[Chem. Pharm. Bull. 19(1) 31 — 36 (1971)]

UDC 547.94.04

Utilization of Protopine and Related Alkaloids. IV.[1] Transformation of Protopine and Protoberberine Alkaloid to Benzo[*c*]phenanthridine Alkaloid

Masayuki Onda, Kyoko Yonezawa, and Kaoru Abe

School of Pharmacy, Kitasato University[2]

(Received May 29, 1970)

Anhydroprotopine and anhydromethylberberine were photocyclized to yield 5,6,11,12-tetrahydrobenzo[*c*]phenanthridine derivatives, which were derived *via* two steps to sanguinarine and chelerythrine, respectively, in good yield. 5,6,11,12-Tetrahydrobenzo[*c*]-phenanthridine derivative resulted from the initial photoproduct *via* rearrangement, which was trapped with dimethyl acetylenedicarboxylate as 4b,12-etheno-compound.

The numerous attempts to obtain the benzo[*c*]phenanthridine alkaloid from protopine and related alkaloids have been carried out in our laboratory. An attractive attempt was the cyclization of Hofmann-base (III) which was readily available from protopine alkaloid (I) *via* dihydroberberine-type compound (II). In our previous papers[1,3] we described the acid catalyzed cyclization of III. However, contrary to expection, III was cyclized to yield the five membered spiro compounds (IV and V) with dilute hydrochloric acid and we proposed the reaction pathway *via* the immonium intermediate (VI) which was formed from III in the presence of acid.

Recently, Dyke, *et al.*[4] have reported the conversion of anhydrocryptopine (VII), which was closely related to III, to epicryptopirubin chloride (VIII) by the treatment with concentrated hydrochloric acid and then with phosphorus oxychloride.

After several unsuccessful attempts III was photocyclized to yield the benzo[*c*]phenanthridine derivative. We now wish to report, in full, the reactions described in our preliminary communication,[5] together with some further results.

The irradiation of III was carried out at room temperature under nitrogen by using a high pressure mercury lamp (100 W) in the pure benzene solution. The progress of the reaction was followed by thin-layer chromatography (TLC). Thus, IIIa and IIIb were converted to the compound (IXa), mp 163.5—165°, $C_{20}H_{17}O_4N$ and the compound (IXb), mp 168.5—169.5°, $C_{21}H_{21}O_4N$, respectively. The nuclear magnetic resonance (NMR) spectra of these compounds show the signals for the four aromatic protons and the six protons of methylene groups, indicating that the compound (IX) coincides with 5,6,11,12-tetrahydrobenzo[*c*]-phenanthridine derivative. III possesses the hexatriene system including one of the double bond of benzene ring. If the photocyclization of III can be considered as the electrocyclic reaction of hexatriene, the initial photoproduct must be 5,6,10b,11-tetrahydro-compound (X) which immediately rearranges to IX. An attempt to trap X was carried out by using the active Diels-Alder dienophile to confirm the above deduction. The irradiation of IIIb in the presence of dimethyl acetylenedicarboxylate (XI) afforded the compound (XII), $C_{27}H_{27}O_8N$. The infrared (IR) spectrum of XII shows the absorption band at 1715 cm^{-1} corresponding to the carbonyl groups of esters. On the other hand, when IXb was irradiated in the presence of XI, the compound (XII) was not formed. These facts indicate that XII is not an adduct of IXb with XI but either IIIb or X with XI. As shown

---

[1] Part III: M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **17**, 2565 (1969).

[2] Location: *Minato-ku, Tokyo.*

[3] M. Onda, K. Abe, and K. Yonezawa, *Chem. Pharm. Bull.* (Tokyo), **16**, 2005 (1968).

[4] S.F. Dyke and D.M. Brown, *Tetrahedron*, **25**, 5375 (1969).

[5] M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **17**, 404 (1969).

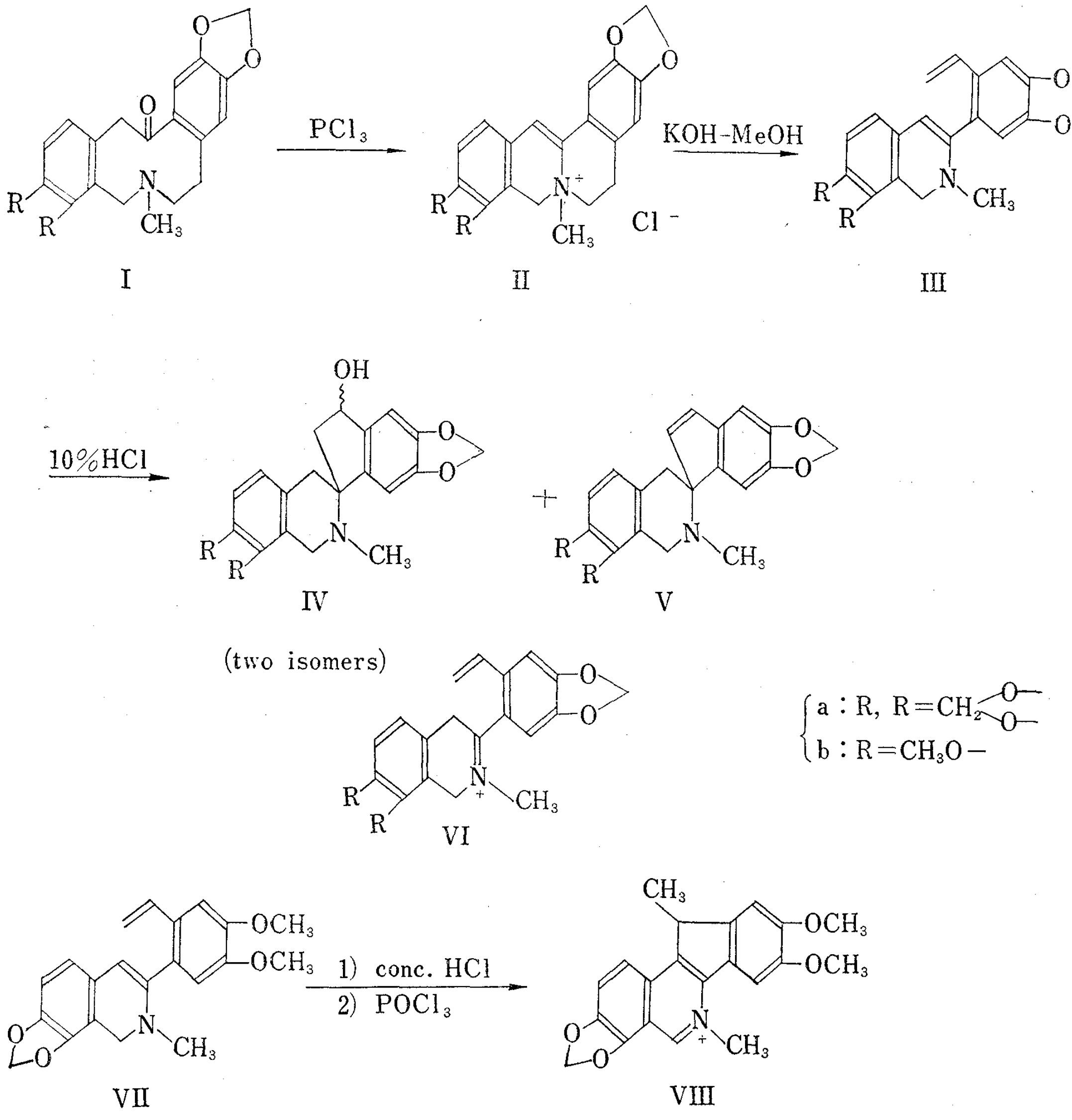

Chart 1

in Fig. 1, the NMR spectrum of the cycloaddition product is in good agreement with the structure presented as XII, exhibiting the signals for N–CH_3 at 7.04 (s), two $COOCH_3$ at 6.22 (s), two aromatic OCH_3 at 6.17 (s) and 6.19 (s), C_6–H_2 at 5.65 (s), $CH_2\langle{}^{O-}_{O-}$ at 4.22 (s), and four aromatic protons at 3.27 (s, 2H), 3.39 (d, $J=9$), and 3.47 (d, $J=9$). The remaining four protons were analysed as the following manner by a spin-decoupling study. A quartet at 5.58 couples both with an octet at 7.68, $J=4$, and with an octet at 8.30, $J=2.5$. A quartet at 6.75, also, couples both with an octet at 7.68, $J=10$, and with an octet at 8.30, $J=7$. Two octets mutually couple by $J=12$. From these observations C_{12}–H, C_{10b}–H, C_{11}–H_A, and C_{11}–H_B reasonably assigned to the signals at 5.58 (q) 6.75 (q), 7.68 (oct), and 8.30 (oct). The configuration of XII will be described elsewhere, but the adduct (XII) is surely considered to be 4b,12-etheno-compound.

On the other hand, although it seems to be rather unlikely from the reaction conditions, the alternative reaction pathway remains to be considered. If this reaction can be considered as a photoinduced intramolecular alkylation on carbon in the enamine with olefine, the first step in this reaction appears to be the formation of the dipolar species (XIII) which can immediately rearrange to IX. However, since both XIII and X are the canonical forms in resonance, it seems likely that the initial product (XIII) is also trapped as the adduct (XII).

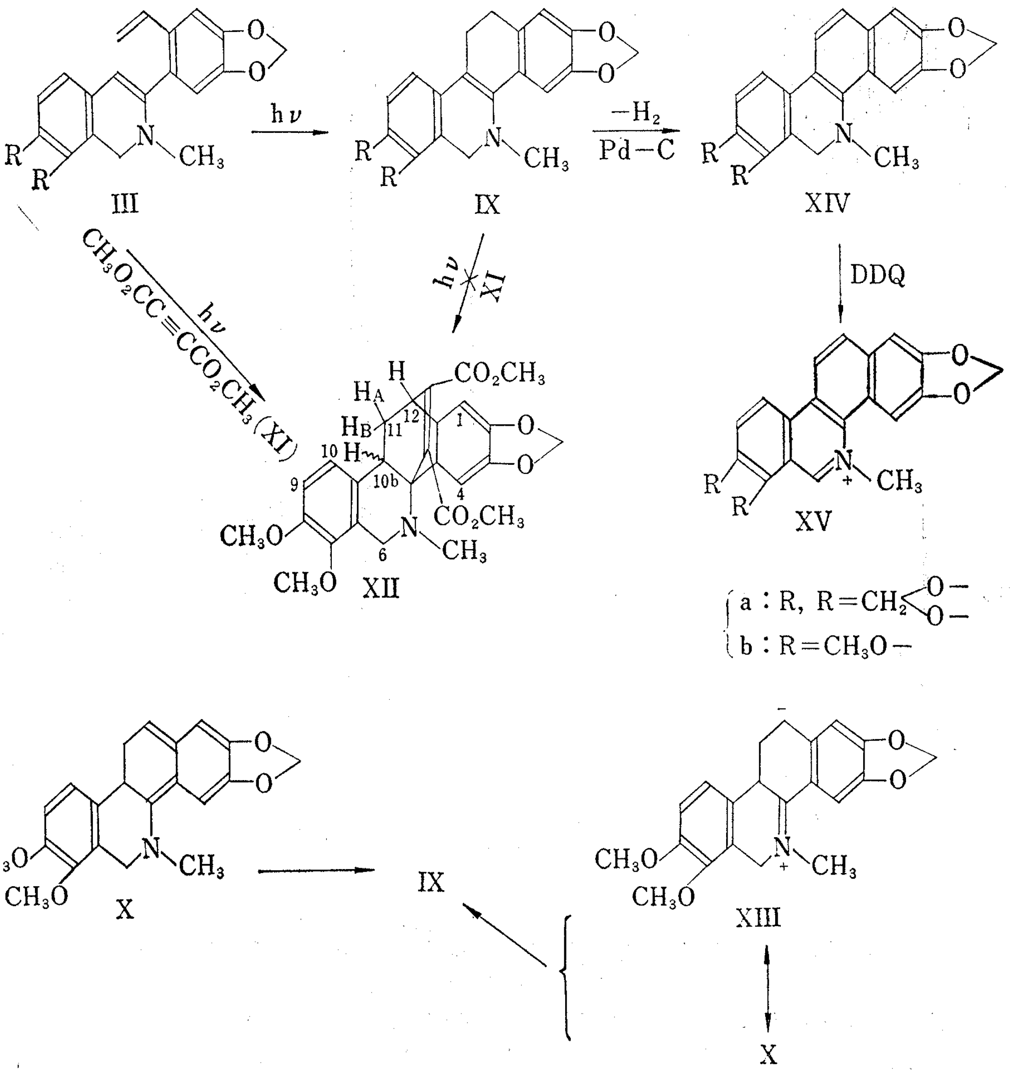

Chart 2

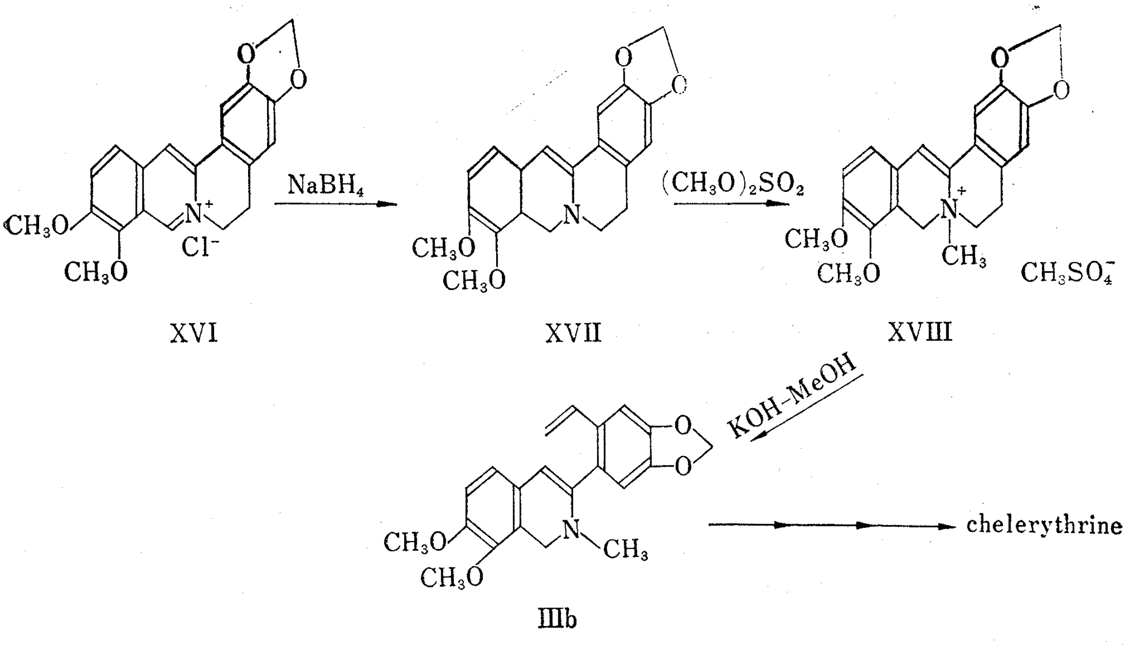

Chart 3

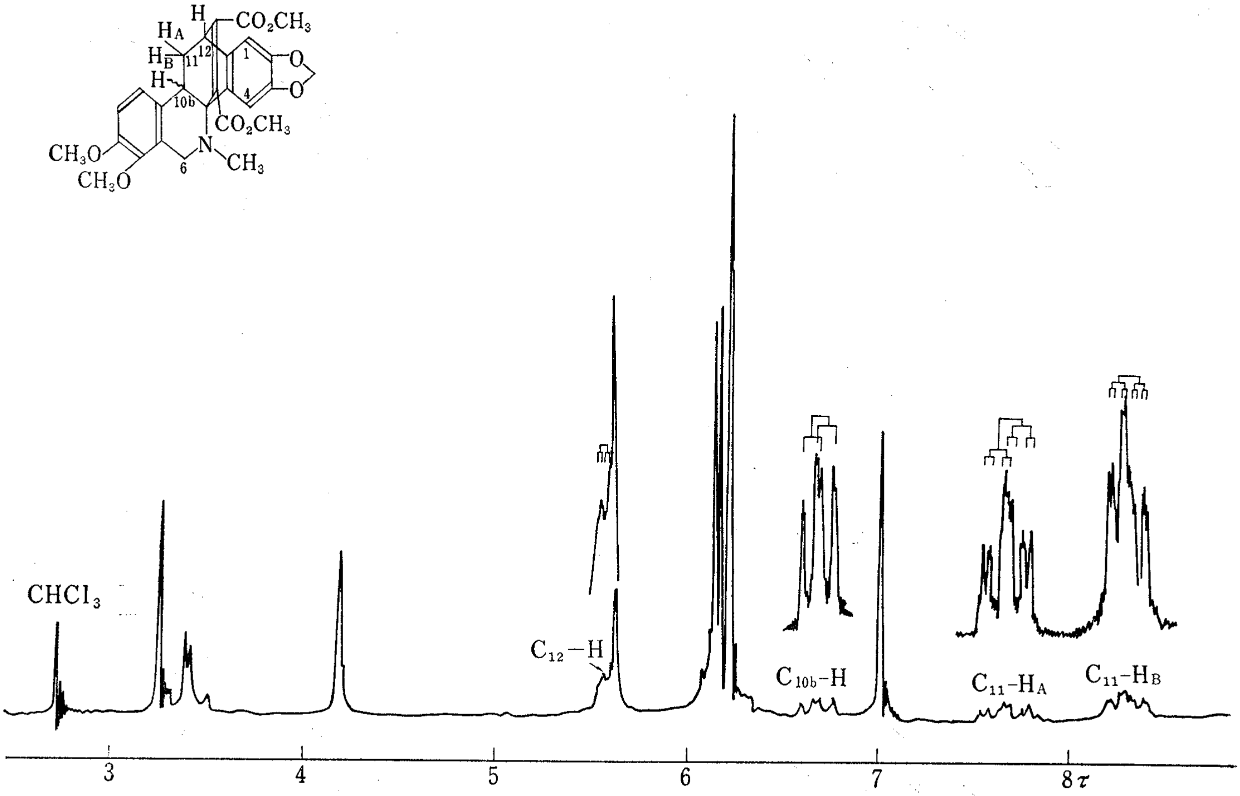

Fig. 1. NMR Spectrum of XII (100 Mc)

In any case, it is obvious that 5,6,11,12-tetrahydro-compound (IX) is not the initial photoproduct but results from the initial photoproduct *via* rearrangement.

IXa and IXb were dehydrogenated over palladium-carbon to yield the compound (XIVa), mp 190—191°, $C_{20}H_{15}O_4N$ and the compound (XIVb), mp 169—171°, $C_{21}H_{19}O_4N$, respectively. The NMR spectrum of XIVa shows the signals for the six aromatic protons at 2.28 (s), 2.31 (d, $J=9$), 2.52 (d, $J=9$), 2.70 (d, $J=8$), 2.90 (s), and 3.17 (d, $J=8$). The ultraviolet (UV) spectrum of XIVa shows the absorption bands at $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 237.2 (5.28), 284.8 (5.28), 323.7 (4.90), 336 (s) (4.80), 350 (s) (4.38). The NMR spectrum of XIVb shows the signals for the aromatic protons at 2.29 (s), 2.31 (d, $J=8$), 2.50 (d, $J=8$), 2.53 (d, $J=8$), 2.90 (s), and 3.08 (d, $J=8$). The UV spectrum shows the absorption bands at $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 228 (5.52), 282.9 (5.69), 319.3 (5.15), 338.8 (s) (4.96), and 349.3 (s) (4.43). Both compounds (XIVa and XIVb) are identified to be dihydrosanguinarine and dihydrochelerythrine, respectively, by the comparison of the NMR spectra, the UV spectra, and the mixed melting points.

XIVa and XIVb were also oxidized to yield the compounds (XVa and XVb) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) which were identified with naturally occurring sanguinarine and chelerythrine, respectively.

Meanwhile, berberine chloride (XVI), one of protoberberine alkaloid, was smoothly reduced with sodium borohydride to yield dihydroberberine (XVII)[6] which was methylated with dimethyl sulfate to give dihydroberberine methosulfate (XVIII). The methosulfate (XVIII) was easily converted to anhydromethylberberine (IIIb) by Hofmann degradation. Hence, berberine can be transformed to chelerythrine *via* the above procedure. Further, whenever protoberberine-type compounds (II), which are easily obtainable from 1-benzyl-1,2,3,4-tetrahydroisoquinolines, are transformed to the III-type compounds in good yield, this

---

[6] I.W. Elliott, Jr., *J. Hetero. Chem.*, 4, 639 (1967).

photocyclization shoud be promised to be the key reaction of the synthesis of benzo[*c*]phenanthridine alkaloids.

Experimental

Melting points were determined on a micro hot-stage and were uncorrected. Ultraviolet spectra were measured with a Hitachi EPS-2U and infrared spectra with a JASCO Model IR-S. Nuclear magnetic resonance spectra were measured in $CDCl_3$ unless otherwise stated with a Hitachi Perkin-Elmer H-60 (60 Mc) and a JEOL's JNM-4H-100 (100 Mc). Chemical shifts were given in τ values, using tetramethylsilane as internal reference and coupling constants (J) in cps. The following abbreviations were used to describe the signals: s, singlet; d, doublet; t, triplet; oct, octet; m, multiplet. Mass spectra were measured with a JEOL's JMS-01S.

Dihydroberberine Methosulfate (XVIII)——To a boiling solution of dihydroberberine[6] (1.5 g) in dry benzene (20 ml) was added dropwise $(CH_3O)_2SO_2$ (1.5 ml) and the solution was refluxed for 2 hr. After the reaction mixture was cooled, the precipitate was filtered and recrystallized from EtOH to give yellow prisms (1.9 g), mp 208—211°. NMR (D_2O, 60 Mc): 2.97 (s) (4 aromatic protons), 3.25 (s) (C_{12}-H). *Anal.* Calcd. for $C_{22}H_{25}O_8NS \cdot 1\frac{1}{2}H_2O$: C, 53.86; H, 5.75; N, 2.85. Found: C, 53.65; H, 5.65; N, 2.82. Dihydroberberine methiodide, mp 214—218°, which was derived from XVIII by the treatment with KI, was identified with the methiodide which was derived from α-allocryptopine.

Anhydroprotopine (IIIa)——IIIa was prepared from protopine (Ia) *via* isoprotopine chloride (IIa).[3,7] There was obtained pale yellow granules, mp 113—115°.

Anhydromethylberberine (IIIb)——IIIb was prepared from α-allocryptopine (Ib) *via* dihydroberberine methochloride (IIb) by the same procedure as described in our previous paper.[1] There was obtained pale yellow granules, mp 80—85°. Also IIIb was prepared from XVIII by the same procedure as above.

5,6,11,12-Tetrahydrosanguinarine (IXa)——Using a high pressure mercury lamp (100 W), a solution of IIIa (200 mg) in pure benzene (100 ml) was irradiated for 20 min at room temperature under N_2. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized from *n*-hexane–acetone to give pale yellow plates (133 mg), mp 163.5—165°. UV λ_{max}^{EtOH} mμ (log ε): 213 (4.07), 225 (3.99), 258 (3.65), 286 (3.50), 335 (s) (3.84), 352 (3.99), 364 (3.94). NMR: 2.80 (s) (C_4-H), 3.22 (s) (C_9-H and C_{10}-H), 3.33 (s) C_1-H), 4.04 (s) $(CH_2\langle{}^{O-}_{O-})$, 4.08 (s) $(CH_2\langle{}^{O-}_{O-})$, 5.89 (s) ($C_6$-$H_2$), 7.27 (m) ($C_{11}$-$H_2$ and C_{12}-H_2), 7.55 (s) (N–CH_3). *Anal.* Calcd. for $C_{20}H_{17}O_4N$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.93; H, 5.22; N, 4.17.

5,6,11,12-Tetrahydrochelerythrine (IXb)——IXb was prepared in *ca.* 70% yield by the same procedure as described above. There was obtained paleyellow rosettes, mp 168.5—169.5°. UV λ_{max}^{EtOH} mμ (log ε): 214 (3.84), 244 (3.55), 250 (3.53), 334 (3.66), 350 (3.80), 362 (3.75). NMR: 2.81 (s) (C_4-H), 2.97 (d, $J=8.4$) (C_{10}-H), 3.18 (d, $J=8.4$) (C_9-H), 3.33 (s) (C_1-H), 4.09 (s) $(CH_2\langle{}^{O-}_{O-})$, 5.82 (s) ($C_6$-$H_2$), 6.12 (s) (O–$CH_3$), 7.29 (m) ($C_{11}$-$H_2$ and C_{12}-H_2), 7.57 (s) (N–CH_3). *Anal.* Calcd. for $C_{21}H_{21}O_4N$: C, 71.78; H, 6.02; N, 3.99. Found; C, 71.88; H, 6.11; N, 3.99.

4b,12-Dicarbomethoxyetheno-4b,5,6,10b,11,12-hexahydrochelerythrine (XII)——Using a high pressure mercury lamp (100 W), a solution of IIIb (771 mg) and dimethyl acetylenedicarboxylate (300 mg) in pure benzene (400 ml) was irradiated for 20 min at room temperature under N_2. TLC[8] showed one main spot (*Rf*, 0.1) and one faint spot (*Rf*, 0.44) which was identified with IXb. The reaction mixture was evaporated *in vacuo* and the residue was chromatographed over Al_2O_3 (neutral, grade III) (50 g). Elution with benzene afforded a syrup (490 mg), whose TLC[8] showed one spot (*Rf*, 0.1). Mass Spectrum: M^+, 493.1710; $C_{27}H_{27}O_8N$ (493.1736).

Dihydrosanguinarine (XIVa)——A mixture of IXa (130 mg) and Pd–C (80 mg) in *p*-cymene (4 ml) was refluxed for 20 min. After the reaction mixture was cooled, Pd–C was filtered off and washed with benzene. The combined filtrates were treated with dry HCl gas to give the HCl-salt. The precipitate was filtered, made alkaline with aqueous ammonia and then extracted with AcOEt. The residue (91 mg) was chromatographed over Al_2O_3 (neutral, grade III) (7 g), by using benzene as eluent to afford colorless needles (71 mg), mp 190—191°. *Anal.* Calcd. for $C_{20}H_{15}O_4N$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.10; H, 4.45; N, 4.15.

Dihydrochelerythine (XIVb)——A mixture of IXb (115 mg) and Pd–C (70 mg) in *p*-cymene (4 ml) was refluxed for 20 min. The reaction mixture was treated by the same procedure as described above to furnish colorless needles (80 mg), mp 169—171°. *Anal.* Calcd. for $C_{21}H_{19}O_4N$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.10; H, 5.55; N, 4.03.

Sanguinarine (XVa)——To a mixture of XIVa (50 mg) in benzene (2 ml) and 5% NaOH aq. solution (0.9 ml) was added dropwise a solution of DDQ (49 mg) in benzene (2 ml) with stirring. The stirring was

---

7) W.H. Perkin, *J. Chem. Soc.*, **1916**, 815.

8) Alumina plate, 0.25 mm; solvent, benzene.

continued for 30 min. The reaction mixture was made alkaline with 10% NaOH aq. solution and extracted with AcOEt. The residue was dissolved in acetone and acidified with conc. HCl to give the HCl-salt (35 mg), orange needles, mp 286—288°, which was identified with naturally occurring sanguinarine chloride by the mixed mp.

Chelerythrine (XVb)——To a mixture of XIVb (100 mg) in benzene (8 ml) and 5% NaOH aq. solution (1 ml) was added dropwise a solution of DDQ (97 mg) in benzene (2 ml) with stirring. The reaction mixture was treated by the same procedure as described above to give chelerythrine chloride (71 mg), yellow needles, mp 196—197°, which was identified with naturally occurring chelerythrine chloride by the mixed mp.