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Utilization of Protopine and Related Alkaloids. VI.[1] Transformation of Berberine to 10b-Methylhexahydrobenzo[*c*]phenanthridine Derivative

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The methine base (X) derived from berberine chloride *via* several steps is photocyclized to the two isomeric carbinolamine forms (XI and XII) of 10b-methyl-4b,10b,11,12-tetrahydrochelerythrine. Spectral data and chemical evidences reveal that the positions of the hydroxyl groups are C-6 in XI and C-4b in XII. The *cis* B/C ring juncture in XI is determined by observation of the nuclear Overhauser effect between 10b-Me and 4b-H. The formation pathways of XI and XII are examined and deduced to be the photoinduced intramolecular alkylation on carbon in the enamine system with olefin.

Attempts to obtain corynoline and its analogues from the protopine and related alkaloids have been carried out in our laboratory.[3] The total synthesis of *dl*-chelidonine has recently been reported.[4] We now wish to report synthesis of 10b-methylhexahydrobenzo[*c*]phenanthridine derivative which was prepared as a model compound.

In a previous paper[5] we described the transformation of berberine chloride (I) to chelerythrine. The key step in this transformation is the photolysis of the methine base (IV). If 4-methylisoquinoline derivative (X), analogous to IV, is readily available, the aimed compound will be prepared by the above mentioned procedure.

Methylation of dihydroberberine (II) to obtain 13-methyldihydroberberine (VIII) was described in the literatures.[6] We followed this procedure and found that the N-methyl compound (III) was obtained instead of VIII.

8-Acetonylberberine (VI) derived from I was methylated with methyl iodide in a sealed tube to afford 13-methylberberine iodide (VII)[7] in 60% yield. On reduction with sodium borohydride in pyridine VII was converted into the dihydro compound (VIII) in a fairly yield, which gave the methosulfate (IX). IX afforded the methine base (X) by the Hofmann degradation, which showed a main spot on the thin-layer chromatography (TLC)[8] and was used for the next step without purification because of its unstability.

Irradiation of X was carried out at room temperature under nitrogen by using a high pressure mercury lamp (100 W) in the pure benzene solution and gave a mixture of products, whose TLC showed a main spot accompanied with two faint spots. There was isolated a mixture of the carbinolamines (XI and XII) from the photolysate, whose infrared (IR) spectrum (CCl_4) showed the absorption at 3600 cm^{-1} due to the hydroxyl group and nuclear magnetic resonance (NMR) spectrum showed no signal for the vinyl proton aside from the

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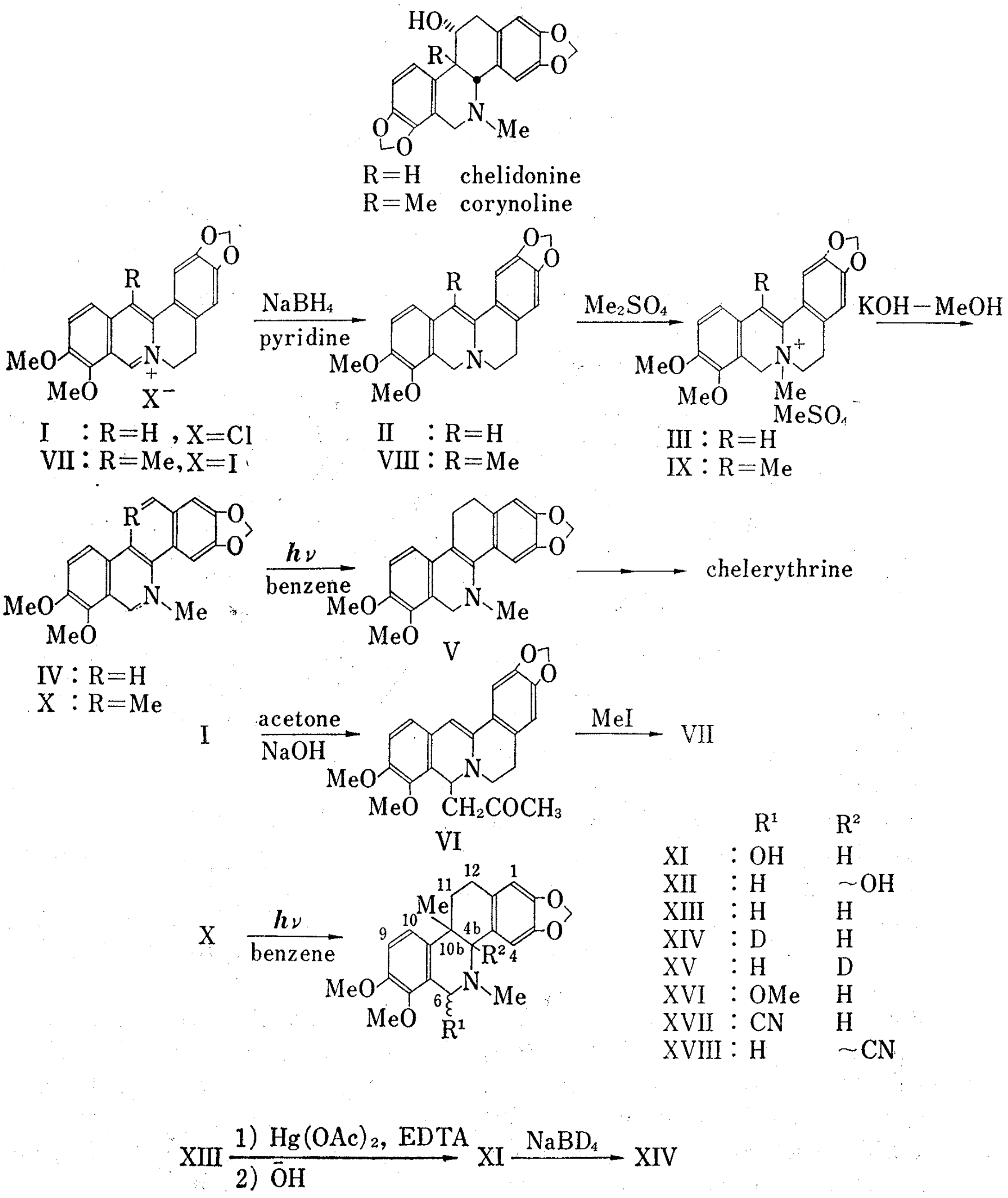
1) Part V: M. Onda, K. Yonezawa, K. Abe, H. Toyama, and T. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **19**, 317 (1971).
2) Location: *Minato-ku, Tokyo, 108, Japan.*
3) Unpublished data.
4) W. Oppolzer and K. Keller, *J. Am. Chem. Soc.*, **93**, 3836 (1971).
5) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **19**, 31 (1971).
6) J. Gadamer, *Arch. Pharm.*, **248**, 610 (1911); M. Freund and K. Fleischer, *Ann.*, **409**, 229 (1915).
7) M. Freund and K. Walbaum, *Ann.*, **409**, 266 (1915); T. Takemoto and Y. Kondo, *Yakugaku Zasshi*, **82**, 1408 (1962); S. Naruto and H. Kaneko, *ibid.*, **92**, 1017 (1972).
8) Silica gel, 0.25 mm; solvent: C_6H_6: AcOEt=1: 1.



	R^1	R^2
XI	OH	H
XII	H	~OH
XIII	H	H
XIV	D	H
XV	H	D
XVI	OMe	H
XVII	CN	H
XVIII	H	~CN

Chart 1

four aromatic protons. These spectral data suggest that XI and XII are the carbinolamine forms of 10b-methyl-4b,10b,11,12-tetrahydrochelerythrine.

The sodium borohydride reduction of the photolysate afforded the hexahydro compound (XIII). Also, the sodium borodeuteride reduction of the photolysate gave a mixture of the deuterated compounds (XIV and XV). The deuterated positions are confirmed to be C-6 in XIV and C-4b in XV, respectively, by comparison of the NMR spectrum of the above mixture with that of XIII. Treatment of the photolysate with sodium cyanide afforded the ψ-cyanides (XVII and XVIII) which were reduced with lithium aluminum deuteride to yield XIV and XV, respectively. The positions of the cyano groups are determined by their NMR spectra which show the signals for 6-H at δ 5.09 s and 4b-H at δ 3.49 s in XVII, and 6-H_2 at δ 4.20 d (J=18) and 3.73 d (J=18) in XVIII. These observations firmly support that the two carbinolamines (XI and XII) exsit in the photolysate and the positions of the hydroxyl groups are C-6 in XI and C-4b in XII.

If X is photocyclized by the electrocyclic reaction, 10b-methyl-4b,5,6,10b-tetrahydrochelerythrine (XX) could be expected *via* an initial photoproduct (XIX) in the same manner of formation of V from IV.$^{5)}$ It is of interest that, contrary to expectation, photolysis of X gave the carbinolamines (XI and XII) instead of XX. On irradiation of X in the presence of dimethyl acetylenedicarboxylate an adduct (XXI), $C_{28}H_{29}O_8N$, was obtained. Its IR spectrum ($CHCl_3$) shows the absorptions at 1729 and 1702 cm^{-1} corresponding to the carbonyl groups of esters. The NMR spectrum of XXI is in good agreement with the structure containing the 4b,12-dicarbomethoxyetheno group, exhibiting the signals for 6-H_2 at δ 4.53 d (J=16) and 4.07 d (J=16), 12-H at δ 4.38 t (J=3) and 11-H_2 at δ 2.52 q (J=12 and 3) and 1.70 q (J=12 and 3). Accordingly, it is obvious that C-4b and C-12 in the initial photoproduct participate in the Diels-Alder reaction.

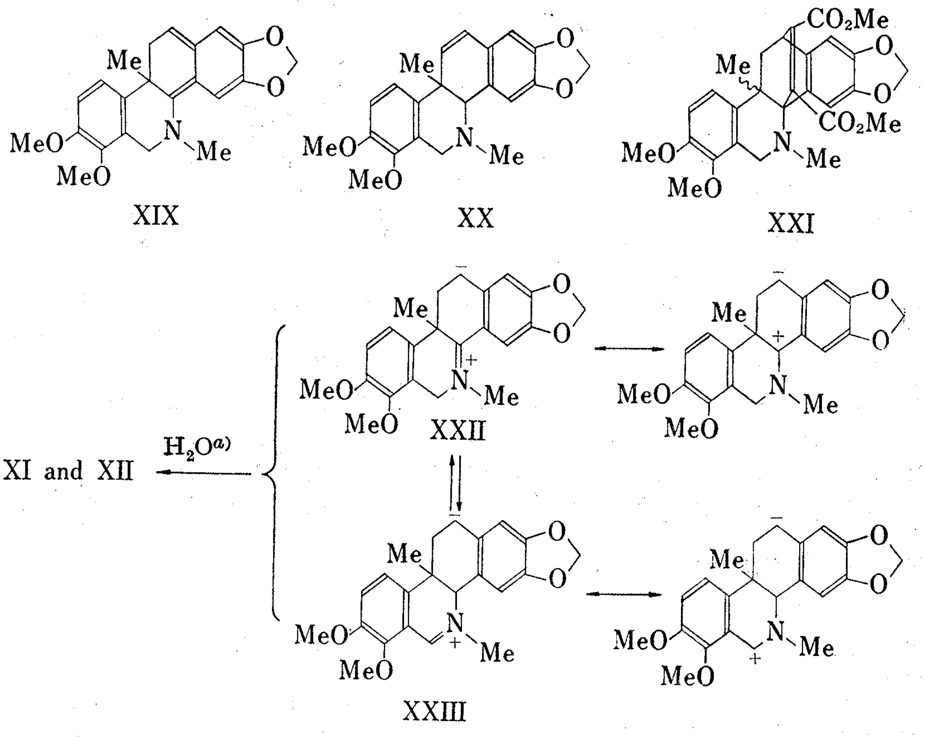


Chart 2

a) It is considered that water would come from the reaction system or the atmosphere during work-up.

When the formation pathways of V from IV were discussed,$^{5)}$ it was mentioned that the photoinduced intramolecular alkylation on carbon in the enamine with olefin should be considered, although it seemed to be rather unlikely, in addition to the electrocyclic reaction of hexatriene system. In the present case, from the structures of the photoproducts (XI and XII) and the adduct (XXI), it seems that the intramolecular alkylation is more reasonable than the electrocyclic reaction. The initial photoproduct would be a dipolar species (XXII) which reacts with dimethyl acetylenedicarboxylate to give the adduct (XXI). We can not state the reason why XXII does not rearrange to XX. However, it might be connnected with the fact that introduction of the double bond between C-11 and C-12 in XI and XIII is very difficult.$^{9)}$ XXII would be equilibrated with another dipolar species (XXIII) *via* the prototropy of allyl-like system. XXII and XXIII would be the precursors responsible for the formation of XI and XII.

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9) Unpublished data.

On oxidation with the system of mercuric acetate and ethylenediaminetetraacetic acid (EDTA) XIII afforded XI which was resulted from the 5,6-dehydro compound.[10] This is confirmed by the facts that XI affords XIV by the sodium borodeutride reduction and the 6-methoxy compound (XVI) by treatment with methanol. Treatment of the photolysate with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of sodium hydroxide, unexpectedly, gave XVII and XVIII instead of the 11,12-dehydro compound. It is considered that these compounds would be resulted from reactions of XI and XII with sodium cyanide generated from DDQ and sodium hydroxide.

When XIV was irradiated at δ 1.18 corresponding to 10b-Me in the NMR spectrum, an increase in the area of 11% was observed for the signal at δ 3.08 corresponding to 4b-H. The structure, in which the B/C ring juncture is *cis*, can explain the existence of the nuclear Overhauser effect between 10b-Me and 4b-H.

Attempts to introduce the double bond between C-11 and C-12 or the hydroxyl group at C-11 in XIII are in progress in our laboratory.

Experimental

Melting points were determined on a micro hot-stage and were uncorrected. IR spectra were measured with a JASCO Model IR-G. NMR Spectra were taken on a Varian HA-60 in $CDCl_3$ unless otherwise stated. Nuclear Overhauser effect was measured in a degassed $CDCl_3$ solution with a Varian HA-100. Mass spectra were taken on a JEOL's JMS-01S.

13-Methylberberine Iodide (VII)——A solution of 8-acetonylberberine (VI) (2.9 g) and methyl iodide (11.6 ml) in methylene chloride (70 ml) was heated at 90—100° for 2.5 hr in a sealed tube. After cooling, the reaction mixture was filtered to remove berberine iodide (1.18 g). The filtrate was evaporated *in vacuo* and the residue was recrystallized from methanol to give VII (2.2 g) as yellow plates of mp 197° (decomp.). NMR (CF_3COOH): δ 9.63 s (8-H), 8.13 s (11-H and 12-H), 7.33 s (1-H), 7.02 s (4-H), 6.15 s $(\mathrm{CH_2}{<}^{\mathrm{O}}_{\mathrm{O}})$, 4.87 t ($J$=6, 6-$H_2$), 4.33 s (9-OMe), 4.22 s (10-OMe), 3.23 t (J=6, 5-H_2), 3.10 s (13-Me). *Anal.* Calcd. for $C_{21}H_{20}O_4NI\cdot 1/2H_2O$: C, 51.85; H, 4.32; N, 2.88. Found: C, 51.76; H, 4.41; N, 2.62.

13-Methyldihydroberberine (VIII)——To a solution of VII (6.0 g) in dry pyridine (60 ml) was added $NaBH_4$ (1.2 g) in a small portion. After stirring for 1 hr at room temperature, the reaction mixture was poured into ice-water to give VIII (4.2 g) as yellowish green crystals of mp 134—135°. NMR: δ 7.07 s (1-H), 6.93 d (J=6, 12-H), 6.83 d (J=6, 11-H), 6.65 s (4-H), 5.97 s $(\mathrm{CH_2}{<}^{\mathrm{O}}_{\mathrm{O}})$, 4.30 s (8-$H_2$), 3.87 s, 3.85 s (9-OMe and 10-OMe), 3.10 m, 2.77 m (5-H_2 and 6-H_2), 2.30 s (13-Me). Mass Spectrum Calcd. for $C_{21}H_{21}O_4N$: mol. wt., 351.1470. Found: M^+, 351.1474.

Methosulfate (IX)——A solution of VIII (3.4 g) and Me_2SO_4 (6.4 ml) in dry benzene (69 ml) was refluxed for 1 hr. The precipitate was collected and recrystallized from methanol to give IX (3.9 g) as yellow prisms of mp 243—245°. *Anal.* Calcd. for $C_{23}H_{27}O_8NS$: C, 57.84; H, 5.66; N, 2.93. Found: C, 57.93; H, 5.71; N, 3.13.

Methine Base (X)——A suspension of IX (2.0 g) in 25% KOH–MeOH (10 ml) was refluxed for 15 min with stirring. After cooling, the reaction mixture was poured into ice-water to give X (1.5 g) as yellow powder of mp 30—36°, whose TLC[11] showed a main spot. NMR: δ 7.13 s (1H), 6.80 s (2H), 6.63 s (1H) (aromatic protons), 6.80 q (J=16 and 10, CH=), 5.55 q (J=16 and 2), 5.10 q (J=10 and 2) (CH_2=), 6.00 s $(\mathrm{CH_2}{<}^{\mathrm{O}}_{\mathrm{O}})$, 4.35 s ($CH_2$-N), 3.87 s (2×OMe), 2.43 s (N-Me), 1.63 s (Me-C=).

Photolysis of X——Using a high pressure mercury lamp (100 W), a solution of X (2.96 g) in pure benzene (900 ml) was irradiated for 1 hr at room temperature under nitrogen. After removal of benzene, the residue was recrystallized from ether to give a mixture of the carbinolamines (XI and XII) (890 mg) as light yellow crystals of mp 124—130°, whose NMR spectrum showed that the ratio of XI and XII was approximately 2: 1 from the signal for 6-H in XI. NMR: δ 7.05 d (J=8, 10-H), 6.90 d (J=8, 9-H), 6.77 s (4-H), 6.60 s (1-H), 5.90 s $(\mathrm{CH_2}{<}^{\mathrm{O}}_{\mathrm{O}})$, 5.60 s (6-H in XI), 3.93 s (4b-H in XI), 4.23 d (J=18), 3.70 d (J=18) (6-H_2 in XII), 3.93 s (7-OMe), 3.85 s (8-OMe), 2.73 m (12-H_2), 2.30 s (N-Me in XI), 2.22 s (N-Me in XII), 1.67 m (11-H_2), 1.20 s (10b-Me in XII), 1.13 s (10b-Me in XI). Mass Spectrum Calcd. for $C_{22}H_{24}O_4N$: mol. wt., 366.1705.

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[10] M.H. Benn and R.E. Mitchell, *Can. J. Chem.*, 47, 3701 (1969); N. Takao, *Chem. Pharm. Bull.* (Tokyo), 19, 247 (1971).

[11] Silica gel, 0.25 mm; solvent: C_6H_6: AcOEt=1: 1.

Found: $(M-OH)^+$, 366.1702. The ether filtrate was evaporated, and the residue (2.4 g) was dissolved in benzene–methanol (1: 1) (20 ml) and then reduced with $NaBH_4$ (1.2 g). Work-up gave a syrup (2.1 g) which was chromatographed over neutral Al_2O_3 (Grade III) (25 g). Elution with benzene afforded a syrup (1.39 g) which gave the oxalate (1.01 g) of XIII, mp 162—165°.

10b-Methyl-4b,5,6,10b,11,12-hexahydrochelerythrine (XIII)——The photolysate obtained from X (1.5 g) was dissolved in benzene–methanol (1: 1) (20 ml) and $NaBH_4$ (1.0 g) was added. After work-up, there was obtained a syrup (1.57 g) which was chromatographed over neutral Al_2O_3 (Grade III) (20 g). Elution with benzene gave a syrup (1.12 g) which afforded the oxalate (960 mg) of XIII. The oxalate was treated with 10% NH_4OH and extracted with benzene. The benzene residue (680 mg) was recrystallized from ether to give colorless plates (550 mg) of mp 118—119°. NMR: δ 7.03 d ($J=8$, 10-H), 6.80 d ($J=8$, 9-H), 6.72 s (4-H), 6.57 s (1-H), 5.90 s ($CH_2{<}^{O}_{O}$), 4.10 d ($J=16$), 3.47 d ($J=16$), (6-H_2), 3.83 s ($2\times$OMe), 3.08 s (4b-H), 2.70 m (3H), 2.30 s (N-Me), 1.67 m (1H), 1.10 s (10b-Me). Mass Spectrum Calcd. for $C_{22}H_{25}O_4N$: mol. wt., 367.1783. Found: M^+, 367.1784.

Reduction of the Photolysate with $NaBD_4$——The same procedure as above was carried out with $NaBD_4$. There was obtained a mixture of XIV and XV, whose NMR spectrum showed that the ratio of XIV and XV was approximately 1.2: 1 from the signal for 6-H in XIV.

***p*-Cyanides (XVII and XVIII)**——a) The photolysate obtained from X (2.2 g) was added to a mixture of benzene (950 ml) and 5% aq. NaOH (30 ml), and then DDQ (3.0 g) was added in a small portion. After stirring for 1.5 hr, the reaction mixture was filtered. The filtrate was washed with 5% aq. NaOH and H_2O. The residue was chromatographed over neutral Al_2O_3 (Grade III) (60 g) by using benzene as eluent to give a mixture of XVII and XVIII (389 mg). On recrystallization of the above mixture from acetone–ether there was obtained XVII (169 mg) as colorless needles of mp 187—190°. IR ($CHCl_3$): 2220 cm^{-1} (CN). NMR: δ 7.05 d ($J=8$, 10-H), 6.95 d ($J=8$, 9-H), 6.75 s (4-H), 6.63 s (1-H), 5.96 s ($CH_2{<}^{O}_{O}$), 5.09 s (6-H), 4.05 s (7-OMe), 3.89 s (8-OMe), 3.49 s (4b-H), 2.71 m (3H), 2.30 s (N-Me), 1.70 m (1H), 1.16 s (10b-Me). *Anal.* Calcd. for $C_{23}H_{24}O_4N_2$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.32; H, 6.26; N, 7.06. Mass spectrum Calcd. for $C_{23}H_{24}O_4N_2$: mol. wt., 392.1736. Found: M^+, 392.1687. The acetone–ether filtrate gave XVIII (20 mg) as colorless granules of mp 167—171° (from acetone–ether). IR ($CHCl_3$): 2220 cm^{-1} (CN). NMR: δ 7.15 s (4-H), 7.03 d ($J=10$, 10-H), 6.83 d ($J=10$, 9-H), 6.64 s (1-H), 5.98 s ($CH_2{<}^{O}_{O}$), 4.20 d ($J=18$), 3.73 d ($J=18$), (6-H_2), 3.89 s ($2\times$OMe), 2.70 m (3H), 2.21 s (N-Me), 1.71 m (1H), 1.42 s (10b-Me). *Anal.* Calcd. for $C_{23}H_{24}O_4N_2$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.31; H, 6.24; N, 7.12. Mass Spectrum Calcd. for $C_{23}H_{24}O_4N_2$: mol. wt., 392.1736. Found: M^+, 392.1698.

b) To a solution of the photolysate obtained from X (370 mg) in benzene (15 ml) was added a solution of NaCN (100 mg) in H_2O (5 ml). After refluxing for 1.5 hr, the benzene layer was washed with H_2O and dried over Na_2SO_4. Removal of benzene gave a syrup (409 mg). Its chromatography over neutral Al_2O_3 (Grade III) (12 g) by using benzene as eluent afforded a mixture of XVII and XVIII (170 mg), whose NMR spectrum showed that the ratio of XVII and XVIII was approximately 2:1 from the signals for 10b-Me.

Reduction of XVII with $LiAlD_4$——To a solution of XVII (70 mg) in dry benzene (16 ml) was added a solution of $LiAlD_4$ (35 mg) in dry ether (6 ml) with stirring at room temperature. The reaction mixture was refluxed for 1 hr. After work-up ,there was obtained a syrup (66 mg), which gave XIV (30 mg) as colorless plates of mp 117—119° by recrystallization from acetone–ether. NMR: δ 4.10 s (6-H).

Reduction of XVIII with $LiAlD_4$——XVIII (138 mg) gave XV (41 mg) as colorless plates of mp 118—120° *via* the same procedure as above. NMR: δ 3.08 s (4b-H).

Oxidation of XIII with $Hg(OAc)_2$——To a solution of XIII (62 mg) in 5% AcOH (15 ml) was added dropwise a solution of $Hg(OAc)_2$ (170 mg) and EDTA-2Na (200 mg) in 5% AcOH (10 ml) under nitrogen, and refluxing was continued for 2 hr. The reaction mixture was filtered, made alkaline with 10% aq. NaOH and extracted with benzene. Removal of benzene afforded XI (57 mg) as solid of mp 109—115°, which was converted with $NaBD_4$ into XIV and also transformed with methanol to the 6-methoxy compound (XVI) as colorless crystals of mp 115—122° in a nearly quantitative yield. XVI, NMR: δ 7.10 d ($J=8$, 10-H), 6.93 d ($J=8$, 9-H), 6.92 s (4-H), 6.60 s (1-H), 5.93 s ($CH_2{<}^{O}_{O}$), 5.13 s (6-H), 4.07 s (4b-H), 3.95 s (7-OMe), 3.90 s (8-OMe), 3.70 s (6-OMe), 2.73 m (12-H_2), 2.22 s (N-Me), 1.83 m (11-H_2), 1.17 s (10b-Me). Mass Spectrum Calcd. for $C_{23}H_{27}O_5N$: mol. wt., 397.1889. Found: M^+, 397.1841.

4b,12-Dicarbomethoxyetheno-10b-methyl-4b,5,6,10b,11,12-hexahydrochelerythrine (XXI)——A solution of X (750 mg) and dimethyl acetylenedicarboxylate (400 mg) in pure benzene (400 ml) was irradiated with a high pressure mercury lamp (100 W) for 30 min at room temperature under nitrogen. After evaporation, the residue was chromatographed over neutral Al_2O_3 (Grade III) (13 g) by using benzene–*n*-hexane (9: 1) as eluent to afford XXI (57 mg) as pink crystals of mp 199—202°. Mass Spectrum Calcd. for $C_{28}H_{29}O_8N$: mol. wt., 507.1893. Found: M^+, 507.1817.