[Chem. Pharm. Bull. 22(10)2365—2371(1974)] UDC 547.94.057

Utilization of Protopine and Related Alkaloids. VIII.[1] Synthesis of an Analogue of Alkaloid Corynoline

Masayuki Onda, Kumiko Yuasa, and Junko Okada

School of Pharmaceutical Sciences, Kitasato University[2]

(Received April 15, 1974)

An analogue of corynoline, *trans*-11-hydroxy-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine, is stereoselectively synthesized from the ϕ-cyanide **7** which has been derived from berberine chloride. This synthetic procedure is also connected with α-allocryptopine by its transformation to berberine chloride.

We previously reported the isolation of nematocidal alkaloids, sanguinarine, chelerythrine, and bocconine, from *Bocconia cordata*.[3] These alkaloids are the minor constituents and the major ones are protopine and α-allocryptopine which are biologically inactive. In the interests of utilization of these biologically inactive alkaloids, sanguinarine **4** (R,R=OCH_2O) and chelerythrine **4** (R=OMe) were synthesized from protopine **1** (R,R=OCH_2O) and α-allocryptopine **1** (R=OMe),[4] respectively. The synthesis of chelerythrine was also related to berberine chloride **5** by its transformation to dihydroberberine methosulfate **2** (R=OMe, R′=H, X=$MeSO_4$).[4] The key step in this synthetic procedure is novel photocyclization of the methine base **3**. Further, the 10b-methylbenzo[*c*]phenanthridines **6**, **7**, and **8** have been recently synthesized by application of the photocyclization to the methine base **3** (R=OMe, R′=Me) derived from berberine chloride **5** *via* 13-methyldihydroberberine methosulfate **2** (R′=Me, X=$MeSO_4$).[5] Attempts to obtain analogs of corynoline **9** from the compounds **6**, **7**, and **8** have been carried out in our laboratory. We herein wish to report, in full, synthesis of an analogue, which contains the methoxyl groups at C-7 and C-8 instead of the methylenedioxy group and has been described in our preliminary communication,[1] together with some further results obtained.

In order to insert the double bond between C-11 and C-12, dehydrogenation of the compounds **6**, **7**, and **8** with usual oxidizing agents were examined. However, all attempts were found to be unsuccessful.

On oxidation with potassium ferricyanide the ϕ-cyanide **7** gave the lactam **10** whose infrared (IR) spectrum ($CHCl_3$) showed an absorption band at 1640 cm^{-1} (lactam CO). Treatment of the lactam **10** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded, unexpectedly, the keto amide **11** as a main product whose IR spectrum (KBr) showed absorption bands at 3340 (NH), 1667 (aromatic ketone CO), and 1648 cm^{-1} (amide CO) and whose nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) revealed signals due to the vinyl protons at δ 6.52 (d, J=10 Hz) and 6.19 (d, J=10 Hz) in addition to the four aromatic protons. These spectral properties suggest that oxidative fission and dehydrogenation occurred between the 4b- and the 5-positions in B ring and the 11- and the 12-positions in C ring, respectively.

1) Part VII: M. Onda, K. Yuasa, and J. Okada, *Heterocycles*, **1**, 27 (1973).
2) Location: *Minato-ku, Tokyo, 108, Japan.*
3) M. Onda, K. Takiguchi, M. Hirakura, H. Fukushima, M. Akagawa, and F. Naoi, *Nippon Nogeikagaku Kaishi*, **39**, 168 (1965); M. Onda, K. Abe, K. Yonezawa, N. Esumi, and T. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1435 (1970).
4) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **19**, 31 (1971).
5) M. Onda, K. Yuasa, J. Okada, K. Kataoka (née Yonezawa), and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **21**, 1333 (1973).

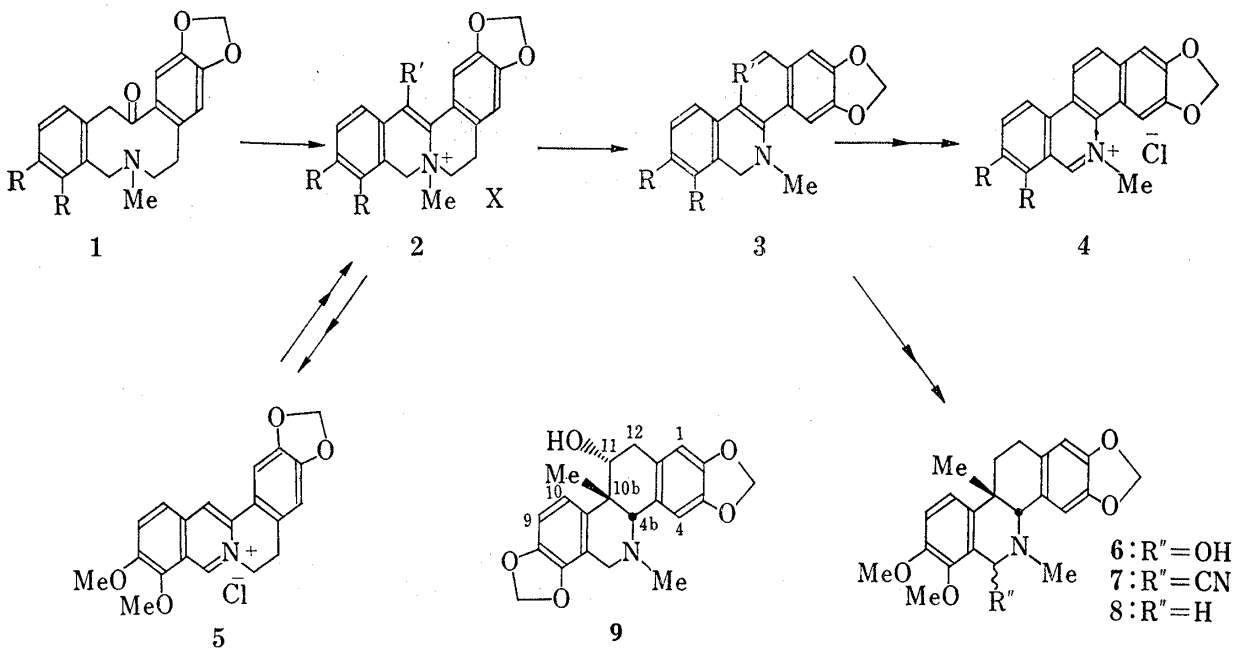


Chart 1

The oxidative fission of B ring is able to explain as follows. The DDQ oxidation inserts the double bond between the 4b- and the 5-positions in the lactam **10**. The resulting iminium salt **12** gives the carbinolamide **13** by the action of alkali, which subsequently undergoes bond breaking to give the keto amide **11**. The keto amide **11** was reduced with lithium aluminum hydride (LAH) to give the carbinolamide **14** which was stereoselectively converted with hydrochloric acid into the lactam **15**. The IR spectrum ($CHCl_3$) of the lactam **15** shows an absorption band at 1640 cm^{-1} (lactam CO) and no absorption band arising from the NH in the *sec*-amide group and the OH in the hydroxyl group, supporting the presence of a lactam group resulted from ring closure. Assignment of the *cis* B/C configuration in the lactam **15** is confirmed by observance of a nuclear Overhauser effect (NOE) (9%) between the 4b-H (δ 4.87) and the 10b-Me group (δ 1.57) in the NMR spectrum (CF_3CO_2D) of the lactam **15**. If the aryl group is assumed to exhibit a significant "2-alkylketone effect" compared to the methyl group, the keto amide **11** would predominantly exist in the conformer **11a**. On reduction the intermediate **16** would give the carbinolamide **14** in which the hydroxyl group is *cis* to the methyl group. Since, from the NMR data, thin-layer chromatography, and melting point, the carbinolamide **14** seems to be a pure compound including no isomer, the above deduction might be correct. If so, the carbinolamide **14** would preferentially exist in the more stable conformer **14a**. This may be able to explain the stereoselective formation of the lactam **15**. Thus, the lactam **15** possesses the same B/C configuration as corynoline and also the double bond which is a precursor group for the hydroxyl group to be introduced at C-11.

Treatment of the lactam **15** with *m*-chloroperbenzoic acid gave the epoxide **17** and small amount of the diol monoester **18**. The epoxide **17** was reduced with LAH to give the carbinol **19** in which position of the hydroxyl group was deduced from the NMR spectrum ($CDCl_3$) showing signals due to the CHOH at δ 4.53 (q, J=10 and 6 Hz) and two protons of the methylene group at δ 3.17 (q, J=18 and 6 Hz) and 2.55 (q, J=18 and 10 Hz). The absence of the intramolecular hydrogen bonding attributed to OH···N in the IR spectrum (CCl_4) and the coupling constants of the 11-H in the NMR spectrum indicate the 11-OH group to be *trans* to the nitrogen and orient equatorially. Hence, the carbinol **19** possesses the structure corresponding to 11-epicorynoline.[6] At this moment, it can be easily seen that epoxidation

6) N. Takao, H.-W. Bersch, and S. Takao, *Chem. Pharm. Bull.* (Tokyo), **21**, 1096 (1973).

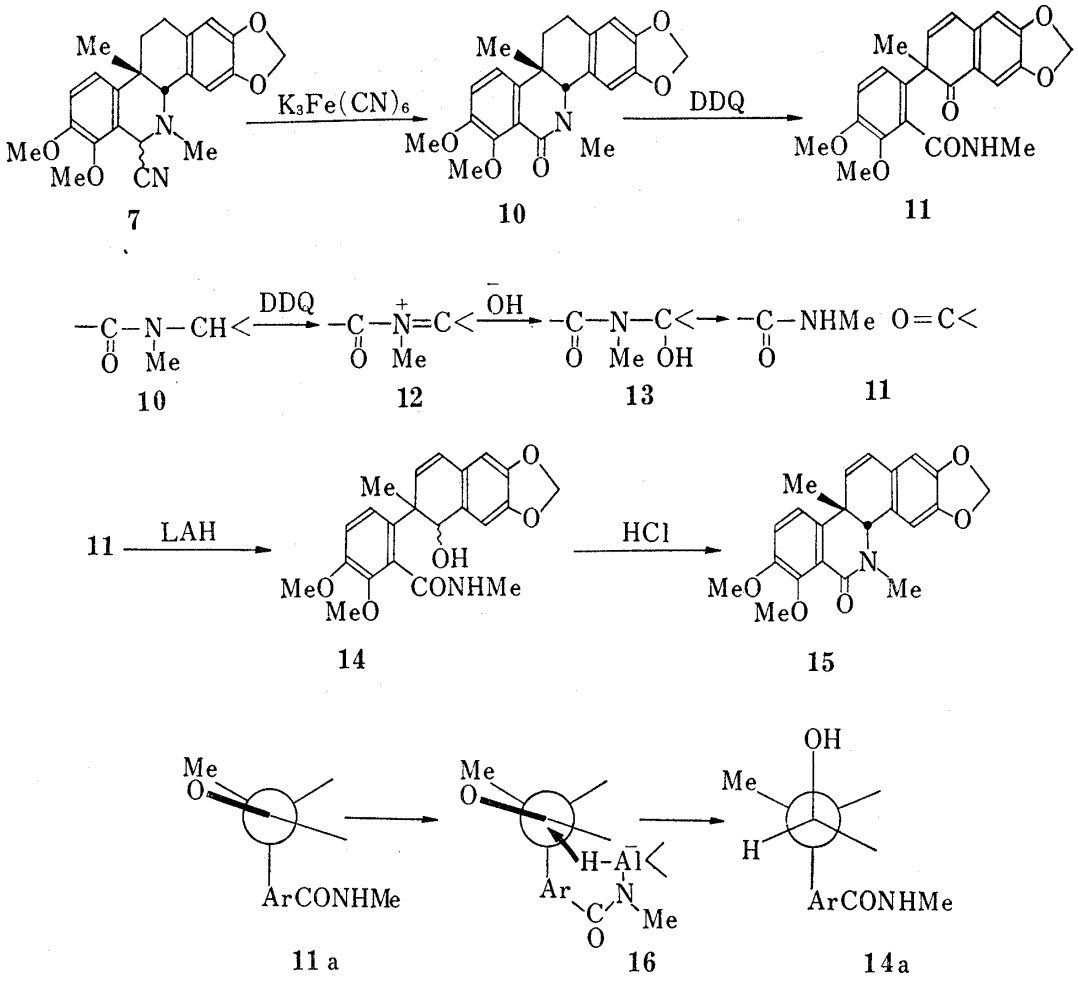


Chart 2

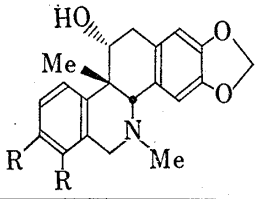
of the lactam **15** stereoselectively occurs from the less hindered side, the *syn* side to the 10b-Me group, and the epoxide **17** is regioselectively reduced at the more reactive position, C-12, to give the carbinol **19**. Taking account of the steric hindrance ($A^{(1,3)}$ strain)[7] between the N-Me group and the 4-H, the epoxide **17** would predominantly exist in the conformer containing the axial 10b-Me group to C ring, in which the approach of LAH at C-11 is hindered in a steric sence. Hence, the carbinol **19** primarily exists in the C ring half-boat conformer with the axial 11-OH group resulted from the LAH attack at the less hindered position, C-12, and changes to the half-chair conformer with the equatorial 11-OH group. The carbinol **19** was converted into the ketone **20** by the Oppenauer oxidation, which showed an absorption band due to the aliphatic carbonyl group at 1705 cm^{-1} in the IR spectrum (KBr). The LAH reduction of the ketone **20** stereoselectively afforded the carbinol **21**, an isomer of the carbinol **19**, which showed the intramolecular hydrogen bonding between the 11-OH group and the nitrogen at 3190 cm^{-1} in the IR spectrum (CCl_4, 1.5×10^{-3} mole/liter). The structure, in which the B/C juncture is *cis* fused and the *cis* 11-OH to the nitrogen axially orients, can alone account for the presence of the intramolecular hydrogen bonding and corresponds to the structure of corynoline.[8,9] The presence of an NOE (9%) between the 4b-H (δ 3.30) and

7) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
8) N. Takao, *Chem. Pharm. Bull.* (Tokyo), **11**, 1312 (1963); M.H. Benn and R.E. Michell, *Can. J. Chem.*, **47**, 3701 (1969); T. Kametani, T. Honda, M. Ihara, H. Shimanouchi, and Y. Sasado, *Tetrahedron Letters*, **1972**, 3729.
9) S. Naruto, S. Arakawa, and H. Kaneko, *Tetrahedron Letters*, **1968**, 1705; G. Nonaka, H. Okabe, I. Nishioka, and N. Takao, *Yakugaku Zasshi*, **93**, 87 (1973).

the 10b-Me group (δ 1.15) in the NMR spectrum ($CDCl_3$) exhibits the *cis* B/C configuration, supporting further the structure of the carbinol **21**. The NMR data of the carbinol **21** and corynoline[9] are remarkably similar and are recorded in Table I.

The diol monoester **18** must be formed by the attack of *m*-chlorobenzoic acid on the epoxide **17**, which is contained in *m*-chloroperbenzoic acid and is resulted from *m*-chloroperbenzoic acid as the reaction progresses. On epoxidation prolonged reaction time or the presence of *m*-chlorobenzoic acid added in the reaction system increased formation of the diol monoester **18**. Position of the hydroxyl and the ester groups in the diol monoester **18** are assignable on the basis of the NMR spectrum ($CDCl_3$) showing signals due to the CHOH at

Table I. NMR Data of The Carbinol **21** and Corynoline[a]



	Carbinol **21** (R=OMe)	Corynoline[b] (R,R=OCH_2O)		Carbinol **21** (R=OMe)	Corynoline[b] (R,R=OCH_2O)
1-H	6.67, s	*c*)	11-H	3.95, m	3.94, m
4-H	6.67, s	*c*)	12-H_2	3.13, d	3.12, d
4b-H	3.30, s	3.32, s		J=3	J=3
6-H_2	4.18, d	4.05, d	N-Me	2.25, s	2.20, s
	3.45, d	3.46, d	10b-Me	1.15, s	1.13, s
	J=16	J=16.3	OCH_2O	5.95, s	5.95, s
9-H	6.92, d J=8	*c*)	OMe	3.90, s	
10-H	7.15 J=8	*c*)			

a) $CDCl_3$; chemical shift(δ); coupling constant (Hz) *b*) lit. 8) *c*) 8.02—6.65

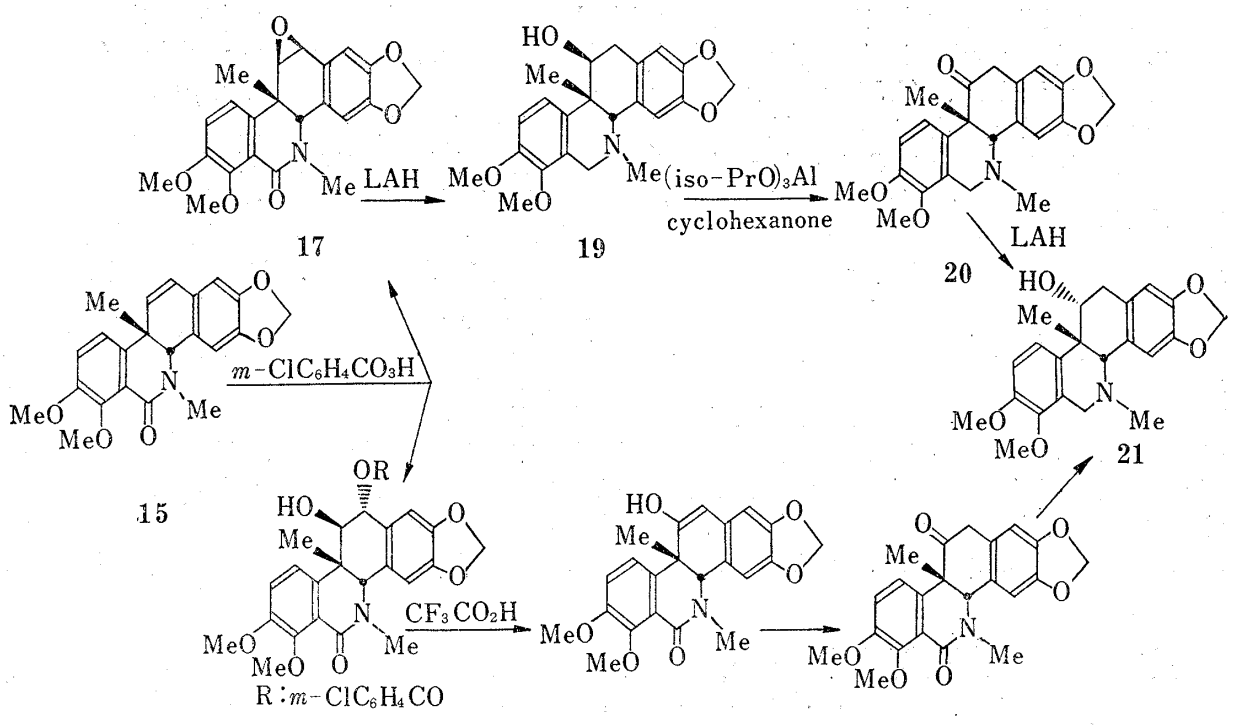


Chart 3

δ 4.90 (d, J=4 Hz) and the C<u>H</u>OCOC$_6$H$_4$Cl(*m*) at δ 6.17 (d, J=4 Hz) and are also in accord with mechanistic considerations. As mentioned above on the LAH reduction of the epoxide **17**, the diol monoester **18** also primarily exists in the C ring half-boat conformer which is remarkably unstable by eclipsing interaction of the 10b-Me and the 11-OH groups. On the other hand, the C ring half-chair conformer would be unstable by A$^{(1,3)}$ strain observed between the 1-H and the equatorial acyloxy group at C-12. Accordingly, C ring would exist in a conformer between the half-boat and the half-chair conformers. This may account for the coupling constants of the 11-H and the 12-H. The diol monoester **18** was converted with trifluoroacetic acid into the keto lactam **23**. Position of the keto group can be decided by the spectral data. The NMR spectrum (CF_3CO_2D) shows signals for two protons of the methylene group at δ 4.52 (d, J=12 Hz) and 3.82 (d, J=12 Hz). The IR spectrum (KBr) shows an absorption band due to the aliphatic carbonyl group at 1710 cm^{-1}. The keto lactam **23** would be formed *via* the enol **22** resulted from *cis* elimination of the *m*-chlorobenzoyloxy group. The unusual conformation of the diol monoester **18** would be responsible for the facile *cis* elimination. The LAH reduction of the keto lactam **23** also stereoselectively gave the carbinol **21**.

Demethylation and subsequent dehydrogenation of dihydroberberine methochloride **2** (R=OMe, X=Cl), which was derived from α-allocryptopine **1** (R=OMe),[10] afforded berberine chloride **5**. Hence, the synthesis of the carbinol **21** can be connected with α-allocryptopine. Further, since berberine iodide was already prepared,[11] a total synthesis of the carbinol **21** has been now established.

Experimental

Melting points were determined on a micro hot-stage and are not corrected. IR spectra and intramolecular hydrogen bonding were recorded on a JASCO IR-G and a Perkin-Elmer 221, respectively. NMR spectra and NOE were measured with a Varian T-60 and a JNM-4H-100, respectively. Mass spectra were taken on a JEOL JMS-01S.

10b-Methyl-6-oxo-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine 10——To a boiling solution of the ϕ-cyanide **7** (1.2 g) in EtOH (80 ml) was added dropwise a solution of $K_3Fe(CN)_6$ (6 g) and KOH (3 g) in H_2O (120 ml). The reaction mixture was refluxed for 1 hr. After cooling, precipitate was collected by filtration and recrystallized from $CHCl_3$ to give **10** (839 mg) as colorless granules, mp 262—265°. NMR (CF_3CO_2H): δ 7.54 (d, J=10 Hz, 10-H), 7.43 (d, J=10 Hz, 9-H), 6.71 (s, 4-H), 6.61 (s, 1-H), 5.94 (s, OCH_2O), 4.76 (s, 4b-H), 4.28 (s, 7-OMe), 4.00 (s, 8-OMe), 3.80 (s, NMe), 2.87 (cm, 12-H_2), 2.21 (cm, 11-H_2), 1.46 (s, 10b-Me). Mass Spectrum: M$^+$, *m/e* 381.1573. Calcd. for $C_{22}H_{23}O_5N$, 381.1576. *Anal.* Calcd. for $C_{22}H_{23}O_5N\cdot 3/4H_2O$: C, 66.92; H, 6.21; N, 3.55. Found: C, 66.61; H, 5.83; N, 3.30.

2,3-Dimethoxy-6-(1′,2′-dihydro-2′-methyl-6′,7′-methylenedioxy-1′-oxo-2′-naphthyl)-N-methylbenzamide 11——To a solution of **10** (600 mg) in $CHCl_3$ (15 ml) was added DDQ (755 mg) with stirring. After stirring for 17 hr at room temperature, the reaction mixture was filtered. The filtrate was washed with 10% aq. NaOH, H_2O and dried over Na_2SO_4. The remaining residue (604 mg) was crystallized from benzene to give **11** (354 mg) as colorless granules, mp 215—217°. NMR ($CDCl_3$): δ 7.51 (s, 8′-H), 7.26 (d, J=10 Hz, 5-H), 6.95 (d, J=10 Hz, 4-H), 6.75 (s, 5′-H), 6.52 (d, J=10 Hz, 3′-H), 6.19 (d, J=10 Hz, 4′-H), 6.06 (s, OCH_2O), 5.50 (bq, J=4 Hz, NH), 3.88 (s, OMe), 3.81 (s, OMe), 2.40 (d, J=4 Hz, NMe), 1.62 (s, 2′-Me). Mass Spectrum: M$^+$, *m/e* 395.1352. Calcd. for $C_{22}H_{21}O_6N$, 395.1368. *Anal.* Calcd. for $C_{22}H_{21}O_6N\cdot 1/4H_2O$: C, 66.08; H, 5.38; N, 3.50. Found: C, 65.90; H, 5.33; N, 3.44.

2,3-Dimethoxy-6-(1′,2′-dihydro-1′-hydroxy-2′-methyl-6′,7′-methylenedioxy-2′-naphthyl)-N-methylbenzamide 14——To a solution of **11** (200 mg) in tetrahydrofuran (40 ml) was added LAH (53 mg). After stirring for 1.5 hr at room temperature, H_2O was added. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The remaining residue (207 mg) was crystallized from $CHCl_3$ to give **14** (184 mg) as pale yellow granules, mp 212—213°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (OH), 3340 (NH), 1643 (amide CO). NMR (Me_2SO-d_6): δ 8.03 (bq, J=4 Hz, NH), 7.10 (d, J=8 Hz, 5-H), 7.00 (d, J=8 Hz, 4-H), 6.93 (s, 8′-H), 6.66 (s, 5′-H), 6.19 (d, J=10 Hz, 3′-H), 5.96 (s, OCH_2O), 5.94 (d, J=10 Hz, 4′-H), 5.30 (s, 1′-H), 3.83 (s, OMe), 3.73 (s, OMe), 2.67 (d, J=4 Hz, NMe), 1.23 (s, 2′-Me). Mass Spectrum: M$^+$, *m/e* 397.1518. Calcd. for C_{22}-

10) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **17** 2565 (1969).
11) T. Kametani, I. Noguchi, K. Saito, and S. Kaneko, *J. Chem. Soc. C*, **1969**, 2036.

$H_{23}O_6N$, 397.1525. *Anal.* Calcd. for $C_{22}H_{23}O_6N \cdot CHCl_3$: C, 53.23; H, 4.62; N, 2.70. Found: C, 53.31; H, 4.67; N, 2.62.

10b-Methyl-6-oxo-*cis*-4b,5,6,10b-tetrahydrochelerythrine 15——To a solution of **14** (583 mg) in MeOH (20 ml) was added conc. HCl (5 drops). After evaporation *in vacuo*, the resulting residue was taken up in $CHCl_3$ and washed with 10% aq. NaOH and H_2O. The remaining residue (490 mg) was crystallized from $CHCl_3$–ether to give **15** (400 mg) as colorless prisms, mp 276—278°. NMR (CF_3CO_2H): δ 7.43 (d, J=8 Hz, 10-H), 7.36 (d, J=8 Hz, 9-H), 6.73 (s, 4-H), 6.67 (s, 1-H), 6.61 (d, J=12 Hz, 11-H), 6.02 (s, OCH_2O), 5.94 (d, J=12 Hz, 12-H), 4.83 (s, 4b-H), 4.35 (s, 7-OMe), 4.00 (s, 8-OMe), 3.56 (bs, NMe), 1.54 (s, 10b-Me). Mass Spectrum: M^+, *m/e* 379.1404. Calcd. for $C_{22}H_{21}O_5N$, 379.1419. *Anal.* Calcd. for $C_{22}H_{21}O_5N \cdot 1/4H_2O$: C, 68.84; H, 5.60; N, 3.65. Found: C, 68.91; H, 5.57; N, 3.81.

***cis*-11,12-Epoxy-10b-methyl-6-oxo-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine 17**——To a solution of **15** (98 mg) in $CHCl_3$ (15 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (85% purity, 90 mg) in $CHCl_3$ (5 ml) with stirring. After stirring for 40 min at room temperature, the reaction mixture was washed with 10% aq. KI, 10% aq. $Na_2S_2O_3$, 10% aq. Na_2CO_3 and H_2O. Work-up afforded a solid (117 mg) which by chromatography on neutral Al_2O_3 (Grade III, 12 g) using benzene–$CHCl_3$ (4: 1 v/v) as eluent gave **17** (67 mg) as colorless granules, mp 215—217° (from CH_2Cl_2–ether). IR ν_{max}^{KBr} cm^{-1}: 1640 (lactam CO). NMR ($CDCl_3$): δ 6.88 (s, 9- and 10-H), 6.73 (s, 4-H), 6.60 (s, 1-H), 5.84 (fine splitting, OCH_2O), 4.23 (s, 4b-H), 4.04 (d, J=4 Hz, 12-H), 3.93 (s, 7-OMe), 3.91 (hidden in the 7-OMe signal, 11-H), 3.78 (s, 8-OMe), 3.40 (s, NMe), 1.69 (s, 10b-Me). Mass Spectrum: M^+, *m/e* 395.1370. Calcd. for $C_{22}H_{21}O_6N$, 395.1368. *Anal.* Calcd. for $C_{22}H_{21}O_6N \cdot 1/4H_2O$: C, 66.08; H, 5.38; N, 3.50. Found: C, 65.80; H, 5.29; N, 3.47. The next eluant with $CHCl_3$ afforded the diol monoester **18** (10 mg).

***trans*-12-*m*-Chlorobenzoyloxy-*cis*-11-hydroxy-10b-methyl-6-oxo-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine 18**——(a) To a solution of **15** (77 mg) in $CHCl_3$ (15 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (85% purity, 81 mg) in $CHCl_3$ (5 ml) with stirring. After stirring for 42 hr at room temperature, work-up gave an oil (123 mg) which was crystallized from $CHCl_3$–ether to give **18** (42 mg) as colorless prisms, mp 237—240°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 1720 (ester CO), 1640 (lactam CO). NMR ($CDCl_3$): δ 7.87 (cm, 2′- and 6′-H), 7.60 (cm, 4′- and 5′-H), 7.09 (d, J=8 Hz, 10-H), 6.90 (d, J=8 Hz, 9-H), 6.65 (s, 4-H), 6.45 (s, 1-H), 6.11 (d, J=4 Hz, 12-H), 5.80 (fine splitting, OCH_2O), 4.84 (d, J=4 Hz, 11-H), 4.58 (s, 4b-H), 3.85 (s, 7-OMe), 3.79 (s, 8-OMe), 3.46 (s, NMe), 2.86 (bs, OH), 1.48 (s, 10b-Me). *Anal.* Calcd. for $C_{29}H_{26}O_8NCl \cdot 3/2H_2O$: C, 60.15; H, 5.01; N, 2.42. Found: C, 60.11; H, 4.87; N, 2.49.

(b) To a solution of **15** (150 mg) and *m*-chlorobenzoic acid (74 mg) in $CHCl_3$ (20 ml) was added a solution of *m*-chloroperbenzoic acid (85% purity, 120 mg) in $CHCl_3$ (5 ml). After stirring for 4 hr at room temperature, the reaction mixture was treated as above to give **18** (250 mg) as semi-solid, a part of which was crystallized from $CHCl_3$–ether to give colorless prisms, mp 237—240°. This semi-solid showed only one spot on thin-layer chromatography and was used for the next step without further purification.

***cis*-11-Hydroxy-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine 19**——To a solution of **17** (100 mg) in tetrahydrofuran (40 ml) was added LAH (80 mg) and the reaction mixture was refluxed for 5 hr. Work-up gave an oil (84 mg) which was crystallized from ether to give **19** (53 mg) as colorless prisms, mp 158—160°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH). NMR ($CDCl_3$): δ 7.10 (d, J=10 Hz, 10-H), 6.81 (d, J=10 Hz, 9-H), 6.63 (s, 4-H), 6.60 (s, 1-H), 5.91 (s, OCH_2O), 4.53 (q, J=10 and 6 Hz, 11-H), 4.13 (d, J=16 Hz, 6-H_A), 3.85 (s, 2×OMe), 3.44 (d, J=16 Hz, 6-H_B), 3.17 (q, J=18 and 6 Hz, 12-H_A), 3.13 (s, 4b-H), 2.55 (q, J=18 and 10 Hz, 12-H_B), 2.16 (s, NMe), 1.08 (s, 10b-Me). Mass Spectrum: M^+, *m/e* 383.1729. Calcd. for $C_{22}H_{25}O_5N$, 383.1732. *Anal.* Calcd. for $C_{22}H_{25}O_5N$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.02; H, 6.61; N, 3.70.

10b-Methyl-11-oxo-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine 20——A mixture of **19** (60 mg), aluminum isopropoxide (130 mg), and cyclohexanone (1 ml) in toluene (10 ml) was refluxed for 8 hr under N_2. Work-up afforded an oil (60 mg) which by chromatography on neutral Al_2O_3 (Grade III, 6 g) using benzene as eluent gave **20** (35 mg) as colorless granules, mp 125—128° ($CHCl_3$–ether). NMR ($CDCl_3$): δ 7.48 (d, J=9 Hz, 10-H), 7.28 (d, J=9 Hz, 9-H), 6.77 (s, 4-H), 6.65 (s, 1-H), 5.98 (s, OCH_2O), 4.13 (d, J=18 Hz, 6-H_A), 3.85 (s, 7-OMe), 3.77 (s, 8-OMe), 3.6—3.1 (cm, 4×H), 2.08 (s, NMe), 1.20 (s, 10b-Me). Mass Spectrum: M^+, *m/e* 381.1578. Calcd. for $C_{22}H_{23}O_5N$, 381.1576.

10b-Methyl-6,11-dioxo-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine 23——A solution of **18** (610 mg) in trifluoroacetic acid (3 ml) was allowed to stand overnight at room temperature. The reaction mixture was made alkaline with 10% aq. NaOH and extracted with $CHCl_3$. The remaining residue (376 mg) was crystallized from $CHCl_3$–ether to give **23** (328 mg) as pale yellow prisms, mp 292—295°. NMR (CF_3CO_2D): δ 7.57 (d, J=8 Hz, 10-H), 7.43 (d, J=8 Hz, 9-H), 6.93 (s, 4-H), 6.86 (s, 1-H), 6.06 (s, OCH_2O), 5.23 (s, 4b-H), 4.52 (d, J=12 Hz, 12-H_A), 4.40 (s, 7-OMe), 4.08 (s, 8-OMe), 3.82 (d, J=12 Hz, 12-H_B), 3.40 (s, NMe), 1.66 (s, 10b-Me). Mass Spectrum: M^+, *m/e* 395.1368. Calcd. for $C_{22}H_{21}O_6N$, 395.1357. *Anal.* Calcd. for $C_{22}H_{21}O_6N \cdot 2/3H_2O$: C, 64.86; H, 5.47; N, 3.43. Found: C, 64.77; H, 5.35; N, 3.44.

***trans*-11-Hydroxy-10b-methyl-*cis*-4b,5,6,10b,11,12-hexahydrochelerythrine 21**——(a) To a solution of **23** (128 mg) in dioxane (13 ml) was added LAH (37 mg) and the reaction mixture was refluxed for 30 min with stirring. Work-up afforded an oil (105 mg) which by chromatography on neutral Al_2O_3 (Grade III, 11 g) using benzene–ethyl acetate (95: 5 v/v) as eluent gave **21** (81 mg) as colorless prisms, mp 194—196°

(from $CHCl_3$–ether). Mass Spectrum: M^+, *m/e* 383.1729. Calcd. for $C_{22}H_{25}O_5N$, 383.1732. *Anal.* Calcd. for $C_{22}H_{25}O_5N$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.11; H, 6.71; N, 3.66.

(b) To a solution of **20** (28 mg) in tetrahydrofuran (5 ml) was added LAH (6 mg) and the reaction mixture was refluxed for 30 min. After work-up and chromatography on neutral Al_2O_3 (Grade III), colorless prisms (15 mg) were obtained, which was identified as the carbinol **21** by IR, NMR, mass spectra, and mixed melting point.

Transformation of Dihydroberberine Methochloride 2 (R=OMe, X=Cl) to Berberine Chloride 5——The chloride **2** (880 mg) was dissolved in MeOH (30 ml) and passed through a column of Amberlite IRA 401 (12.8 ml) treated by the Wilson's procedure.[12] The eluate was evaporated *in vacuo* to give the acetate **2** (R=OMe, X=OAc) (902 mg) as yellow solid, mp 134—137°. The acetate was dissolved in acetonitrile (30 ml) and was refluxed for 1 hr. The solvent was evaporated *in vacuo* to give dihydroberberine (761 mg) as oil. To a solution of dihydroberberine in $CHCl_3$ (10 ml) was added a solution of DDQ (510 mg) in $CHCl_3$ (20 ml) with stirring. After stirring for 1 hr at room temperature, the reaction mixture was washed with 15% NH_4OH. The organic layer was filtered, dried over Na_2SO_4 and evaporated *in vacuo*. The remaining residue (598 mg) was treated with conc. HCl (1 drop) and acetone to afford **5** (375 mg) as yellow granules, mp 190—192°, which was identified with an authentic sample by mixed melting point and NMR spectra.

12) N.D.V. Wilson and J.A. Joule, *Tetrahedron*, **24**, 5493 (1968).