (59.6 mg) and conc. HCl (2 drops) in acetic acid (1 ml) was heated at 80° for 1 hr. The reaction mixture was diluted with water and made alkaline with 10% aq. NaOH solution for extraction with benzene. Work-up gave an oil, and prep.

8) Assignments were based on comparison with the NMR data of related compounds described in the references cited herein and in I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, **5**, 67 (1976).
9) A nuclear Overhauser effect (11%) was observed between this proton and the 12-H.
10) This proton is *trans* to the 10b-Me group.
11) This proton is *cis* to the 10b-Me group.
12) On addition of D_2O this signal disappeared.

TLC afforded **17** (20 mg, 43%), *Rf* 0.41, as light yellow crystals of mp 157.5—159° (from chloroform/hexane). IR ν_{max} cm^{-1}: 2770 and 2750 (Bohlmann bands). NMR δ: 7.13 (1H, d, *J* 8 Hz, 10-H), 6.89 (1H, d, *J* 8 Hz, 9-H), 6.78 (1H, s, 4-H), 6.61 (1H, s, 1-H), 6.24 (1H, d, *J* 10 Hz, 12-H), 5.85 (2H, s, 2,3-OCH_2O–), 5.83 (1H, dd, *J* 10 and 2 Hz, 11-H), 4.14 and 3.45 (1H each, d, *J* 16 Hz, 6-H_2), 3.85 (3H, s, 7-OMe), 3.81 (3H, s, 8-OMe), 3.11 (1H, d, *J* 2 Hz, 4b-H), 2.13 (3H, s, 5-Me), 1.25 (3H, s, 10b-Me). MS *m/e*: M$^+$, 365.163. Calcd for $C_{22}H_{23}NO_4$: M, 365.163.

***cis*-12-Formyloxy-*trans*-11-hydroxy-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine (19)**——30% H_2O_2 (0.014 ml) was added to a solution of **17** (21.4 mg) in formic acid (0.1 ml) and stirring was continued at 40° for 20 min. The reaction mixture was diluted with water and made alkaline with Na_2CO_3 for extraction with benzene. Work-up gave light yellow crystals, and prep. TLC afforded **19** (21.3 mg, 85%), *Rf* 0.41, as colorless needles of mp 190—191° (from ethanol). IR ν_{max} cm^{-1}: 3200 (OH), 2770 and 2755 (Bohlmann bands), 1724 (OC=O). NMR δ: 8.39 (1H, d, *J* 1 Hz, 12-OCHO), 7.76 (1H, br s, 11-OH),[12] 7.13 (1H, d, *J* 9 Hz, 10-H), 6.89 (1H, d, *J* 9 Hz, 9-H), 6.87 (1H, s, 1-H), 6.68 (1H, s, 4-H), 6.27 (1H, br s, 12-H), 5.99 (2H, s, 2,3-OCH_2O–), 4.16 and 3.45 (1H each, *J* 16 Hz, 6-H_2), 3.85 (7H, s, 11-H, 7- and 8-OMe), 3.31 (1H, d, *J* 2 Hz, 4b-H), 2.18 (3H, s, 5-Me), 1.23 (3H, s, 10b-Me). *Anal.* Calcd for $C_{23}H_{25}NO_7$: C, 64.62; H, 5.90; N, 3.28. Found: C, 64.32; H, 6.05; N, 3.25. MS *m/e*: M$^+$, 427.164 (M, 427.163).

***trans*-11-*cis*-12-Dihydroxy-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine (20)**——30% H_2O_2 (0.014 ml) was added to a solution of **17** (21 mg) in formic acid (0.1 ml) and stirring was continued at 40° for 20 min. The reaction mixture was made alkaline with 20% aq. KOH solution and then ethanol (2 ml) was added until the solution became clear. After heating at 80° for 10 min, the reaction mixture was evaporated down *in vacuo* and extracted with benzene. The residue obtained from the benzene solution was purified by prep. TLC to afford **20** (20.9 mg, 91%), *Rf* 0.03, as colorless prisms of mp 225.5—226.5° (from ethanol). IR ν_{max} cm^{-1}: 3400 (OH), 2770 and 2760 (Bohlmann bands). NMR δ: 7.16 (1H, d, *J* 8Hz, 10-H), 7.01 (1H, s, 1-H), 6.91 (1H, d, *J* 8 Hz, 9-H), 6.66 (1H, s, 4-H), 5.96 and 5.93 (1H each, d, *J* 1Hz, 2,3-OCH_2O–), 4.90 (1H, d, *J* 2Hz, 12-H), 4.15 and 3.43 (1H each, d, *J* 16Hz, 6-H_2), 3.86 (9H, s, 7-, 8-OMe, 11-H, 11- and 12-OH),[12] 3.26 (1H, d, *J* 2 Hz, 4b-H), 2.18 (3H, s, 5-Me), 1.25 (3H, s, 10b-Me). *Anal.* Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.90; H, 6.38; N, 3.52. MS *m/e*: M$^+$, 399.168 (M, 399.168).

10b-Methyl-11-oxo-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine (22) and *trans*, *trans*-11,12-Dihydroxy-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine (23)——A solution of benzoic acid (17 mg) and *p*-toluenesulfonic acid (3 mg) in trifluoroacetic acid (0.3 ml) was heated at 80° for 20 min, and then a solution of **20** (52.5 mg) in trifluoroacetic acid (0.3 ml) was added. The mixture was stirred at 80° for 3 hr, and during this time *p*-toluenesulfonic acid (5 and 10 mg) was added after 40 min and a further 1 hr, respectively. The reaction mixture was diluted with water and made alkaline with Na_2CO_3 for extraction with benzene. Work-up gave an oil, purification of which was performed by prep. TLC. The zone with *Rf* 0.68 gave **22** (21.8 mg, 44%) as colorless granules of mp 147—147.5° (from chloroform/ether). IR ν_{max} cm^{-1}: 2775 and 2760 (Bohlmann bands), 1710 (C=O). NMR δ: 7.28 (1H, d, *J* 8 Hz, 10-H), 6.90 (1H, *J* 8 Hz, 9-H), 6.77 (1H, s, 4-H), 6.65 (1H, s, 1-H), 5.97 (2H, s, 2,3-OCH_2O–), 4.13 and 3.37 (1H each, d, *J* 16 Hz, 6-H_2), 4.11 and 3.31 (1H each, d, *J* 19 Hz, 12-H_2), 3.86 (3H, s, 7-OMe), 3.83 (3H, s, 8-OMe), 3.22 (1H, s, 4b-H), 2.11 (3H, s, 5-Me), 1.21 (3H, s, 10b-Me). MS *m/e*: M$^+$, 381.158. Calcd for $C_{22}H_{23}NO_5$: M, 381.158. The zone with *Rf* 0.20 afforded **23** (10.3 mg, 20%) as colorless prisms of mp 220—221° (from ethanol). IR ν_{max} cm^{-1}: 3530 (OH), 2778 and 2775 (Bohlmann bands). NMR δ: 7.25 (1H, s, 1-H), 7.13 (1H, d, *J* 8 Hz, 10-H), 6.92 (1H, d, *J* 8 Hz, 9-H), 6.62 (1H, s, 4-H), 5.97 (2H, s, 2,3-OCH_2O–), 4.59 (1H, d, *J* 4 Hz, 12-H), 4.18 and 3.46 (1H each, d, *J* 16 Hz, 6-H_2), 3.91 (1H, dd, *J* 4 and 2 Hz, 11-H), 3.86 (8H, s, 7-, 8-OMe, 11- and 12-OH),[12] 3.22 (1H, d, *J* 2 Hz, 4b-H), 2.19 (3H, s, 5-Me), 1.17 (3H, s, 10b-Me). MS *m/e*: M$^+$, 399.167. Calcd for $C_{22}H_{25}NO_6$: M, 399.168. The diol (**20**) (7.2 mg, 14%) was recovered unchanged from the zone with *Rf* 0.03.

***trans*-11-Hydroxy-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine (7)**——A solution of **20** (47.6 mg) and 70% $HClO_4$ (0.2 ml) in 10% HCl (16 ml) was shaken with H_2 over 10% Pd-C (20 mg) and PdO (14 mg) at 55° under a pressure of 5 atm for 48 hr. After filtration, the catalysts were treated with 10% aq. Na_2CO_3 solution and extracted with chloroform to give light yellow crystals (48.1 mg). The filtrate was made alkaline with Na_2CO_3 and extracted with benzene to give additional crystals (0.7 mg). The crystals obtained above were purified by prep. TLC (benzene/ethyl acetate=1/1, v/v) to afford **7** (30.8 mg, 67%), *Rf* 0.42, as colorless prisms of mp 202—203.5° (from chloroform/ether). IR ν_{max} cm^{-1}: 3200 (OH), 2775 and 2760 (Bohlmann bands). NMR δ: 7.72 (1H, s, 11-OH),[12] 7.13 (1H, d, *J* 8 Hz, 10-H), 6.90 (1H, d, *J* 8 Hz, 9-H), 6.65 (2H, s, 1- and 4-H), 5.94 (2H, s, 2,3-OCH_2O–), 4.17 and 3.43 (1H each, d, *J* 16 Hz, 6-H_2), 3.95 (1H, dt, *J* 3 and 2 Hz, 11-H), 3.86 (6H, s, 7- and 8-OMe), 3.26 (1H, d, *J* 2 Hz, 4b-H), 3.12 (2H, d, *J* 3 Hz, 12-H_2), 2.23 (3H, s, 5-Me), 1.14 (3H, s, 10b-Me). MS *m/e*: M$^+$, 383.173. Calcd for $C_{22}H_{25}NO_5$: M, 383.173.