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92. Masao Tomita, Toshiro Ibuka,[*1] Yasuo Inubushi,[*2] and Kyoji Takeda[*3] : Studies on the Alkaloids of Menispermaceous Plants. CCXIV.[*4] Alkaloids of *Stephania japonica* MIERS. (Suppl. 12)[*4]. Structure of Metaphanine.[*5] (1).

(*Faculty of Pharmaceutical Sciences, Kyoto University,*[*1] *Faculty of Pharmaceutical Sciences, Osaka University*[*2] *and ITSUU Laboratory*[*3])

Metaphanine, a non-phenolic alkaloid, was first isolated from home-grown *Stephania japonica* MIERS (Fam. Menispermaceae) by Kondo, *et al.*[1] in 1924. Later, this alkaloid

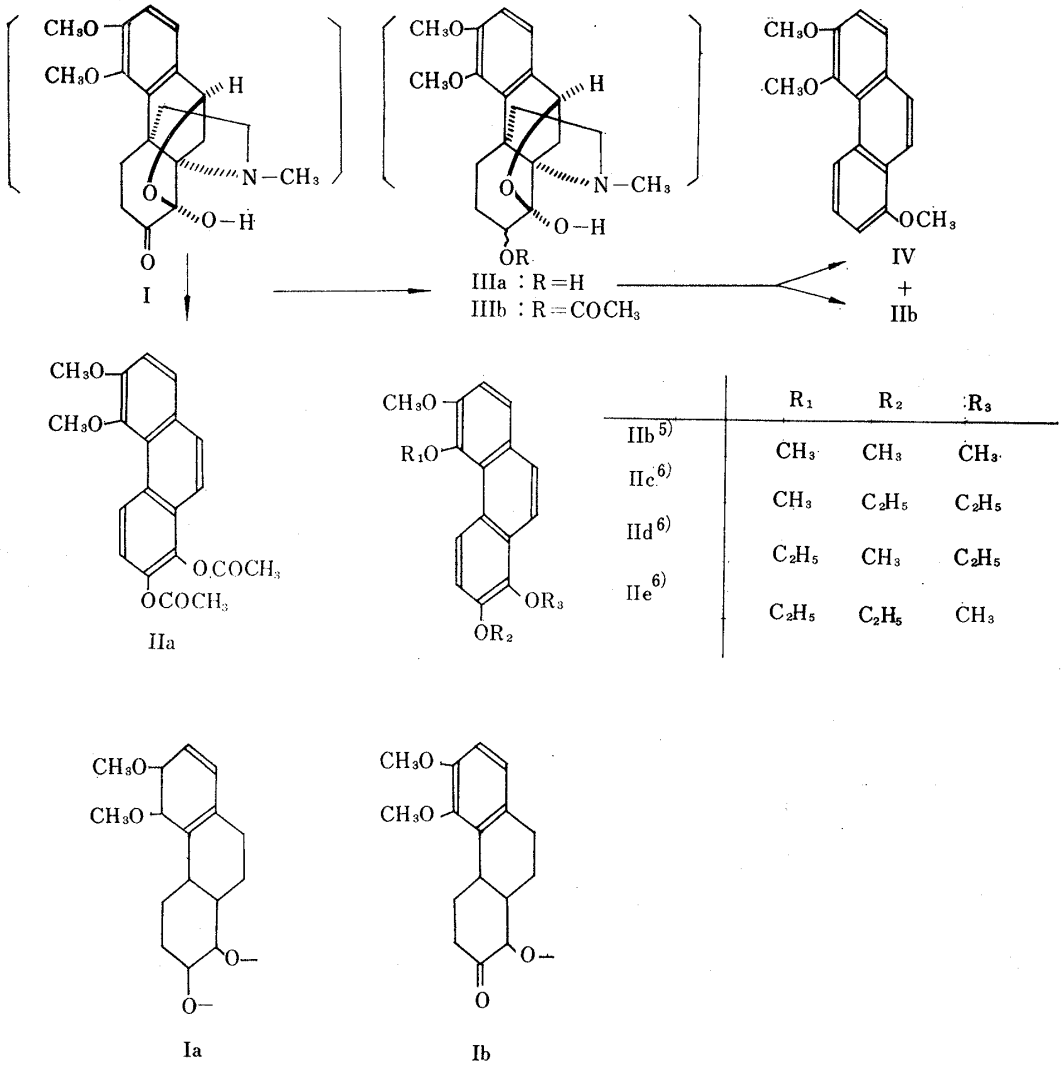


Chart 1.

*1 Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto (富田真雄，井深俊郎).
*2 Toneyama, Toyonaka, Osaka (犬伏康夫).
*3 Konno-cho, Shibuya-ku, Tokyo (武田強二).
*4 Part CCXIII. and Suppl. 11. Y. Watanabe, M. Matsui, K. Ido: Yakugaku Zasshi, in press.
*5 A preliminary communication of this work appeared in Tetrahedron Letters, No. 48, 3605 (1964).

1) H. Kondo, T. Sanada : Yakugaku Zasshi, 45, 5, 1034 (1924); *Idem* : *Ibid.*, 48, 177, 930 (1927); H. Kondo, T. Watanabe : *Ibid.* 58, 268 (1938).

was also isolated from the same plant growing in Tanegashima[2] and Formosa.[3] Although investigations of the structure elucidation of this alkaloid had been continued, a little progress was achieved. Recently, the authors made real progress toward the establishment of the complete structure of metaphanine and in this paper they wish to report that the partial structure (Ic) should be assigned to metaphanine whose skeleton is anticipated to be closely related to that of hasubanonine.[4]

Metaphanine, m.p. 232°, $C_{19}H_{23}O_5N$ (mol. wt., 345.38 (mass spectrum*[6] : parent peak at 345)), *Pka'* : 6.03, contains one N-methyl group (NMR*[7] : 7.43 τ (3H)), two methoxyl groups (NMR : 6.14 τ (6H)), one hydroxyl group (IR $\nu_{max}^{CHCl_3}$: 3480 cm^{-1}, NMR : 4.92 τ (1H, sharp singlet)), two aromatic hydrogens (NMR : 3.23 τ (1H, doublet, J=8.1 c.p.s.), 3.30 τ (1H, doublet, J=8.1 c.p.s.)) and one carbonyl group (IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1730). Treatment of metaphanine with hydroxyl amine afforded a monoxime, m.p. 215°, $C_{19}H_{24}O_5N_2$, which showed no carbonyl absorption band in the infrared spectrum. Thus, four of five oxygen atoms of metaphanine are present as one carbonyl group, one hydroxyl group and two methoxyl groups, and the remainder is presumably an ether oxygen. Therefore, the rational formula, $C_{15}H_{13}\cdot(C{=}O)\cdot(OCH_3)_2\cdot(OH)\cdot(-O-)\cdot(N-CH_3)$ was given for metaphanine and metaphanine should be a pentacyclic alkaloid.

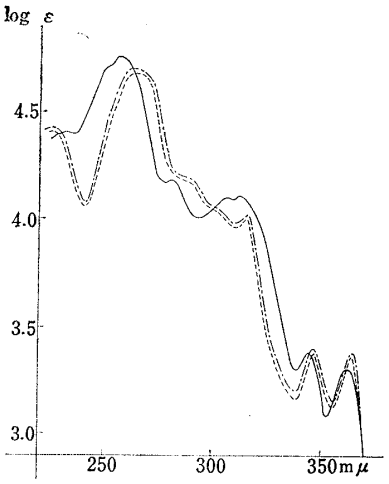


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

——— 1,2-Diacetoxy-5,6-dimethoxyphenanthrene (IIa)
– – – – 1,2-Diethoxy-5,6-dimethoxyphenanthrene (IIc) (Natural)
····· 1,2-Diethoxy-5,6-dimethoxyphenanthrene (IIc) (Synthetic)

Acetolysis of metaphanine (I)*[8] with acetic anhydride in a sealed tube gave a neutral compound (IIa), m.p. 150°, $C_{20}H_{18}O_6$. The infrared spectrum (in KBr) revealed an acetate carbonyl band at 1775 cm^{-1} (phenol acetate carbonyl band). The nuclear magnetic resonance spectrum of IIa showed two methoxyl groups at 6.06 τ and 6.10 τ and two acetyl methyls at 7.62 τ and 7.75 τ. The ultraviolet absorption spectrum (Fig. 1) of the neutral compound (IIa) was characteristic of phenanthrene derivatives : 232 (4.41), 257 (4.77), 281 (4.19), 306 (4.11), 312 (4.12), 343 (3.39), and 361 mμ (log ε, 3.32). The above results indicated that the neutral compound (IIa), which was generated from acetolysis of metaphanine (I), is presumably diacetoxydimethoxyphenathrene.

Hydrolysis of the neutral compound (IIa) with methanolic potassium hydroxide followed by methylation with methyl iodide gave 1,2,5,6-tetramethoxyphenanthrene (IIb), m.p. 63~65°, whose nuclear magnetic resonance spectrum showed signals at 6.05 τ (6H), 6.09 τ (3H) and 6.15 τ (3H) for four methoxyl groups. Then, IIb was identified with an authentic sample[5] of 1,2,5,6-tetramethoxyphenanthrene by mixed melting point determination and comparison of their infrared spectra (Nujol). Hydrolysis of IIa with

*6 Mass spectrum was taken on Hitachi Model RMU 6C mass spectrometer.
*7 All NMR spectra were taken on Varian Associates A-60 recording spectrometer with tetramethylsilane as an internal standard.
*8 The complete structure of metaphanine will be presented in the succesive paper : Structure of Metaphanine. (2).

2) K. Takeda : Ann. Rept. ITSUU Lab. (Tokyo), **11**, 64 (1960).
3) M. Tomita, T. Ibuka : Yakugaku Zasshi, **83**, 996 (1963).
4) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, M. Matsui : Tetrahedron Letters, No. 40, 2937 (1964); *Idem* : This Bulletin, **13**, 538 (1965).
5) H. Kondo, T. Nakamura, M. Fujii, T. Kato : Ann. Rept. ITSUU Lab. (Tokyo), **1**, 41 (1950).

ethanolic potassium hydroxide followed by ethylation with ethyl iodide gave diethoxydimethoxyphenthrene (IIc), m.p. 63~64°, whose nuclear magnetic resonance spectrum showed two methoxyl groups at 6.06 τ (3H), 6.14 τ (3H) and two ethoxyl groups at 8.52 τ (3H, $-OCH_2\underline{CH_3}$), 8.54 τ (3H, $-OCH_2\underline{CH_3}$). In the ultraviolet spectrum (Fig. 1) of IIc a characteristic absorption band of phenanthrene was observed. Attempts were made to determine the position of two methoxyl groups of diethoxydimethoxyphenanthrene (IIc), m.p. 63~65°, which was derived from metaphanine, by comparison of its infrared spectrum with those of synthetic authentic samples of 1,5-diethoxy-2,6-dimethoxyphenanthrene[6] (IId) (m.p. 72°), 1,6-dimethoxy-2,5-diethoxyphenanthrene[6] (IIe) (m.p. 140°) and 1,2-diethoxy-5,6-dimethoxyphenanthrene[6] (IIc) (m.p. 64~65°). A marked difference was observed among diethoxydimethoxyphenanthrene from metaphanine, 1,5-diethoxy-2,6-dimethoxyphenanthrene (IId) and 1,6-dimethoxy-2,5-dimethoxyphenanthrene (IIe) but the infrared spectrum of diethoxydimethoxyphenanthrene from metaphanine was superimposable with that of synthetic 1,2-diethoxy-5,6-dimethoxyphenanthrene (IIc), and the mixed melting point did not depress (cf. Fig. 2).

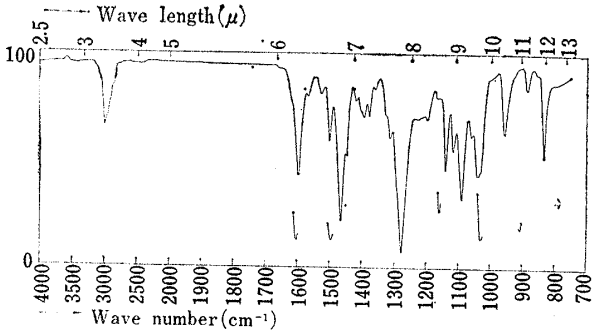


Fig. 2-A. Infrared Spectrum of 1,2-Diethoxy-5,6-dimethoxyphenanthrene (IIc) (Natural) (in chloroform)

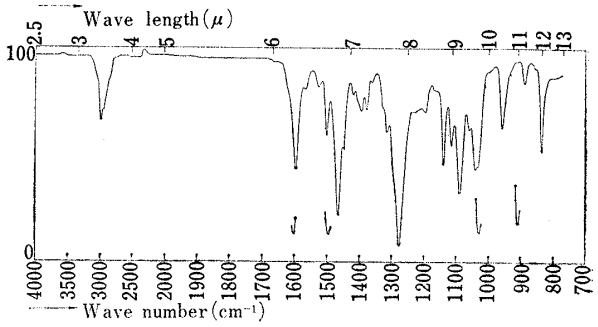


Fig. 2-B. Infrared Spectrum of 1,2-Diethoxy-5,6-dimethoxyphenanthrene (IIc) (Synthetic) (in chloroform)

Above experimental results supported that 1,2-diacetoxy-5,6-dimethoxyphenthrene (IIa) was generated from acetolysis of metaphanine (I), and that the partial structure (Ia) was present in the metaphanine molecule, if no rearrangement taken place during acetolysis process.

Catalytic hydrogenation of metapanine (I) over platinic oxide in acetic acid absorbed one mole of hydrogen to give dihydrometaphanine (IIIa), m.p. 211°, $C_{19}H_{25}O_5N$. The absence of carbonyl absorption band in its infrared spectrum indicated that the carbonyl group of metaphanine was reduced to a secondary hydroxyl group. This was supported by nuclear magnetic resonance spectrum of IIIa in dimethylsulfoxide[7] showing signals at 4.76 τ (1H, singlet, tertiary hydroxyl) and at 5.88 τ (1H, doublet, J=6.5 c.p.s., secondary hydroxyl) for two hydroxyl groups, and both signals disappeared on the addition of deuterium oxide.

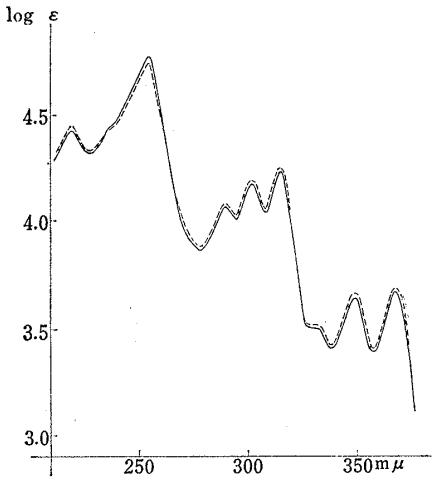


Fig. 3. Ultraviolet Absorption Spectra (in EtOH)

—— Natural 1,5,6-Trimethoxyphenanthrene
--- Synthetic 1,5,6-Trimethoxyphenanthrene

6) T. Ibuka : Yakugaku Zasshi, in press.
7) O. L. Chapman, R. W. King : J. Am. Chem. Soc., 86, 1256 (1964).

Treatment of IIIa with acetic anhydride in pyridine gave monoacetyldihydrometaphanine (IIIb), m.p. 221°, $C_{21}H_{27}O_6N \cdot 1/2H_2O$, whose infrared spectrum showed an acetyl carbonyl band at 1730 cm^{-1} as well as hydroxyl band at 3450 cm^{-1}. The nuclear magnetic resonance spectrum of IIIb revealed signals due to an acetyl methyl at 7.90 τ and a hydrogen geminal to an acetoxyl group at 4.88 τ (1H, quartet, J_A=5 c.p.s., J_B=11 c.p.s.).

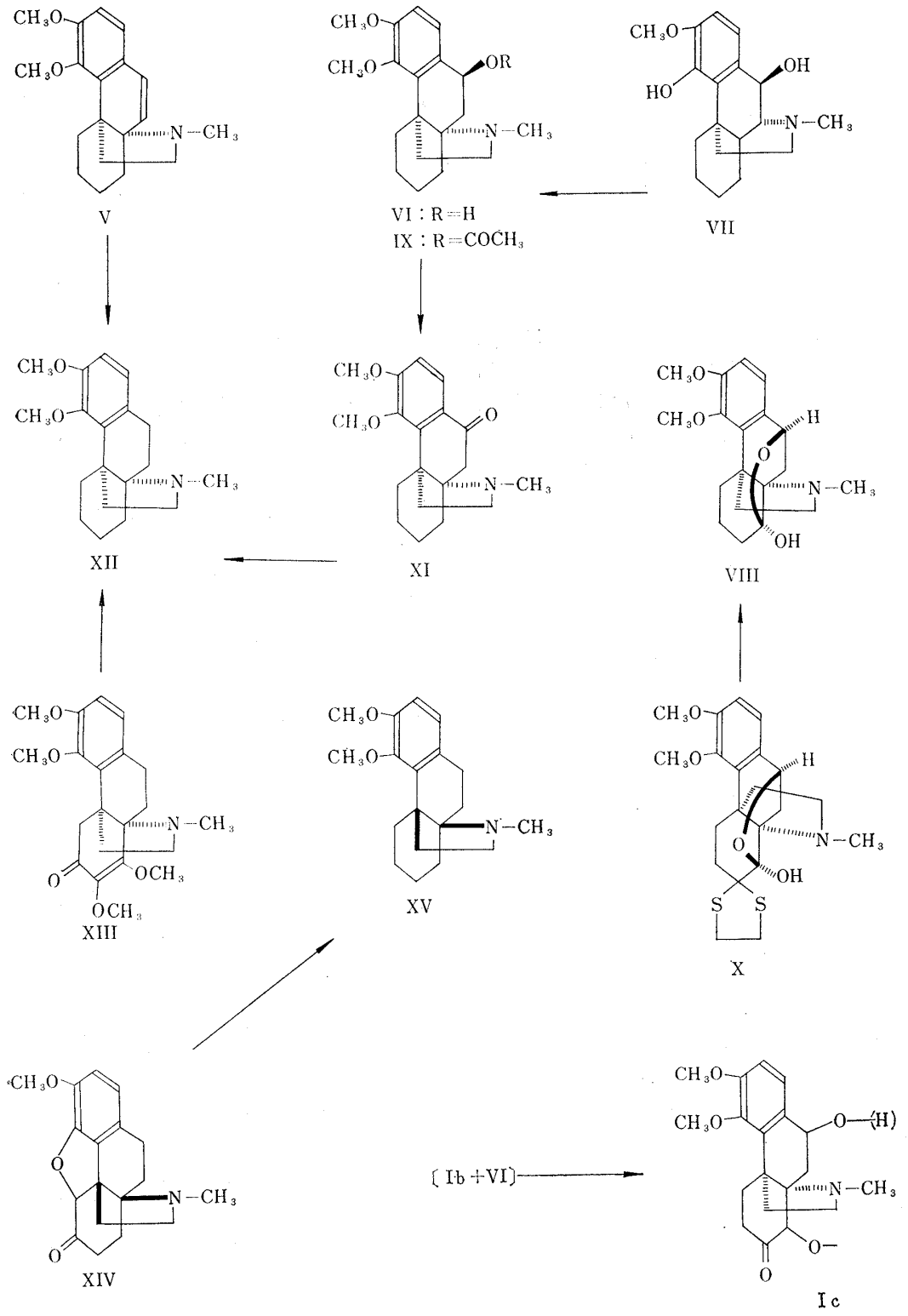


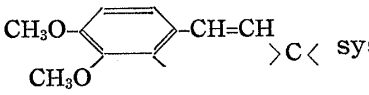
Chart 2.

Acetolysis of Ⅲa with acetic anhydride in a sealed tube followed by hydrolysis and methylation gave 1,2,5,6-tetramethoxyphenanthrene (Ⅱb) and 1,5,6-trimethoxyphenanthrene (Ⅳ). The former was identified as its picrate, m.p. 148~149°, with an authentic sample of 1,2,5,6-tetramethoxyphenanthrene picrate[5] by mixed melting point determination and comparison of their infrared spectra and the latter was identified with an authentic sample of 1,5,6-trimethoxyphenanthrene (Ⅳ), prepared by Pshorr's method,[8] by mixed melting point determination, infrared comparison and ultraviolet comparison (Fig. 3). It has been well known that on acetolysis of morphine-sinomenine series alkaloids an oxygen atom of a carbonyl group remains as an acetoxyl group on the derived phenanthrene nucleus, whereas an alcohlic hydroxyl group was eliminated by dehydration in the course of aromatization process.[9]

Accordingly, the above results suggested that the partial structure (Ib) might be present in the metaphanine molecule.

Huang-Minlon reduction of metaphanine (I) under mild condition, recommended by Gates, *et al.*,[10] and carful chromatography on alumina column gave four deoxo-derivatives: deoxometaphanine-A (Ⅴ), -B (Ⅵ), -C (Ⅶ), and -D (Ⅷ).

Deoxometaphanine-A (Ⅴ) revealed a sharp AB type quartet corresponding to two olefinic hydrogens at 3.55 τ (doublet, J=10 c.p.s.) and 4.35 τ (doublet, J=10 c.p.s.) in the nuclear magnetic resonance spectrum (Fig. 5). Bathochromic shift of the absorption maximum of deoxometaphanine-A (Ⅴ) perchlorate in the ultraviolet spectrum (Fig. 4), which is characteristic of styrene type chromophore, coupled with the AB type quartet signal in the nuclear magnetic resonance spectrum indicated that the



system is present in deoxometaphanine-A (Ⅴ). Deoxometaphanine-A was characterized as its perchlorate, m.p. 229~230° (decomp.), $C_{19}H_{25}O_2N \cdot HClO_4$.

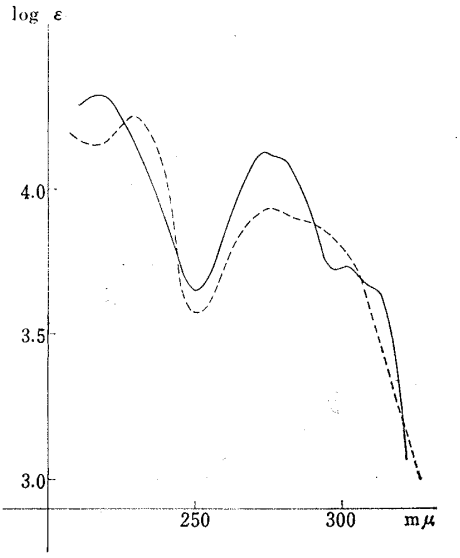


Fig. 4. Ultraviolet Absorption Spectra (in EtOH)

—— Deoxometaphanine-A (Ⅴ) perchlorate
--- Dehydrodeoxometaphanine-B (Ⅺ)

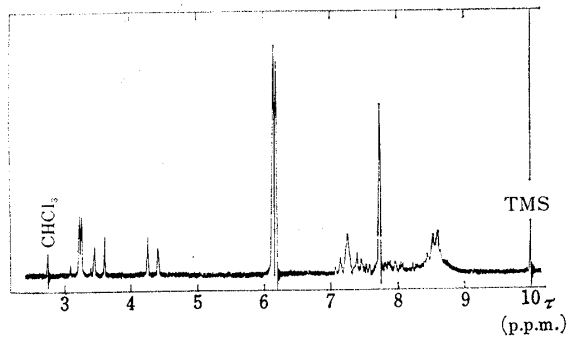


Fig. 5. Nuclear Magnetic Resonance Spectrum of Deoxometaphanine-A (Ⅴ) (in $CDCl_3$)

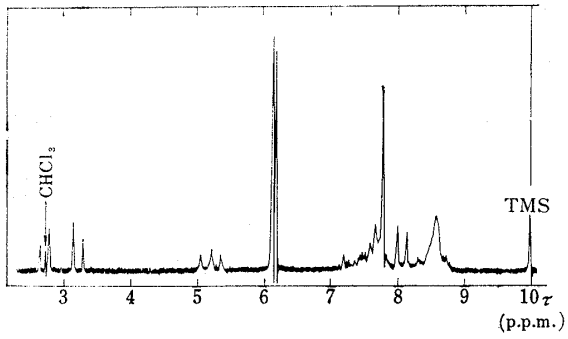


Fig. 6. Nuclear Magnetic Resonance Spectrum of Deoxometaphanine-B (Ⅵ) (in $CDCl_3$)

8) R. Pschorr, H. Busch: Ber., **40**, 2001 (1907).
9) K. Fischer, E. V. Vongerichten: Ber., **19**, 792 (1886); L. Knorr, S. Smiles: *Ibid.* **35**, 3010 (1902); L. Knorr, H. Butler, H. Hörlein: Ann., **368**, 305 (1909); E. Leete: J. Am. Chem. Soc., **81**, 3948 (1959).
10) M. Gates, G. Tshudi: *Ibid.* **78**, 1380 (1956).

Deoxometaphanine-B (Ⅵ) possesed a hydroxyl group at 3400 cm^{-1} in the infrared spctrum and a signal (centered at 5.22 τ) attributable to a hydrogen geminal to a hydroxyl group in the nuclear magnetic resonance spectrum (Fig. 6). Ⅵ was characterized as its perchlorate, m.p. 226~227° (decomp.), $C_{19}H_{27}O_3N \cdot HClO_4$. Acetylation of Ⅵ with acetic anhydride under the presence of pyridine gave acetyldeoxometaphanine-B (Ⅸ). Ⅸ showed a carbonyl band at 1730 cm^{-1} in the infrared spectrum and revealed the presence of an acetoxyl methyl at 7.84 τ and a hydrogen geminal to an acetoxyl group at 3.97 τ in its nuclear magnetic resonance spectrum (Fig. 8).

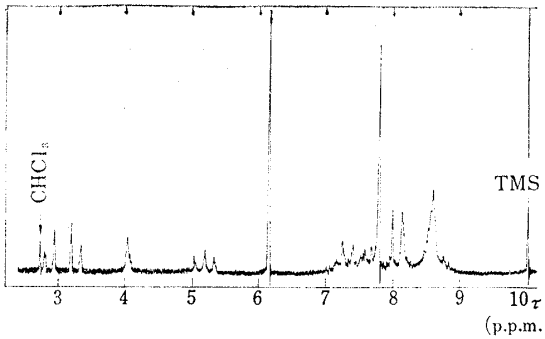


Fig. 7. Nuclear Magnetic Resonance Spectrum of Deoxometaphanine-C (Ⅶ) (in $CDCl_3$)

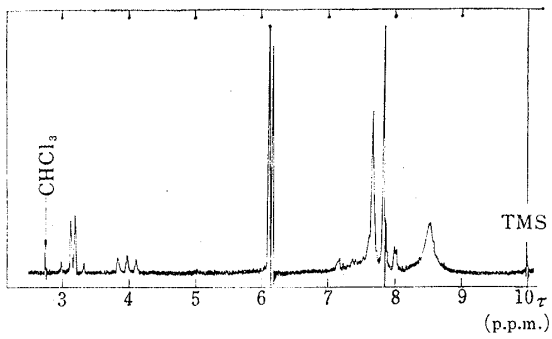


Fig. 8. Nuclear Magnetic Resonance Spectrum of Acetyldeoxometaphanine-B (Ⅸ) (in $CDCl_3$)

Deoxometaphanine-C (Ⅶ) showed a strong blue color with 2,6-dichloroquinone-4-chloroimide indicating that the C-4 phenolic hydroxyl group is present. The nuclear magnetic resonance spectrum (Fig. 7) of Ⅶ showed a hydroxyl hydrogen at 4.05 τ (1H), a hydrogen geminal to a hydroxyl group centered at 5.21 τ (1H) and a methoxyl group at 6.17 τ. Methylation of Ⅶ with diazomethane was failed but with Rodionov reagent[11] gave deoxometaphanine-B (Ⅵ). Gates, *et al.*[10] have reported that the methoxyl groups at C-4 of β-dihydrothebainol methyl ether and *rac*-β-dihydrothebainol methyl ether were demethylated under Huang-Minlon reduction condition. These results are suggestive of demethylation at the C-4 position of deoxometaphanine-B (Ⅵ) producing deoxometaphanine-C (Ⅶ).

Deoxometaphanine-D (Ⅷ), m.p. 249~250°, $C_{19}H_{25}O_4N$, showed a hydroxyl group at 3500~3300 cm^{-1} in its infrared spectrum. This compound was also obtainable by Raney-W-2 nickel desulfurization of metaphanine thioketal (X), m.p. 238~239°, $C_{21}H_{27}O_4NS_2$.

Oxidation of deoxometaphanine-B (Ⅵ) with activated manganese dioxide[12] in chloroform gave dehydrodeoxometaphanine-B (Ⅺ), m.p. 143~144°, $C_{19}H_{25}O_3N$, which showed a conjugated carbonyl band at 1678 cm^{-1} in the infrared spectrum. The ultraviolet spectrum (Fig. 4) was characteristic of acetophenone chromophore. In the nuclear magnetic resonance spectrum two benzene protons were appeared at 2.37 τ (1H, doublet, J=8.5 c.p.s.) and 3.17 τ (1H, doublet, J=8.5 c.p.s.). It is probable that the anisotropy of the conjugated carbonyl group is sufficient to account for the displacement to the low-field side (2.37 τ) of one of two protons.

Catalytic hydrogenation of deoxometaphanine-A (Ⅴ) over platinic oxide gave dihydrodeoxometaphanine-A (Ⅻ). This dihydro compound was identified with the compound (Ⅻ)[4] derived from hasubanonine (XIII) and the compound (XV)[4] derived from dihydro-

11) *a*) W. Rodionov: Bull. soc. chim. France, **39**, 305 (1926); *b*) I. Seki: Ann. Takamine Lab., **12**, 56 (1960); *c*) K. Okabe: Yakugaku Zasshi, **82**, 1498 (1962).
12) H. Ropoport, G. W. Stevenson: J. Am. Chem. Soc., **76**, 1796 (1954).

indolinocodeinone[13] (XIV) by comparison of their thin-layer chromatography,*9 infrared spectra and nuclear magnetic resonance spectra. Properties of XII hydrobromide (m.p. 270~271° (decomp.)), $C_{19}H_{27}O_2N \cdot HBr$, $[\alpha]_D$ +37°) and the compound (XV) hydrobromide[4] (m.p. 270~271° (decomp.), $C_{19}H_{27}O_2N \cdot HBr$, $[\alpha]_D$ −42°) were quite identical except the sign of optical rotations. XII was also obtainable by Huang-Minlon reduction of dehydrodeoxometaphanine-B (XI).

On the basis of the above results (coupled with partial structure (Ib) and deoxometaphanine-B (VI)), it can be deduced that metaphanine should have the partial structure (Ic).

The complete structure of metaphanine will be reported in the succesive paper.

Experimental*10

Metaphanine (I)——b.$p_{2\times10^{-4}}$ 170~175°. m.p. 232° (acetone-$CHCl_3$ mixture). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (OH), 1730 (six membered C=O). *PKa'*: 6.03. NMR τ ($CDCl_3$): two benzene protons, 3.23 (1H, doublet, J=8.1 c.p.s.), 3.30 (1H, doublet, J=8.1 c.p.s.); O<u>H</u>, 4.92 (1H, singlet); $OCH_3 \times 2$, 6.14 (6H); N-CH_3, 7.43 (3H). *Anal.* Calcd. for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.12; H, 6.99; N, 4.29. Hydrochloride: m.p. 226° (acetone), *Anal.* Calcd. for $C_{19}H_{23}O_5N \cdot HCl \cdot \frac{1}{2}H_2O$: C, 58.33; H, 6.45; N, 3.59. Found: C, 58.62; H, 6.62; N, 3.42. Hydroiodide: m.p. 230° (decomp.) (tetrahydrofuran), *Anal.* Calcd. for $C_{19}H_{23}O_5N \cdot HI \cdot \frac{1}{2}H_2O$: C, 47.24; H, 5.24. Found: C, 47.21; H, 5.10. Sulfate: m.p. 174° (acetone), *Anal.* Calcd. for $C_{19}H_{23}O_5N \cdot \frac{1}{2}H_2SO_4 \cdot 2H_2O$: C, 53.07; H, 6.56; N, 3.26. Found: C, 52.89; H, 6.36; N, 3.55. Monoxime: m.p. 215° (acetone-H_2O mixture), *Anal.* Calcd. for $C_{19}H_{24}O_5N_2$: C, 63.32; H, 6.71. Found: C, 63.62; H, 6.91.

1,2-Diacetoxy-5,6-dimethoxyphenanthrene (IIa) (Acetolysis of Metaphanine (I))——A mixture of metaphanine (I) (150 mg.). Ac_2O (3 ml.) and conc. HCl (1 drop) was heated in a sealed tube at 170~180° for 10 hr., and after cooling the reaction mixture was poured into ice-water (20 g.) and extracted with AcOEt. The AcOEt solution was washed, dried over Na_2SO_4 and evaporated *in vacuo* to give dark brown oil. The oil was chromatographed over silicagel column from $CHCl_3$ and elution with the same solvent gave a crude crystalline solid. Recrystallization from EtOH gave 1,2-diacetoxy-5,6-dimethoxyphenanthrene (IIa) (20 mg.) as slightly yellow pillars. m.p. 150°. IR ν_{max}^{KBr} cm^{-1}: 1775 (OAc). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.41), 257 (4.77), 281 (4.19), 306 (4.11), 312 (4.12), 343 (3.39), 361 (3.32). NMR τ (CCl_4): $OCOC\underline{H}_3 \times 2$, 7.62 (3H), 7.75 (3H); $OCH_3 \times 2$, 6.06 (3H), 6.10 (3H). *Anal.* Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12; OCH_3, 19.25. Found: C, 67.69; H, 5.27; OCH_3, 19.56.

1,2,5,6-Tetramethoxyphenanthrene (IIb)——1,2-diacetoxy-5,6-dimethoxyphenanthrene (IIa) (9 mg.) was dissolved in 1.55*N* methanolic KOH (3 ml.) and refluxed for 2 hr. under the current of N_2 gas, and then CH_3I (0.3 ml.) was added and refluxed for 1 hr. The solvent was removed *in vacuo* and the residue was dissolved in H_2O (15 ml.) and extracted with benzene. The benzene extract was washed, dried over K_2CO_3 and the solvent was evaporated to give slightly yellow oil which was chromatographed over silicagel column from $CHCl_3$ and eluted with the same solvent. The eluate, after the solvent was evaporated, was recrystallized from ether to give 1,2,5,6-tetramethoxyphenanthrene (IIb) as colorless needles, m.p. 63~65°. Yield 4.5 mg. NMR τ (CCl_4): $OCH_3 \times 4$, 6.05 (6H), 6.09 (3H), 6.15 (3H). On admixture of the product with an authentic sample of 1,2,5,6-tetramethoxyphenanthrene, no melting point depression was observed and the IR spectra (in Nujol) of two compounds were identical. Picrate: m.p. 147~148° (EtOH), dark reddish needles. On admixture of this picrate with an authentic sample of 1,2,5,6-tetramethoxyphenanthrene picrate, no melting point deperession was observed and the IR spectra (in Nujol) of two compounds were superimposable. *Anal.* Calcd. for $C_{24}H_{21}O_{11}N_3$: C, 54.65; H, 4.01; OCH_3, 23.53. Found: C, 54.38; H, 4.22; OCH_3, 23.74.

1,2-Diethoxy-5,6-dimethoxyphenanthrene (IIc)——A solution of IIa (47 mg.) in EtOH (5 ml.) and 5*N* ethanolic KOH (3 ml.) was heated under reflux for 30 min., and C_2H_5I (0.5 ml.) was added and refluxed for 20 hr. The solvent was removed *in vacuo* and the residue was extracted with ether. The ether solution was washed, dried over Na_2SO_4. Evaporation of the solvent and the residue was chromatographed over silicagel column from $CHCl_3$ and eluted with the same solvent gave a crystalline solid. Recrystallization from EtOH gave 1,2-diethoxy-5,6-dimethoxyphenanthrene (IIc) (30 mg.) as colorless needles, m.p. 63~64°,

*9 Aluminium Oxyd G nach Stahl, solvent, chloroform or Kieselgel G nach Stahl, solvent, methanol.

*10 All melting points were uncorrected (determined with Yanagimoto Micro Melting Point Apparatus). All *PKa'* values were determined in 80% aq. methylcellosolve.

13) S. Okuda, K. Tsuda, S. Yamaguchi: J. Org. Chem., **27**, 4121 (1962); *Idem*: "The 7th Symposium on the Chemistry of Natural Products, Japan" (Fukuoka, Oct., 1963), symposium abstracts, p. 72 (1963).

b.$p_{0.05}$ 175°. On admixture of the product with an authentic synthetic specimen of 1,2-diethoxy-5,6-dimethoxyphenanthrene, no depression of melting point was observed and the IR spectra (in $CHCl_3$) of two compounds were identical. NMR τ (CCl_4): $OCH_3 \times 2$, 6.06 (3H), 6.14 (3H); $OCH_2\underline{CH_3} \times 2$, 8.52 (3H), 8.54 (3H). Picrate: m.p. 144~145° (EtOH). The IR spectrum of this picrate was identical with that of a synthetic sample of 1,2-diethoxy-5,6-dimethoxyphenanthrene picrate. *Anal.* Calcd. for $C_{26}H_{25}O_{11}N_3$: C, 56.21; H, 4.53. Found: C, 56.46, 56.42; H, 4.80, 4.61.

Dihydrometaphanine (IIIa)——A solution of metaphanine (48 mg.) in AcOH (10 ml.) was hydrogenated over Pt-black (prepared from PtO_2 (50 mg.)) for 3 hr. at room temperature. The catalyst was filtered off, washed with 3% AcOH and the combined filtrate was made alkaline with dil. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried over K_2CO_3 and evaporated to give a crystalline solid. Recrystallization from ether-$CHCl_3$ mixture gave 45 mg. of dihydrometaphanine (IIIa) as colorless needles, m.p. 211°. $[\alpha]_D^{20}$ +72° (c=0.48, $CHCl_3$). *PKa'*: 6.76. NMR τ (dimethylsulfoxide): OH, 4.76 (tertiary O$\underline{H}$, singlet); OH, 5.88 (secondary O$\underline{H}$, doublet, J=6.5 c.p.s.). *Anal.* Calcd. for $C_{19}H_{25}O_5N$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.78; H, 7.52; N, 3.87. Hydroiodide: m.p. 223° (decomp.) (MeOH-ether mixture), *Anal.* Calcd. for $C_{19}H_{25}O_5N \cdot HI$: C, 48.01; H, 5.52. Found: C, 48.05; H, 5.63.

Monoacetyldihydrometaphanine (IIIb)——Dihydrometaphanine (IIIa) (16.6 mg.) was treated with Ac_2O (1 ml.) and pyridine (0.5 ml.) at room temperature for 20 hr. The excess Ac_2O and pyridine were removed *in vacuo* and the residue was dissolved in H_2O (15 ml.), made alkaline with dil. NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried over $MgSO_4$. Evaporation of the solvent gave a crystalline solid. Recrystallization from AcOEt-ether mixture gave 15 mg. of monoacetyldihydrometaphanine (IIIb) as colorless prisms, m.p. 221°. $[\alpha]_D^{15}$ +35° (c=0.54, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1730 (OAc). *PKa'*: 6.15. NMR τ ($CDCl_3$): $OCH_3 \times 2$, 6.15 (3H), 6.16 (3H); N-CH_3, 7.40 (3H); $OCOC\underline{H}_3$, 7.90 (3H); $>C<^{OAc}_{\underline{H}}$, 4.88 (1H, quartet, J_A=5 c.p.s., J_B=11 c.p.s.). *Anal.* Calcd. for $C_{21}H_{27}O_6N \cdot \frac{1}{2}H_2O$: C, 63.31; H, 7.08; N, 3.51. Found: C, 63.40, 63.66; H, 7.27, 7.39; N, 3.53.

Acetolysis of Dihydrometaphanine (IIIa)——A mixture of dihydrometaphanine (397 mg.), Ac_2O (4 ml.) and conc. HCl (1 drop) was heated in a sealed tube at 180° for 10 hr. After cooling, the excess Ac_2O was removed *in vacuo* and the residual oil was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 3% HCl, 5% $NaHCO_3$ and then H_2O. Evaporation of the solvent *in vacuo* to dryness gave a brown oil, which was chromatographed over silicagel column from $CHCl_3$ and elution with the same solvent gave slightly yellow oil (190 mg.). The oil revealed two spots on the thin-layer chromatography and all attempts to separate two compounds was failed. A solution of above oil (190 mg.) in acetone (50 ml.) and 1% KOH (10 ml.) was heated under reflux for 30 min., and CH_3I (3 ml.) was added and refluxed for 30 min. The solvent was removed *in vacuo* and the residue was extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated. Trituration with MeOH separated crystals. Recrystallization from MeOH gave 1,5,6-trimethoxyphenanthrene (IV) as colorless plates, m.p. 136°. Yield, 45 mg. On admixture of IV with a synthetic sample of 1,5,6-trimethoxyphenanthrene no depression of melting point was observed and the IR spectra (in $CHCl_3$) and UV spectra (Fig. 3) of two compounds were identical. UV λ_{max}^{EtOH} mμ (log ε): 219 (4.44), 255 (4.77), 289 (4.07), 301 (4.18), 315 (4.24), 331 (3.51), 348 (3.64), 367 (3.67). *Anal.* Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.36; H, 5.89. Picrate: m.p. 128~129° (EtOH), *Anal.* Calcd. for $C_{23}H_{19}O_{10}N_3$: C, 55.53; H, 3.85; N, 8.45. Found: C, 55.80; H, 4.03; N, 8.27. The solvent of mother liquor from recrystallization of 1,5,6-trimethoxyphenanthrene was removed *in vacuo* and the residue was chromatographed over silicagel column from $CHCl_3$ and elution with the same solvent gave 1,5,6-trimethoxyphenanthrene (IV), m.p. 136° (15 mg.), as first eluate fraction. Continued elution with $CHCl_3$ gave 1,2,5,6-tetramethoxyphenanthrene (IIIb), characterized as its picrate, m.p. 148~149°, yield: 26 mg. The IR spectrum (in Nujol) of this picrate was superimposable with that of an authentic sample of 1,2,5,6-tetramethoxyphenanthrene picrate.

Deoxometaphanine-A (V), Deoxometaphanine-B (VI), Deoxometaphanine-C (VII) and Deoxometaphanine-D (VIII) (Huang-Minlon Reduction of Metaphanine)——A mixture of metaphanine (522 mg.) and 85% hydrazine hydrate (5 ml.) was heated for 1 hr. at 100°. After cooling, KOH pellets (4 g.) and diethylene glycol (7 ml.) were added and heated at 180° for 5 hr. The reaction mixture was poured into ice-water (30 g.) and made alkaline with addition of NH_4Cl and extracted with benzene. The benzene extract was washed, dried over Na_2SO_4. Evaporation of the solvent gave a yellow oil (310 mg.), which was chromatographed over alumina column from following solvents: a) at first, elution with benzene-$CHCl_3$ (1:1) gave deoxometaphanine-A (V) (30 mg.), b) secondary, elution with $CHCl_3$ gave deoxometaphanine-B (VI) (37 mg.), c) thirdly, elution with $CHCl_3$-AcOEt (1:1) gave deoxometaphanine-C (VII) (20 mg.) and d) at last, elution with $CHCl_3$-EtOH (10:1) gave deoxometaphanine-D (VIII) (5 mg.). Deoxometaphanine-A (V), -B (VI), -C (VII) and -D (VIII) revealed following properties:

a) Deoxometaphanine-A (V). NMR τ ($CDCl_3$): two benzene protons, 3.23 (1H, doublet, J=8.1 c.p.s.), 3.26 (1H, doublet, J=8.1 c.p.s.); olefinic protons, 3.55 (1H, doublet, J=10 c.p.s.), 4.35 (1H, doublet, J=10 c.p.s.); $OCH_3 \times 2$, 6.16 (3H), 6.18 (3H); N-CH_3, 7.74 (3H). V was characterized as its perchlorate, m.p. 229~230° (decomp.) (acetone). UV λ_{max}^{EtOH} mμ (log ε): 217 (4.32), 274 (4.13), 280 (4.11), 296 (3.73), 310 (3.66). $[\alpha]_D^{14}$ +250° (c=0.40, MeOH). *Anal.* Calcd. for $C_{19}H_{25}O_2N \cdot HClO_4$: C, 57.05; H, 6.55; N, 3.50.

Found : C, 57.20; H, 6.80; N, 3.48. b) Deoxometaphanine-B (VI). NMR τ ($CDCl_3$) : two benzene protons, 2.73 (1H), 3.21(1H); $>C<^{OH}_{H}$ (hydrogen geminal to hydroxyl group), 5.22 (1H); $OCH_3 \times 2$, 6.14 (3H), 6.19 (3H); N-CH_3, 7.80 (3H). VI was characterized as its perchlorate, m.p. 226~227° (decomp.) (EtOH-acetone mixture). $[\alpha]_D^{22}$ +122° (c=1.0, MeOH). *Anal.* Calcd. for $C_{19}H_{27}O_3N \cdot HClO_4$: C, 54.64; H, 6.76. Found : C, 54.93; H, 6.60.

c) Deoxometaphanine-C (VII). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500 (OH), 3400 (OH). NMR τ ($CDCl_3$) : two benzene protons, 2.90 (1H), 3.28 (1H); O<u>H</u>, 4.05 (1H); $>C<^{OH}_{H}$ (hydrogen geminal to hydroxyl group), 5.21 (1H); OCH_3, 6.17 (3H); N-CH_3, 7.79 (3H). All attempts to crystallize this deoxometaphanine-C (VII) was failed.

d) Deoxometaphanine-D (VIII). m.p. 249~250° (MeOH-$CHCl_3$ mixture). $[\alpha]_D^{22}$ +68° (c=0.5, $CHCl_3$). On admixture of VIII with the desulfurization product of metaphanine thioketal (X), no depression of melting point was observed and the IR spectra (in Nujol) of two compounds were superimposable.

Dihydrodeoxometaphanine-A (XII)——A solution of V (14 mg.) in MeOH (2 ml.) was hydrogenated over 5% Pd-C (15 mg.) for 2 hr. The catalyst was filtered off, washed with MeOH and the combined filtrate was evaporated *in vacuo* to dryness. The residue, after addition of 1% NH_4OH (15 ml.), was extracted with ether. The ether extract was washed, dried over K_2CO_3 and evaporated to give dihydrodeoxometaphanine-A (XII) (13 mg.). The IR spectrum ($CHCl_3$), NMR spectrum ($CDCl_3$) and thin-layer chromatography were quite identical with those of XV which was derived from dihydroindolinocodeinone (XIV). For characterization XII was derived to its hydrobromide, m.p. 270~271° (decomp.) (acetone). $[\alpha]_D^{24}$ +37° (c=0.75, MeOH). The IR spectrum of XII hydrobromide was identical with that of XV hydrobromide (in Nujol). *Anal.* Calcd. for $C_{19}H_{27}O_2N \cdot HBr$: C, 59.69; H, 7.38; N, 3.67. Found : C, 59.53; H, 7.59; N, 3.49.

Acetyldeoxometaphanine-B (IX)——Deoxometaphanine-B (70 mg.) was treated with pyridine (1 ml.) and Ac_2O (1 ml.) at room temperature for 20 hr. The excess pyridine and Ac_2O were evaporated to dryness *in vacuo* and 3% Na_2CO_3 (5 ml.) was added and extrcted with ether. The ether extract was washed, dried over K_2CO_3 and evaporated to give acetyldeoxometaphanine-B (IX) as colorless oil. Yield, 67 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1730 (OAc). NMR τ ($CDCl_3$) : two benzene protons, 3.10 (1H), 3.20 (1H); $>C<^{OAc}_{H}$ (hydrogen geminal to acetoxyl group), 3.97 (1H); $OCH_3 \times 2$, 6.12 (3H), 6.17 (3H); N-CH_3, 7.68 (3H); $OCOCH_3$, 7.84 (3H). IX was characterized as its perchlorate : m.p. 189° (decomp.) (EtOH). *Anal.* Calcd. for $C_{21}H_{29}O_4N \cdot HClO_4 \cdot \frac{1}{2}H_2O$: C, 54.12; H, 6.69; N, 3.01. Found : C, 54.29, 54.19; H, 6.78, 6.84; N, 3.16.

Dehydrodeoxometaphanine-B (XI)——A solution of deoxometaphanine-B (50 mg.) in $CHCl_3$ (10 ml.) was treated with activated manganese dioxide (500 mg.) with stirring at room temperature for 20 hr. and worked up as usual. XI, m.p. 143~144° (from MeOH, EtOH or ether). Yield, 35 mg. $[\alpha]_D^{23}$ −44° (c=0.5, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1678 (conj. C=O). UV λ_{max}^{EtOH} mμ (log ε) : 230 (4.24), 275 (3.93), 285~310 (shoulder). NMR τ ($CDCl_3$) : benzene protons, 2.37 (1H, doublet, J=8.5 c.p.s.), 3.17 (1H, doublet, J=8.5 c.p.s.); $OCH_3 \times 2$, 6.10 (3H), 6.11 (3H); N-CH_3, 7.82 (3H). *Anal.* Calcd. for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99; N, 4.44. Found : C, 72.27; H, 8.17; N, 4.48.

Huang-Minlon Reduction of Dehydrodeoxometaphanine-B (XI)——A mixture of XI (10 mg.) and 85% hydrazine hydrate (1 ml.) was heated at 100° for 1 hr. After cooling, KOH pellets (0.3 g.) and diethyleneglycol (1 ml.) was added and heated at 155~160° for 4 hr. The reaction mixture was poured into ice-water (30 ml.) and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated to give colorless oil (12 mg.) which was chromatographed over alumina column from benzene and elution with the same solvent gave dihydrodeoxometaphanine-A (XII) (9 mg.). XII was characterized as its hydrobromide, m.p. 270~271° (decomp.) (acetone). The IR spectrum of the hydrobromide was superimposable with that of XV hydromide.

Methylation of Deoxometaphanine-C (VII) with Rodionov Reagent——VII (15 mg.) was dissolved in anhyd. toluene (5 ml.), and then Rodionov reagent (0.5 ml. of MeOH solution) was added. The mixture was heated at 100° for 1 hr. to remove MeOH, and then refluxed at 130° with stirring for 8 hr. After cooling, H_2O (10 ml.) was added and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporation of the solvent to give colorless oil which was chromatographed over alumina column from benzene and elution with the same solvent gave deoxometaphanine-B (VI) as colorless oil. The IR spectrum ($CHCl_3$), NMR spectrum ($CDCl_3$) and thin-layer chromatography of this compound were quite identical with those of deoxometaphanine-B (VI) which was derived from Huang-Minlon reduction of metaphanine. Yield, 13 mg.

Metaphanine Thioketal (X)——A solution of metaphanine (109 mg.) in ethanedithiol (0.3 g.) and BF_3-ether (1 ml.) was allowed to stand at room temperature for 20 hr. The reaction mixture was poured into 5% NaOH (20 ml.) with stirring and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated. The residue was chromatographed over alumina column from $CHCl_3$ and elution with the same solvent gave 42 mg. of thioketal (X) as colorless needles, m.p. 238~239° (from EtOH). *Anal.* Calcd. for $C_{21}H_{27}O_4NS_2$: C, 59.83; H, 6.46; N, 3.33. Found. C, 59.72; H, 6.72; N, 3.62.

Deoxometaphanine-D (VIII) (From Metaphanine thioketal (X))——A mixture of thioketal (X) (80 mg.), MeOH (5 ml.), tetrahydrofuran (0.5 ml.) and Raney-W-2 nickel (1.2 g.) was refluxed for 7 hr. The catalyst was filtered off, washed with MeOH and the combined filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed over silicagel column from $CHCl_3$ and elution with the same solvent gave a crystalline solid. Recrystallization from a mixture of MeOH and $CHCl_3$ gave deoxometaphanine-D (Ⅷ) as colorless needles, m.p. 249～250°. Yield, 30 mg. On admixture of this desulfurization product (Ⅷ) with deoxometaphanine-D (derived from Huang-Minlon reduction of metaphanine) no depression of melting point was observed and the IR spectra (in Nujol) of these two compounds were quite identical. *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.61; H, 7.61; N, 4.22.

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Summary

The structure of metaphanine was examined and the partial structure (Ic) was presented.

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93. Masao Tomita, Toshiro Ibuka,*1 Yasuo Inubushi,*2 and Kyoji Takeda*3: Studies on the Alkaloids of Menispermaceous Plants. CCXV.*4 Alkaloids of *Stephania japonica* Miers. (Suppl. 13).*4 Structure of Metaphanine. (2).*4

(*Faculty of Pharmaceutical Sciences, Kyoto University,*1 *Faculty of Pharmaceutical Sciences, Osaka University*2 *and ITSUU Laboratory*3)

In the preceding paper*4 of this series the authors reported that the partial structure of metaphanine should be represented by formula (Ia). In this paper, the complete structure of metaphanine is shown to be represented by formula (I) including the absolute stereostructure.

A degradative pathway of considerable importance was found in the benzilic acid type rearrangement of metaphanine (I) with aqueous methanolic potassium hydroxide or sodium hydroxide. From the evidence discussed below, this compound was established as Ⅵ. The rearranged compound (Ⅵ) showed a δ-lactone group at 1733 cm^{-1} ($CHCl_3$), 1717 cm^{-1} (KBr) and a hydroxyl group at 3475 cm^{-1} ($CHCl_3$) in the infrared spectra. In the nuclear magnetic resonance spectrum*5 a proton geminal to the hydroxyl group forming the lactone group $\left(>C<\underset{H}{O-C=O}\right)$ revealed a signal at 4.60 τ as a quartet (J_A=4 c.p.s., J_B=2.5 c.p.s.). The analytical value corresponded to a composition

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*1 Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto (富田真雄，井深俊郎).
*2 Toneyama, Toyonaka, Osaka (犬伏康夫).
*3 Konno-cho, Shibuya-ku, Tokyo (武田強二).
*4 Part CCXIV. Suppl. 12 and (1). M. Tomita, T. Ibuka, Y. Inubushi, K. Takeda: This Bulletin, **13**, 695 (1965). A preliminary communication of this wark appeared in Tetrahedron Letters, No. 48, 3605 (1964).
*5 All NMR spectra were taken on Varian Associates A-60 recording spectrometer.