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Transformation of Phthalideisoquinoline Alkaloid to Benzo[*c*]phenanthridine Alkaloid

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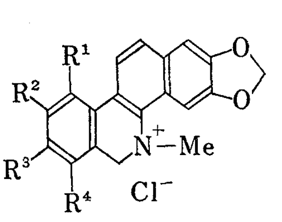
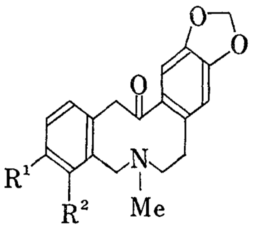
l-*α*-Narcotine is easily converted into dihydroprotoberberine methiodide. The Hofmann degradation of this methiodide gives methine base which is transformed to benzo[*c*]phenanthridine derivative by photocyclization and dehydrogenation.

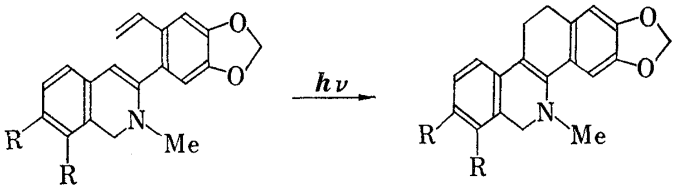
Since the isolation of benzo[*c*]phenanthridine alkaloids, sanguinarine (Ia), chelerythrine (Ib), and bocconine (Ic), possessing nematocidal and antibacterial activities, from *Bocconia cordata*,[2] we have carried out transformation of easily available but biologically non-utilized alkaloids to benzo[*c*]phenanthridines to examine their biological activity. We have already reported the transformation of protopine (IIa) and *α*-allocryptopine (IIb) to Ia and Ib, respectively.[3] The key step in this transformation is the photocyclization of the methine base (III), derived from dihydroprotoberberine methohalides, to 5,6,11,12-tetrahydrobenzo[*c*]phenanthridines (IV). If the III-type compounds can be obtained easily, this method of transformation including photocyclization would be useful for the syntheses of benzo[*c*]phenanthridine alkaloids in general. In the present series of work, the foregoing method was utilized for transformation of *l*-*α*-narcotine to benzo[*c*]phenanthridine derivative, details of which are reported herein.



I a : R^1=H, R^2=H, R^3,R^4=OCH_2O
I b : R^1=H, R^2=H, R^3=OMe, R^4=OMe
I c : R^1,R^2=OCH_2O, R^3=H, R^4=OMe



IIa : R^1,R^2=OCH_2O
IIb : R^1=R^2=OMe



III IV

Chart 1

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[1] Location: *Minato-ku, Tokyo*.
[2] M. Onda, K. Takiguchi, M. Hirakura, H. Fukushima, M. Akagawa, and F. Naoi, *J. Agr. Chem. Soc. Japan*, **39**, 168 (1965).
[3] M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **19**, 31 (1971).

Treatment of *l*-α-narcotinediol (VI), obtained by reduction of *l*-α-narcotine (V) with lithium aluminum hydride (LAH), with methanesulfonyl chloride in the presence of pyridine converted it into 13α-hydroxy-2,3-methylenedioxy-1,9,10-trimethoxytetrahydroprotoberberine methochloride (VII)[4] in 49% yield. Attempted dehydration of VII to dihydroprotoberberine methochloride (VIII, X=Cl) did not materialize. Treatment of VI with thionyl chloride in chloroform, in the presence of potassium carbonate, resulted in its cyclization and dehydration to form the methochloride (VIII, X=Cl), which was converted to the methiodide (VIII, X=I) in an overall yield of 76% by treatment with sodium iodide. The nuclear magnetic resonance (NMR) spectrum of this methiodide shows signals for three aromatic protons at

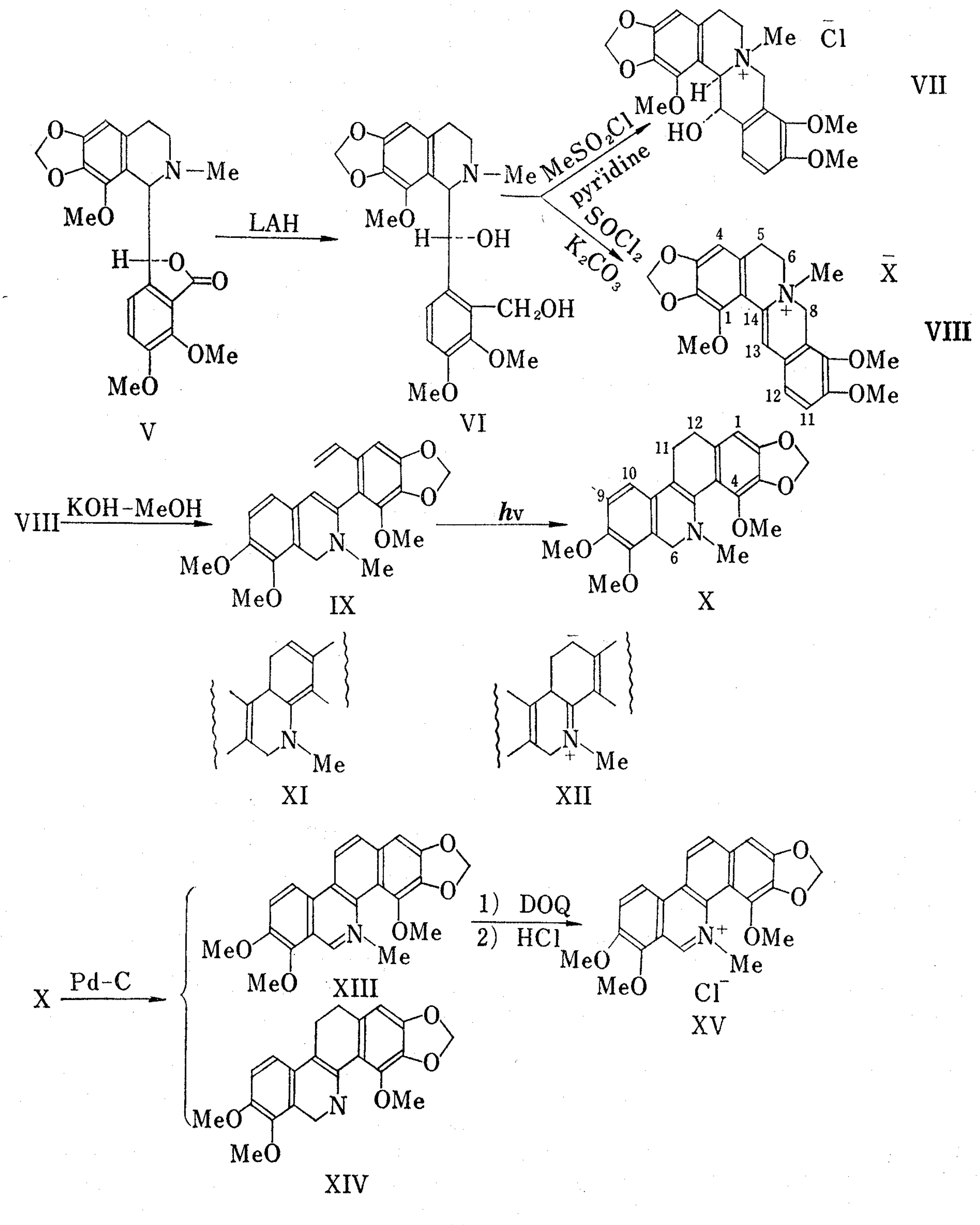

Chart 2

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[4] A.R. Battersby and H. Spencer, *J. Chem. Soc.*, **1965**, 1089; M. Ohta, H. Tani, S. Morozumi, and S Kodaira, *Chem. Pharm. Bull.* (Tokyo), **12**, 1080 (1964).

δ 7.05 d, 6.69 d, and 6.44 s, and a signal for one vinyl proton at δ 7.64 s, indicating the presence of a double bond between C-13 and C-14. The signal for 13-H is shifted to a fairly lower magnetic field and this is considered to be due to the interaction of 13-H with quaternary nitrogen and 7-OMe. Presence of the latter interaction can be explained from the fact that 7-OMe shows a signal in lower field (δ 4.06) than those other OMe groups (δ 3.86 and 3.98). The methiodide (VIII, X=I) easily gave a methine base (IX) by the Hofmann degradation, and irradiation of IX with a high-pressure mercury lamp (100 W) resulted in the formation of the 5,6,11,12-tetrahydrobenzo[*c*]phenanthridine compound (X) in 50% yield. The structure for X is supported by its NMR spectrum which shows the signals for four ring methylene protons at δ *ca.* 2.65 m in place of those for four vinyl protons presented in the NMR spectrum of IX. As was discussed for the formation of IV,[3,5] it is considered that X is formed by aromatization of 5,6,10b,11-tetrahydro compound (XI) formed by the electrocyclic reaction of the hexatriene system or the dipolar species (XII) obtained by the photo-induced intramolecular alkylation on the enamine carbon by olefin.

Dehydrogenation of X over palladium-carbon afforded the compound (XIII) and a small amount of the compound (XIV). The NMR spectrum of XIII shows signals for five aromatic protons at δ 8.59 d, 8.44 d, 8.12 d ,8.07 d, and 7.27 s, a signal for 6-2H at δ 4.33 s, and one for N-Me at δ 2.6 s, from which it is certain that XIII is the objective 5-methyl-5,6-dihydro compound.

On the other hand, the NMR spectrum of XIV shows signals for four aromatic protons at δ 9.35 s, 7.72 d, 7.40 d, and 6.53 s, signals for four ring methylene protons at δ 3.05 m, and no signal for N-Me, so that XIV is the 11,12-dihydro compound, as shown in Chart 2.

Oxidation of XIV with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), followed by treatment with hydrochloric acid afforded benzo[*c*]phenanthridine methochloride (XV) whose NMR spectrum showed a signal for 6-H at δ 9.68 s in place of the signal corresponding to 6-2H presented in the NMR spectrum of XIII.

As described above, *l*-α-narcotine was transformed smoothly to a benzo[*c*]phenanthridine derivative and it is expected that this method might effect transformation of bicuculline and hydrastine, the homologs of *l*-α-narcotine, to sanguinarine (Ia) and chelerythrine (Ib), respectively.

XV exhibited interesting biological activities which will be reported elsewhere.

Experimental

Melting points were determined in a sealed capillary and were uncorrected. Ultraviolet spectra were measured with a Hitachi EPS-2U. Nuclear magnetic resonance spectra with a Varian T-60 were taken in $CDCl_3$ unless otherwise stated. Mass spectra were measured with a JEOL's JMS-01S.

***l*-α-Narcotinediol (VI)**——To a solution of LAH (0.5 g) in dry ether (47 ml) was added dropwise a solution of *l*-α-narcotine (1.0 g) in dry ether (40 ml) and dry tetrahydrofuran (30 ml) at room temperature with stirring. The stirring was continued for 30 min. The reaction mixture was treated in usual ways. There was obtained colorless solid (0.98 g, 97%) of mp 132—133° (lit.,[6] mp 134°).

2,3-Methylenedioxy-1,9,10-trimethoxydihydroprotoberberine Methiodide (VIII, X=I)——To a mixture of VI (1.0 g) and K_2CO_3 (1.3 g) in dry chloroform (20 ml) was added dropwise a solution of $SOCl_2$ (3.4 g) in dry chloroform (13.6 ml) and the mixture was refluxed for 3 hr. After filtration, the filtrate was evaporated *in vacuo* with repeated addition of chloroform to remove excess $SOCl_2$. The residue was dissolved in H_2O (5 ml) and filtered. NaI (0.5 g) was added to the above filtrate to separate methiodide (VIII, X=I). There was obtained yellow needles (0.93 g, 76%) of mp 163—166° from *n*-hexane–*n*-buthanol. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 254 (4.24), 283 (3.88), 330 (4.32). NMR: δ 7.64 s (13-H), 7.05 d (J=8 Hz, 12-H), 6.89 d (J=8 Hz, 11-H), 6.44 s (4-H), 5.93 s (OCH_2O), 5.49 d, 4.72 d (J=13.5 Hz, 8-2H), 4.4 m (6-2H), 4.06 s (1-OMe), 3.98 s (9-OMe), 3.86 s (10-OMe), 3.28 s (N-Me), 3.15 m (5-2H). *Anal.* Calcd. for $C_{22}H_{24}O_5NI$: C, 50.09; H, 4.55; N, 2.66. Found: C, 50.38; H, 4.66; N, 2.63.

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5) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **19**, 317 (1971).
6) K.W. Bently and A.W. Murray, *J. Chem. Soc.*, **1963**, 2491.

Methine Base (IX)——A mixture of the methiodide (VIII, X=I) (1.0 g) in 25% KOH–MeOH (8 ml) was refluxed for 40 min. After cooling, H_2O (5 ml) was added. The precipitate was collected, washed with 50% MeOH and dried *in vacuo* to yield yellow powder (0.72 g, 72%). This compound was easily oxidized with air, especially in solution, and showed only one spot on thin–layer chromatography, so it was used for the next reaction without purification. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 261 (4.0), 338 (3.87). NMR δ 7.1—6.5 m (aromatic-3H and =CH-), 5.95 s (OCH_2O), 5.5 q (J=2.5 and 18 Hz), 5.1 q (J=2.5 and 12 Hz) (=CH_2), 5.12 s (4-H), 4.48 s (1-2H), 3.98 s (OMe), 3.84 s (2×OMe), 2.5 s (N-Me).

5-Methyl-2,3-methylenedioxy-4,7,8-trimethoxy-5,6,11,12-tetrahydrobenzo[*c*]phenanthridine (X)——Using a high pressure mercury lamp (100 W), a solution of IX (1.3 g) in pure benzene (780 ml) was irradiated for 30 min at room temperature under nitrogen. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized from *n*-hexane–acetone to give yellow pillars (0.8 g, 58%) of mp 130—132°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 261 (4.25), 286 (4.08), 355 (4.26). NMR: δ 6.98 d (J=8.5 Hz, 10-H), 6.77 d (J=8.5 Hz, 9-H), 6.48 s (1-H), 5.93 s (OCH_2O), 4.30 s (6-2H), 3.87 s (4- and 7-OMe), 3.82 s (8-OMe), 2.55 s (N-Me). Mass spectrum Calcd. for $C_{22}H_{23}O_5N$: mol. wt., 381.1576. Found: M^+, 381.1624.

5-Methyl-2,3-methylenedioxy-4,7,8-trimethoxy-5,6-dihydrobenzo[*c*]phenanthridine (XIII) and 2,3-Methylenedioxy-4,7,8-trimethoxy-11,12-dihydrobenzo[*c*]phenanthridine (XIV)——A mixture of X (1.34 g) and 5% Pd-C (0.8 g) in *p*-cymene (200 ml) was refluxed for 10 min with stirring. After cooling, Pd-C was filtered off and washed with benzene. The combined filtrate was treated with dry HCl gas to give HCl-salt. The precipitate was collected, made alkaline with aqueous NaOH and then extracted with chloroform. The residue (1.0 g) was chromatographed over Al_2O_3 (neutral, grade III) (120 g) by using benzene as eluent to afford XIII from the first fraction, which was recrystallized from acetone to yield pale pillars (0.78 g, 58%) of mp 165—167°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 229 (4.70), 253 (4.50), 286 (4.96), 323 (4.30), 360 (4.35). NMR: δ: 7.77 d (J=9 Hz, 11-H), 7.56 d (J=9.5 Hz, 10-H), 7.47 d (J=9 Hz, 12-H), 7.0 s (1-H), 6.99 d (J=9.5 Hz, 9-H), 6.0 s (OCH_2O). 4.33 s (6-2H), 4.0 s (4-OMe), 3.88 s (7-OMe), 3.85 s (8-OMe), 2.6 s (N-Me). Mass spectrum Calcd. for $C_{22}H_{21}O_5N$: mol. wt., 379.1419. Found: M^+, 379.1415. The second fraction gave XIV which was recrystallized from acetone to yield yellow needles (36 mg, 2.8%) of mp 150—153°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 268 (4.51), 322 (4.45), 330 (4.46). NMR: δ 9.53 s (6-H), 7.72 d (J=9 Hz, 10-H), 7.4 d (J=9 Hz, 9-H), 6.53 s (1-H), 5.95 s (OCH_2O), 4.05 s (4-OMe), 4.0 s (7-OMe), 3.96 s (8-OMe), 3.05 m (11-2H and 12-2H). Mass spectrum Calcd. for $C_{21}H_{19}O_5N$: mol. wt., 365.1263. Found: M^+, 365.1232.

2,3-Methylenedioxy-4,7,8-trimethoxybenzo[*c*]phenanthridine Methochloride (XV)——To a mixture of XIII (233 mg) in benzene (10 ml) and 10% NaOH solution (60 ml) was added dropwise a solution of DDQ (313 mg) in benzene (80 ml) with stirring. The stirring was continued for 3 hr. The benzene layer was washed with H_2O and dried over Na_2SO_4. The residue was dissolved in acetone and acidified with conc. HCl to give the HCl-salt which was recrystallized from *n*-hexane–EtOH to yield orange needles (205 mg, 81%) of mp 158—161°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 229 (4.42), 254 (4.34), 288 (4.73), 323 (4.03), 355 (3.65). NMR (CF_3COOH): δ 9.68 s (6-H), 8.59 d (J=9 Hz, 11-H), 8.44 d (J=9 Hz, 10-H), 8.12 d (J=9 Hz, 12-H), 8.07 d (J=9 Hz, 9-H), 7.27 s (1-H), 6.27 s (OCH_2O), 4.67 s (4-OMe), 4.42 s (7-OMe), 4.22 s (8-OMe), 4.2 s (N-Me). *Anal.* Calcd. for $C_{22}H_{20}O_5NCl$: C, 58.73; H, 5.34; N, 3.11. Found: C, 58.89; H, 5.15; N, 3.20.

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