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.

The authors express their gratitudes to Dr. J. Koizumi of Nihon-shinyaku Co., Ltd. (Kyoto), for *PKa'* measurements. They are also indebted to Dr. T. Shingu for NMR spectral measurements and Dr. K. Konobu and his colaborators for elementary analyses.

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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*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.

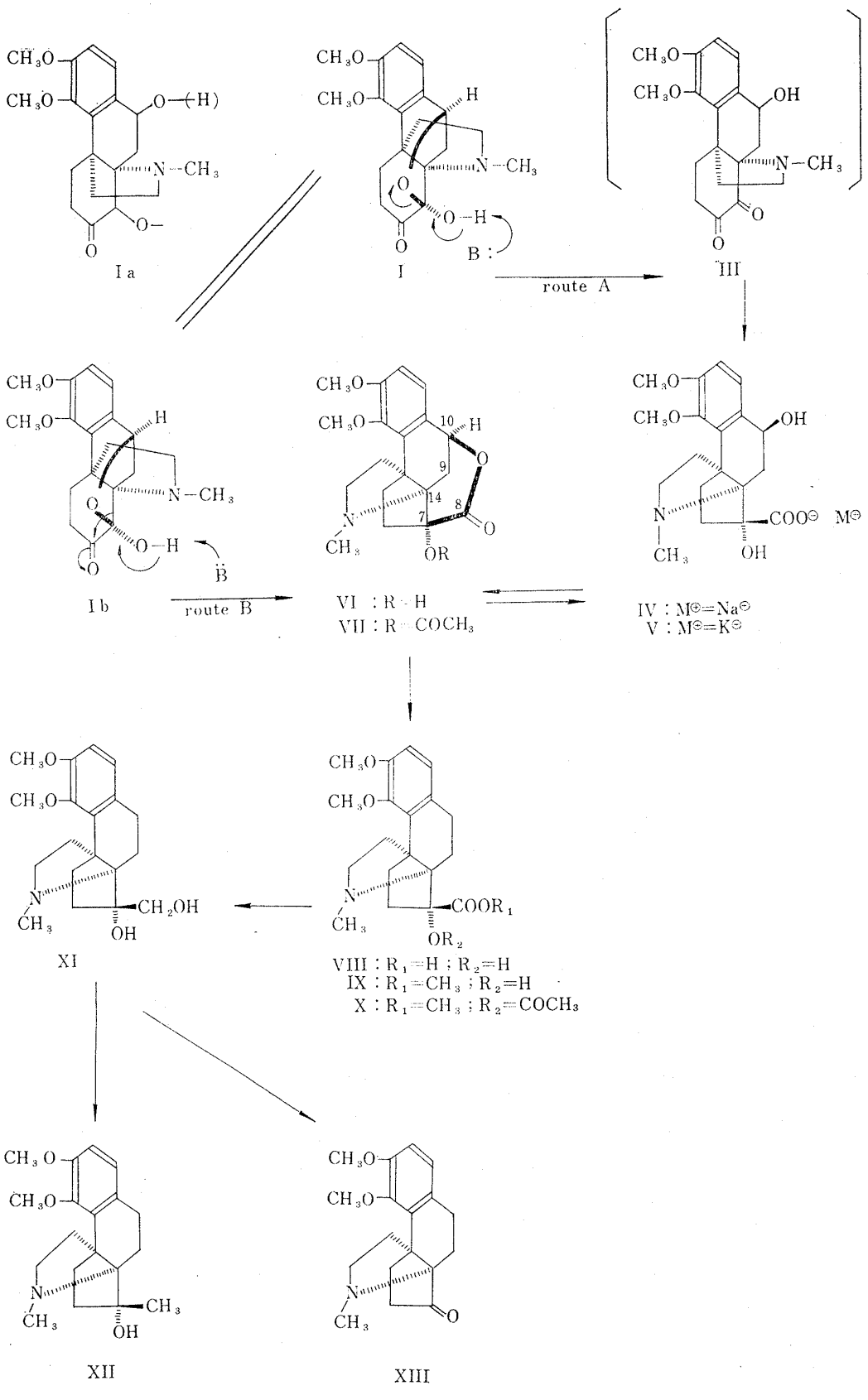


Chart 1.

of $C_{19}H_{23}O_5N \cdot CH_3OH$ (methanol adduct). The molecular weight of this substance, $C_{19}H_{23}O_5N$, was confirmed by its mass spectrum*6 (parent peak at 345 (calcd. 345.38)).

This rearrangement of metaphanine (I) to δ-lactone (Ⅵ) may be considered to proceed through two possible pathways. By treatment of caustic alkali the α-diketone-monohemiketal system in the metaphanine molecule leads to a sodium α-hydroxy carboxylate (Ⅳ) *via* α-diketone intermediate (Ⅲ) which could not be trapped and then Ⅳ is cyclized to the δ-lactone (Ⅵ) by acidification (route A). This process was partly supported by the following finding. Hydrolysis of the δ-lactone (Ⅵ) with potassium hydroxide in methanol gave a potassium α-hydroxy carboxylate (Ⅴ) as an amorphous solid, whose infrared spectrum (in Nujol) revealed a carboxylate band at 1572 cm^{-1}. Treatment of Ⅴ with dil. mineral acid gave the original δ-lactone (Ⅵ) in quantitative yield.

Alternatively, the δ-lactone (Ⅵ) is assumed to arise from Ib through the sequence cited in route B which may be analogue of known cevilinic acid δ-lactone rearrangement.[1] The two routes (route A and route B) were given somewhat arbitrarily and would require further experimental supports for verification.

Treatment of the δ-lactone (Ⅵ) with acetic anhydride and pyridine gave a δ-lactone acetate (Ⅶ), m.p. 205°, $C_{21}H_{25}O_6N$. Ⅶ showed a carbonyl band at 1730 cm^{-1} (δ-lactone and acetyl groups) in the infrared spectrum (in $CHCl_3$). In the nuclear magnetic resonance spectrum (Fig. 1) Ⅶ revealed an acetyl methyl at 7.83 τ and a proton geminal to the hydroxyl group forming the δ-lactone $\left(>C<\underset{H}{O-C=O}\right)$ at 4.52 τ as a quartet (J_A=4.5 c.p.s., J_B=2 c.p.s.) and none of the signal due to a proton geminal to an acetoxyl group. This spectral evidence supported that the tertiary hydroxyl group is present in the δ-lactone molecule.

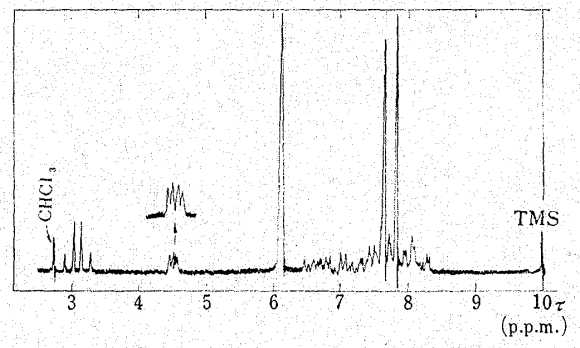


Fig. 1. Nuclear Magnetic Resonance Spectrum of Lactone Acetate (Ⅶ) (in $CDCl_3$)

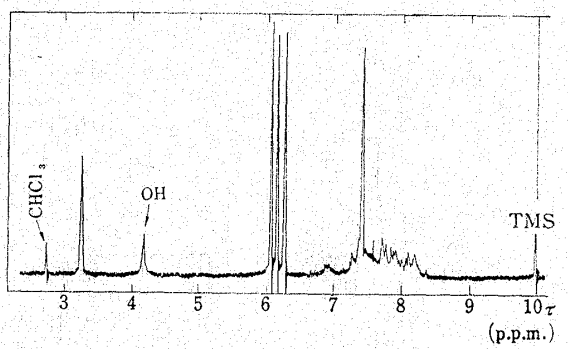


Fig. 2. Nuclear Magnetic Resonance Spectrum of Amino Acid Methyl Ester (Ⅸ) (in $CDCl_3$)

Hydrogenolysis of the δ-lactone (Ⅵ) over platinic oxide in acetic acid gave an amino acid (Ⅷ), m.p. 176~177°, $C_{19}H_{25}O_5N \cdot 2H_2O$, whose infrared spectrum (in Nujol) showed a carboxylate band at 1594 cm^{-1} indicating that the carboxylic acid of Ⅷ is present as zwitter ion. Treatment of Ⅷ with dil. hydrochloric acid gave an amino acid (Ⅷ) hydrochloride, m.p. 233~235°, $C_{19}H_{25}O_5N \cdot HCl \cdot 1/2H_2O$, whose infrared spectrum (in Nujol) showed a carbonyl band at 1700 cm^{-1} (carboxylic acid). Methylation of the amino acid (Ⅷ) hydrochloride with diazomethane in methanol gave an amino acid methylester (Ⅸ), m.p. 143°, $C_{20}H_{27}O_5N$, whose infrared spectrum (in $CHCl_3$) showed an ester carbonyl band at 1728 cm^{-1}. In the nuclear magnetic resonance spectrum (Fig. 2) Ⅸ revealed

*6 Mass spectrum was taken on Hitachi RMU 6C mass spectrometer.

1) *a*) S.M. Kupchan, D. Lavie : J. Am. Chem. Soc., **77**, 683 (1955). *b*) E.W. Warnhoff : "Molecular Rearrangements" Vol. 2, p. 935 (1964), edited by P. DE Mayo, Interscience Publishers, New York, London and Sydney.

three methoxyl groups at 6.07 τ, 6.17 τ and 6.28 τ. Treatment of IX with acetic anhydride and pyridine gave an acetyl methyl ester (X), whose infrared spectrum (in $CHCl_3$) revealed an overlapped carbonyl band at 1733 cm^{-1} ($COOCH_3$ and $OCOCH_3$). The nuclear magnetic resonance spectrum (Fig. 3) of this product showed a signal due to an acetyl methyl at 7.87 τ and no signal of the proton geminal to an acetoxyl group. Reduction of the amino acid methyl ester (IX) or the acetyl methyl ester (X) with lithium aluminum hydride gave a diol (XI), m.p. 174°, $C_{19}H_{27}O_4N$. Tosylation of the diol (XI) with tosylchloride and pyridine followed by reduction with lithium aluminum hydride afforded a tertiary C-methyl compound (XII), m.p. 122°, $C_{19}H_{27}O_3N$. The nuclear magnetic resonance spectrum (Fig. 4) of XII showed a signal attributable to a tertiary C-methyl

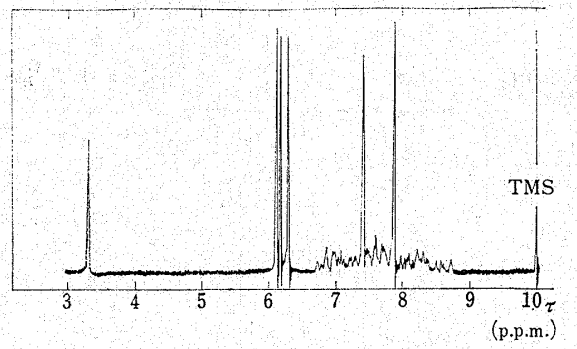


Fig. 3. Nuclear Magnetic Resonance Spectrum of Acetyl Metyl Ester (X) (in $CHCl_3$)

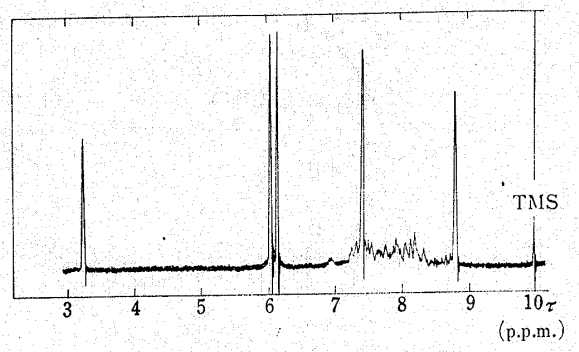


Fig. 4. Nuclear Magnetic Resonance Spectrum of Tertiary C-Methyl Compound (XII) (in $CHCl_3$)

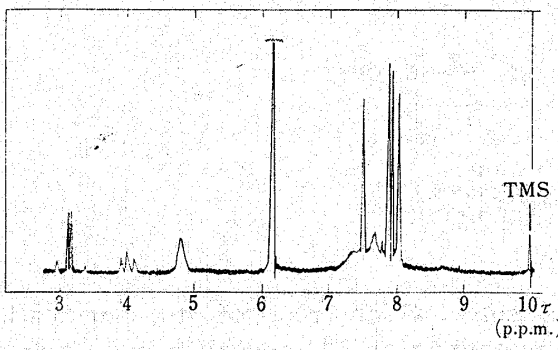


Fig. 5. Nuclear Magnetic Resonance Spectrum of Triol Triacetate (XVII) (in $CHCl_3$)

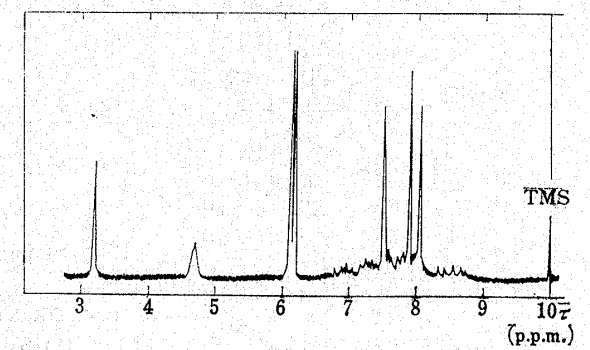


Fig. 6. Nuclear Magnetic Resonance Spectrum of Diol Diacetate (XX) (in $CDCl_3$)

group at 8.81 τ as a singlet. On the other hand, periodate oxidation of the diol (XI) gave a five-membered ketone (XIII) whose infrared spectrum (in $CHCl_3$) showed a carbonyl band at 1730 cm^{-1}. This result indicated that the diol (XI) contains a α-glycol system in the molecule and that rearranged product may have a five-membered ring which is formed as a result of the ring contraction occuring in the course of the rearrangement. All these facts are compatible with the proposed mechanism of the rearrangement.

It was reported that Veratrum alkaloids (cevine,[2] cevagenine,[3] zygadenine,[4]

2) *a*) D. H. R. Barton, J. C. W. Brooks, J. S. Fawcett: J. Chem. Soc., **1954**, 2137. *b*) D. H. R. Barton, J. C. W. Brooks, P. DE Mayo: *Ibid.* **1954**, 3950. *c*) D. H. R. Barton, O. Jeger, V. Prelog, R. B. Woodward: Experientia, **10**, 81 (1954).

3) *a*) A. Stoll, D. Stauffacher, E. Seebeck: Helv. Chim. Acta., **36**, 2027 (1953). *b*) E. Sundt, O. Jeger, V. Prelog: Chem. & Ind. (London), **1953**, 1365.

4) S. M. Kupchan: J. Am. Chem. Soc., **82**, 2242 (1960); S. M. Kupchan, C. V. Deliwala: *Ibid.* **75**, 1025 (1953); *Idem*: *Ibid.*, **76**, 5545 (1954); S. M. Kupchan: *Ibid.* **81**, 1935 (1959).

germine[5] and protoverine[2d] etc.) and a terpenoid (cryptofauronol[6]) containig a hemiketal grouping in the molecule are stable to acid treatment, and the hemiketal hydroxyl group resists to acetylation under usual condition. In the same manner, the α-diketone monohemiketal group in metaphanine was stable to acid and resisted to acetylation under usual condition. On the other hand dihydrometaphanine (II) which showed two hydroxyl groups in the nuclear magnetic resonance spectrum (in dimethylsulfoxide) gave monoacetyldihydrometaphanine (XIV) on treatment with acetic anhydride and pyridine.*4 Under forced conditions, metaphanine (I) and dihydrometaphanine (II) gave a brown

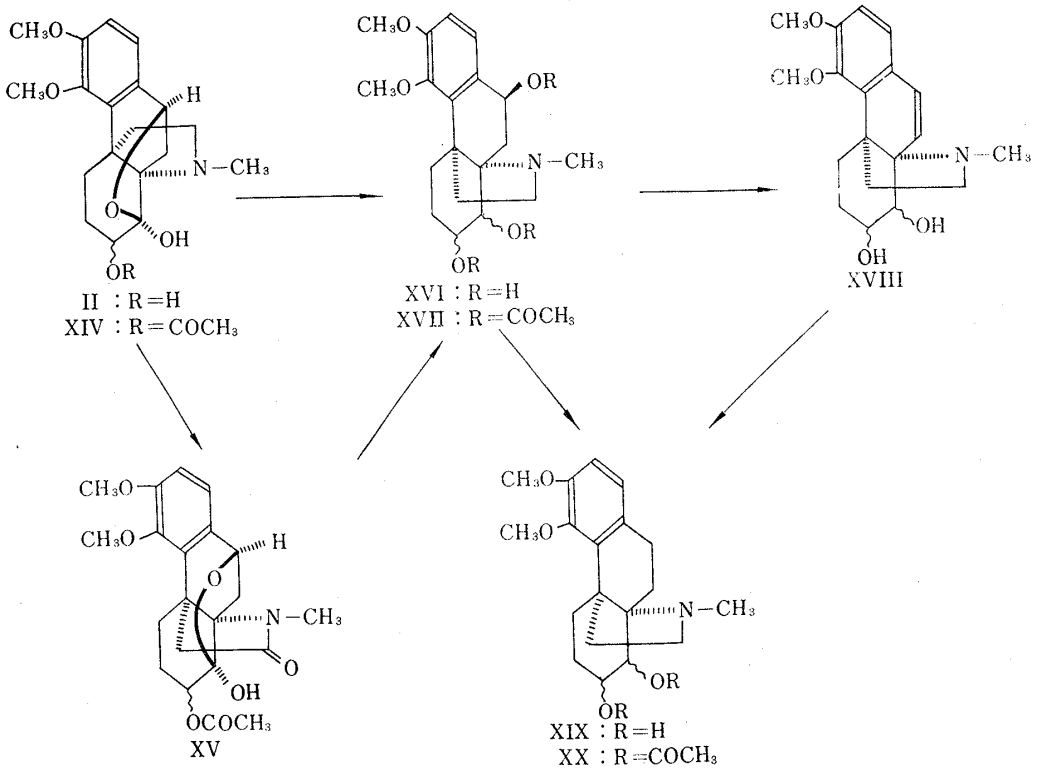
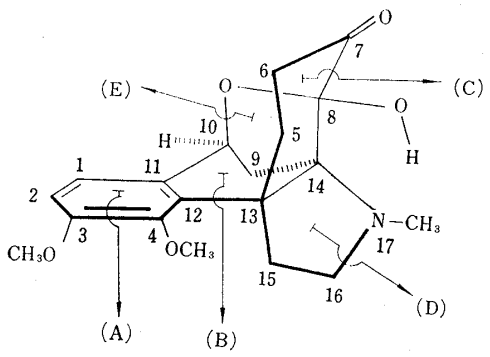


Chart 2.



XXI

Chart 3.

resinous solid which resisted to purification. Dihydrometaphanine (II) revealed no carbonyl band in its infrared spectrum. In connection with the results reported in the preceding paper*4 all these fact established that the hemiketal linkage between the carbonyl group at C-8 and the hydroxyl group substituted on C-10 is present in metaphanine (I) and dihydrometaphanine (II). The stereochemistry of this hemiketal linkage will be discussed later.

Oxidation of monoacetyldihydrometaphanine (XIV) with potassium permanganate in acetone under the presence of magnesium sulfate gave

5) *a*) S.M. Kupchan, C.R. Narayanan : *Ibid.* **81**, 1913 (1959). *b*) C.L. Craig, W.A. Jacobs : J. Biol. Chem., **149**, 271 (1943). *c*) S.M. Kupchan, M. Fieser, C.R. Narayanan, L.F. Fieser, J. Fried : J. Am. Chem. Soc., **77**, 5896 (1955).

6) H. Hikino, Y. Hikino, Y. Takeshita, T. Takemoto : "The 8th Symposium of Chemistry of Natural Products, Japan" symposium abstracts, p. 53 (1964) (Nagoya, Oct., 1964).

a γ-lactam (XV), m.p. 244~245°, $C_{21}H_{25}O_7N$, as major product. The infrared spectrum of XV showed an acetyl carbonyl band at 1730 cm^{-1} and a γ-lactam band at 1683 cm^{-1}. The latter frequency is in good agreement with those found in five-membered lactams. The nuclear magnetic resonance spectrum of XV revealed a signal due to N-methyl group at 6.91 τ. The displacement to lower side of the signal of the N-methyl group (metaphanine, 7.43 τ) explains adequately the structure (XV). This spectral evidence also supported that the ethanamine bridge consists of a five-membered ring. Reduction of II and XIV with lithium aluminum hydride caused the reductive fission of the hemiketal ether bridge to afford a triol (XVI), m.p. 161~162°, $C_{19}H_{27}O_5N$, $[\alpha]_D^{26}$ +4° ($CHCl_3$). This triol (XVI) was also obtainable by reduction of the γ-lactam (XV) with lithium aluminum hydride. These results supported that no transformation of the ring system was occured during oxidation of monoacetyldihydrometaphanine (XIV) with permanganate.

The above reductive fission of the hemiketal ether linkage with lithium aluminum hydride is analogous to the reductive fission of hemiketal group of tazettine by the lithium aluminum hydride reduction[7] and of cevine orthoacetate triacetate by reduction with lithium in liquid ammonia.[2b]

Treatment of the triol (XVI) with acetic anhydride and pyridine gave a triol triacetate (XVII), m.p. 100~104°, $C_{25}H_{33}O_8N$. The infrared spectrum of XVII showed a carbonyl band at 1730 cm^{-1} and its nuclear magnetic resonance spectrum (Fig. 5) revealed signals due to three acetate methyls at 7.90 τ, 7.93 τ, and 8.12 τ. Reduction of XVII with lithium aluminum hydride regenerated the original triol (XVI). Treatment of XVI with dil. perchloric acid under mild condition caused dehydration producing an olefinic compound (XVIII), m.p. 143°, $C_{19}H_{25}O_4N$. The ultraviolet spectrum (Fig. 7) showed a characteristic absorption curve of the styrene type chromophore indicating that the hydroxyl group at C-10 in the triol molecule was dehydrated.

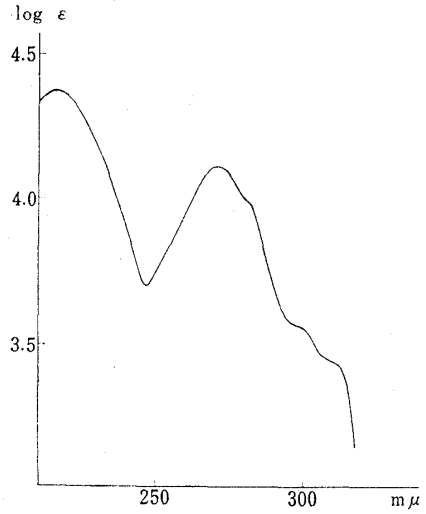


Fig. 7. Ultraviolet Absorption Spectrum of Olefinic Compound (XVIII) (in EtOH)

Catalytic hydrogenation of XVIII over palladium-carbon afforded a diol (XIX), m.p. 161~162°, $C_{19}H_{27}O_4N$, whose nuclear magnetic resonance spectrum (in dimethylsulfoxide) showed two secondary hydroxyl groups at 5.44 τ (1H, doublet, J=4.5 c.p.s.) and 5.72 τ (1H, doublet, J=4.5 c.p.s.). The diol (XIX) was also prepared from the triol (XVI) by catalytic hydrogenolysis over platinic oxide in acetic acid. Acetylation of the diol (XIX) with acetic anhydride and pyridine gave a diol diacetate (XX), m.p. 140°, $C_{23}H_{31}O_6N$. The infrared spectrum of XX showed a carbonyl band at 1730 cm^{-1}. The nuclear magnetic resonance spectrum (Fig. 6) revealed two acetate methyls at 7.90 τ and 8.06 τ, and two protons geminal to the acetoxyl groups at 4.72 τ (2H) as unresolved multiplet.

From these degradative and spectroscopic evidence described above, it can be concluded that the structure (I) must be allocated to metaphanine.

Information on the stereochemistry of metaphanine was provided by the following observations. Since the α-configuration of the ethanamine bridge has been established in the preceding paper,*4 the configuration of C-7~C-14 bond in the δ-lactone (VI) must

7) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, H. Yajima: J. Chem. Soc., **1956**, 4749.

be β-oriented. Consequently, the formation of the δ-lactone (Ⅵ) requires the β-configuration of the hydroxyl group at C-10. If the configuration of this hydroxyl group were α-oriented, the cyclization to the lactone ring would not be achieved. In metaphanine (I), dihydrometaphanine (Ⅱ) and monoacetyldihydrometaphanine (XIV) the existence of strong hydrogen bonding between the hemiketal hydroxyl group at C-8 and nitrogen atom was shown by their *Pka'* values and their infrared spectra, and difficulty of methiodide formation of these compounds is also understandable by taking this interaction into consideration. Thus, the configuration of the hemiketal hydroxyl group should have the same configuration, α-configuration, as that of ethanamine bridge. Consequently, the absolute stereostructure of metaphanine (I) must be represented by the perspective formula (XXI).*7

Experimental*8

δ-Lactone (VI) (Benzilic Acid Type Rearrangement of Metaphanine)——A mixture of metaphanine (I) (70 mg.), 20% aq. NaOH (0.5 ml.) and MeOH (20 ml.) was allowed to stand overnight at room temperature. After evaporation of the solvent *in vacuo* at room temperature 2 ml. of 10% HCl was added to the residue. The aqueous acidic solution was made alkaline with dil. NH_4OH and extracted with ether. The ether extract was washed, dried over $MgSO_4$ and evaporotion to give a colorless oil. Trituration with a small amount of MeOH gave a crystalline solid. Recrystallization from MeOH gave a δ-lactone (VI) as colorless prisms, m.p. 71~72°. Yield, 65 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1733 (δ-lactone), 3475 (OH). IR ν_{max}^{KBr} cm^{-1}: 1717 (δ-lactone). NMR τ ($CDCl_3$): benzene protons, 2.97 (1H, doublet, J=8 c.p.s.), 3.18 (1H, doublet, J=8 c.p.s.); $>C\langle^{O-C=O}_{H}$, 4.60 (1H, quartet, J_A=4 c.p.s., J_B=2.5 c.p.s.); $OCH_3\times2$, 6.15 (6H); N-CH_3, 7.52 (3H). *Anal.* Calcd. for $C_{19}H_{23}O_5N\cdot CH_3OH$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.59; H, 7.01; N, 3.58. Hydroiodide: m.p. 225°(from MeOH). *Anal.* Calcd. for $C_{19}H_{23}O_5N\cdot HI$: C, 48.21; H, 5.11; N, 2.96. Found: C, 48.41; H, 5.39; N, 3.19.

Potassium α-Hydroxycarboxylate (V) (Hydrolysis of δ-Lactone (VI))——A solution of δ-lactone (VI) (37.7 mg.) in 1% MeOH-KOH (0.56 ml.) was refluxed for 1 hr. Evaporation of the solvent *in vacuo* gave a colorless amorphous solid (V). The product (V) resisted to crystallization. Yield, 39 mg. IR ν_{max}^{Nujol} cm^{-1}: 1572 (carboxylate). A solution of potassium α-hydroxy carboxylate (V) (8 mg.) in 3% HCl (1 ml.) was allowed to stand for 5 min. at room temperature and made alkaline with dil. NH_4OH and extracted with ether. The ether extract was washed, dried over Na_2SO_4. Evaporation of the solvent left a colorless oil. Trituration with MeOH gave a crystalline solid. Recrystallization from MeOH gave 6 mg. of δ-lactone (VI) as colorless prisms, m.p. 71~72°. The compound was identified with the δ-lactone (VI) (prepared from benzilic acid type rearrangement of metaphanine) by mixed melting point determination and comparison of their IR spectra (in $CHCl_3$).

δ-Lactone Acetate (VII)——To a solution of δ-lactone (VI) (40 mg.) in pyridine (1 ml.) was added 1 ml. of Ac_2O and the mixture was allowed to stand overnight at room temperature. After evaporation of the excess Ac_2O and pyridine *in vacuo* at room temperature 10 ml. of 3% NH_4OH was added to the residue and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated to give a crystalline solid. Recrystallization from EtOH gave a δ-lactone acetate (Ⅶ) as colorless prisms, m.p. 205°. Yield, 40 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (δ-lactone and acetyl). NMR τ ($CDCl_3$): benzene protons, 3.0 (1H, doublet, J=8 c.p.s.), 3.21 (1H, doublet, J=8 c.p.s.); $>C\langle^{O-C=O}_{H}$, 4.52 (1H, quartet, J_A=4.5 c.p.s., J_B=2 c.p.s.); $OCH_3\times2$, 6.12 (6H); N-CH_3, 7.64 (3H); $OCOCH_3$, 7.83 (3H). *Anal.* Calcd. for $C_{21}H_{25}O_6N$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.16, 65.39; H, 6.67, 6.77; N, 3.54, 3.77.

Amino Acid Compound (VIII) (Hydrogenolysis of δ-Lactone (VI))——A mixture of δ-lactone (VI) (150 mg.), PtO_2 (50 mg.) and AcOH (10 ml) was hydrogenated at room temperature for 2 hr. The catalyst was filtered off, washed with 3% AcOH and the combined filtrate was evaporated *in vacuo*. Recrystallization of the residue from H_2O gave an amino acid (Ⅷ) (130 mg.) as colorless prisms, m.p. 176~177°. IR ν_{max}^{Nujol} cm^{-1}: 1594 (carboxylate). NMR τ ($D_2O+CD_3CO_2D$): benzene protons, 2.65 (2H); $OCH_3\times2$, 5.68 (3H), 5.75 (3H); N-CH_3, 6.61 (3H). *Anal.* Calcd. for $C_{19}H_{25}O_5N\cdot2H_2O$: C, 59.51; H, 7.62; N, 3.65. Found: C, 60.07; H, 7.52; N, 3.82. Hydrochloride: m.p. 233~235°(from $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1700 (CO_2H), 2300~2750 ($\overset{+}{N}$-H). *Anal.* Calcd. for $C_{19}H_{25}O_5N\cdot HCl\cdot\frac{1}{2}H_2O$: C, 58.08; H, 6.93; N, 3.56. Found: C, 58.22, 57.97; H, 6.98, 6.73; N, 3.45, 3.60.

*7 Ring C may take either chair or boat form conformation, but we depicted only chair form herein.
*8 All melting points were uncorrected and determined by Yanagimoto Micro Melting Point Apparatus.

Amino Acid Methyl Ester (IX) (Methylation of the Amino Acid (VIII) Hydrochloride with Diazomethane)——A solution of Ⅷ hydrochloride (55 mg.) in MeOH (3 ml.) was treated with diazomethane in ether (10 ml.) (prepared from nitrosomethylurea (3 g.)) and allowed to stand at room temperature for 3 hr. After evaporation of the solvent 5 ml. of 3% NH_4OH was added to the residue and the mixture was extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporation of the solvent gave crystals. Recrystallization from MeOH gave Ⅸ (45 mg.) as colorless needles, m.p. 143°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester), 3300 (OH). NMR τ ($CDCl_3$): benzene protons, 3.27 (2H); O<u>H</u>, 4.18 (1H); $OCH_3 \times 3$, 6.07 (3H), 6.17 (3H), 6.28 (3H); N-CH_3, 7.42 (3H). *Anal.* Calcd. for $C_{20}H_{27}O_5N$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.77, 66.50; H, 7.47, 7.34; N, 3.91, 3.88.

Acetyl Methyl Ester (X)——A mixture of methyl ester (Ⅸ) (32 mg.), pyridine (0.5 ml.) and Ac_2O (2 ml.) was allowed to stand at room temperature for 2 day. After evaporation of the excess reagent *in vacuo* the residue was treated with dil. NH_4OH (5 ml.) and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated to give an acetyl methyl ester (X) (31 mg.) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1733 (methyl ester and acetate). NMR τ ($CHCl_3$): benzene protons, 3.30 (2H); $OCH_3 \times 3$, 6.11 (3H), 6.18 (3H), 6.30 (3H); N-CH_3, 7.41 (3H); $OCOCH_3$, 7.87 (3H).

Diol Compound (XI)——To a solution of the amino acid methyl ester (Ⅸ) (or acetyl methylester (X)) (200 mg.) in ether (50 ml.) was added 100 mg. of $LiAlH_4$. The mixture was stirred at room temperature for 3 hr. and the excess reagent was decomposed by the addition of H_2O and and the mixture was extracted with ether. The extract was washed, dried over Na_2SO_4 and evaporoted to give a crystalline solid. Recrystallization from MeOH-ether mixture gave Ⅺ as colorless prisms, m.p. 174°. Yield, 175 mg. *Anal.* Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16. Found: C, 68.70; H, 8.22.

Tertiary C-Methyl Compound (XII)——A solution of diol (Ⅺ) (150 mg.) in pyridine (3 ml.) was treated with tosyl chloride (144 mg.) and allowed to stand at room temperature for 2 day. After evaporation of the excess pyridine *in vacuo* 10% Na_2CO_3 (10 ml.) was added to the residue and the alkaline solution was extracted with $CHCl_3$. The $CHCl_3$ solution was washed, dried over Na_2SO_4 and evaporated to give slightly yellow oil (130 mg.). To a solution of the tosylated product (130 mg.) in tetrahydrofuran (20 ml.) was added 100 mg. of $LiAlH_4$ in tetrahydrofuran (20 ml.). The mixture was heated under reflux for 6 hr. and after cooling the excess reagent was decomposed with H_2O and the mixture was extracted with ether. The ether extract was washed, dried over Na_2SO_4. Evaporation of the solvent left a crystalline solid which was chromatographed over alumina column from benzene and eluted with the same solvent. Recrystallization from hexane gave Ⅻ (50 mg.) as colorless prisms, m.p. 122°. NMR τ ($CDCl_3$): benzene protons, 3.26 (2H); $OCH_3 \times 2$, 6.05 (3H), 6.16 (3H); N-CH_3, 7.44 (3H); $>C<^{OH}_{CH_3}$ 8.81 (3H, singlet). *Anal.* Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57. Found: C, 71.62; H, 8.34.

Five Membered Ketone (XIII)——A solution of diol (Ⅺ) (21 mg. in EtOH (3 ml.) was treated with $HIO_4 \cdot 2H_2O$ (10 mg. in H_2O (0.5 ml.)) and allowed to stand at room temperature for 20 hr. The solvent was evaporated *in vacuo* and 10 ml. of 10% Na_2CO_3 was added to the residue and the alkaline solution was extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated to give slightly yellow oil which was chromatographed over alumina column from benzene and elution with the same solvent gave a five membered ketone (XIII) (6 mg.) as colorless oil. The product revealed a single spot on the thin layer chromatography. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (five membered ketone).

γ-Lactam (XV) (Oxidation of Monoacetyldihydrometaphanine (XIV) with Permanganate)——A mixture of XIV (60 mg.), $MgSO_4$ (70 mg.), acetone (15 ml.) and H_2O (2 ml.) was treated with $KMnO_4$ (75 mg.) in acetone (5 ml.) and H_2O (8 ml.) at room temperature with stirring for 5 hr. The excess permanganate was decomposed with a solution of $NaHSO_3$ (150 mg.) in 5% H_2SO_4 (5 ml.). The solvent was evaporated *in vacuo* and the aqueous solution was extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated to give a crystalline solid. Recrystallization from MeOH gave γ-lactam (XV) (41 mg.) as colorless needles, m.p. 244~245°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500~3350 (OH), 1730 (OAc), 1638 (γ-lactam). NMR τ ($CDCl_3$): benzene protons, 3.19 (1H), 3.21 (1H); O<u>H</u>, 5.99 (1H); $>C<^{OAc}_{H}$, 5.14 (1H); $OCH_3 \times 2$, 6.13 (6H); N-CH_3, 6.91 (3H ; $OCOCH_3$, 7.90 (3H). *Anal.* Calcd. for $C_{21}H_{25}O_7N$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.68; H, 6.47; N, 3.68.

Triol Compound (XVI) (Reduction of Dihydrometaphanine (II) with Lithium Aluminum Hydride)——To a solution of Ⅱ (97 mg.) in tetrahydrofuran (2 ml.) and ether (15 ml.) was added 100 mg. of $LiAlH_4$ and the reaction mixture was refluxed for 5 hr. and after cooling the excess reagent was decomposed with H_2O and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried over Na_2SO_4 and evaporated to give a crystalline solid. Recrystallization from MeOH-ether mixture gave a triol (XVI) (55 mg.), m.p. 161~162°, as colorless needles. $[\alpha]_D^{26}$ +4° (c=0.5, $CHCl_3$). NMR τ (pyridine): $OCH_3 \times 2$, 6.11 (3H), 6.27 (3H); N-CH_3, 7.25 (3H). *Anal.* Calcd. for $C_{19}H_{27}O_5N$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.35; H, 7.99; N, 4.27. Hydrochloride: m.p. 235° (from MeOH), colorless needles. *Anal.* Calcd. for $C_{19}H_{27}O_5N \cdot HCl$: C, 59.14; H, 7.32; N, 3.63. Found: C, 59.38; H, 7.47; N, 3.81.

Triol Compound (XVI) (Reduction of γ-Lactam (XV) with Lithium Aluminum Hydride)——To a solution of lactam (XV) (22 mg.) in tetrahydrofuran (3 ml.) and ether (15 ml.) was added 50 mg. of $LiAlH_4$. The

mixture was refluxed with stirring for 11 hr. and after cooling the excess reagent was decomposed with H_2O. Inorganic precipitate was filtered off, washed with $CHCl_3$ and the combined filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in dil. HCl (15 ml.) and extracted with ether. The aq. acidic layer was made alkaline with dil. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed, dried over Na_2SO_4 and evaporated to give a crystalline solid. Recrystallization from MeOH gave the triol (XVI) as colorless needles, m.p. 160~161°. Yield, 14 mg. On admixture of the product with the triol which was prepared from dihydrometaphanine by the $LiAlH_4$ reduction no melting point depression was observed and the infrared spectra (in $CHCl_3$) of two compounds were identical.

Triol Triacetate (XVII)——A mixture of triol (XVI) (20 mg.), pyridine (2 ml.) and Ac_2O (1 ml.) was allowed to stand overnight at room temperature. The excess reagent was removed *in vacuo* and the residue was made alkaline with dil. NH_4OH and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated. Recrystallization from ether gave a triol triacetate (XVII) as colorless needles, m.p. 100~104°. Yield, 15 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (OAc). NMR τ ($CHCl_3$): benzene protons, 3.03 (1H), 3.15 (1H); $>C<^{\underline{H}}_{OAc}\times 3$, 4.0 (1H, triplet), 4.83 (2H, broad miltiplet); $OCH_3\times 2$, 6.14 (6H); N-CH_3, 7.55 (3H); $OCOCH_3\times 3$, 7.90 (3H), 7.93 (3H), 8.12 (3H). *Anal.* Calcd. for $C_{25}H_{33}O_8N$: C, 63.14; H, 7.00; N, 2.95. Found: C, 63.20; H, 7.24; N, 3.02.

Reduction of Triol Triacetate with Lithium Aluminum Hydride——A mixture of triol triacetate (XVII) (12 mg.), tetrahydrofuran (20 ml.) and $LiAlH_4$ (50 mg.) was stirred at room temperature for 1 hr. The excess reagent was decomposed with H_2O. Treatment of the product as usual and recrystallization from MeOH-ether mixture gave the original triol (XVI), m.p. 158~159°, as colorless needles. On admixture of this product with the triol which was prepared from dihydrometaphanine by the $LiAlH_4$ reduction no melting point depression was observed and the IR spectra (in $CHCl_3$) of two compounds were quite identical.

Olefinic Compound (XVIII)——A solution of triol (XVI) (110 mg.) in MeOH (10 ml.) and 60% $HClO_4$ (0.2 ml.) was refluxed for 20 min. and after cooling the solvent was removed *in vacuo* and the residue was made alkaline with dil. NH_4OH and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated to give a crystalline solid. Recrystallization from MeOH gave an olefinic compound (XVIII) as colorless prisms, m.p. 143°. Yield, 91 mg. *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60. Found: C, 68.95; H, 7.87.

Diol Compound (XIX). **a) Catalytic Hydrogenolysis of Triol (XVI)**——A mixture of triol (19 mg.), AcOH (5 ml.) and PtO_2 (5 mg.) was hydrogenated at room temperature for 5 hr. The catalyst was filtered off, washed with MeOH and the combined filtrate was evaporated to dryness *in vacuo* and the residue was made alkaline with dil. NH_4OH and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated. Recrystallization from ether gave the diol (XIX) as colorless needles, m.p. 161~162°. Yield, 5 mg. On admixture of the product with the diol which was derived from the olefinic compound (XVIII) by catalytic hydrogenation no melting point depression was observed and the IR spectra ($CHCl_3$) of two compounds were superimposable.

b) Catalytic Hydrogenation of Olefinic Compound (XVIII)——A mixture of olefinic compound (XVIII) (64 mg.), MeOH (3 ml.), Darco G-60 (30 mg.) and 5% $PdCl_2$ (1 ml.) was hydrogenated for 3 hr. at room temperature. The catalyst was filtered off, washed with MeOH and the combined filtrate was evaporated to dryness and the residue was made alkaline with 3% NH_4OH and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated. Recrystallization from ether gave the diol (XIX) as colorless needles, m.p. 161~162°. Yield, 55 mg. NMR τ (dimethylsulfoxide): O$\underline{H}$, 5.44 (1H, doublet, J=4.5 c.p.s.); O$\underline{H}$, 5.72 (1H, doublet, J=4.5 c.p.s.). *Anal.* Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16. Found: C, 68.69; H, 8.14.

Diol Diacetate (XX)——A mixture of diol (XIX) (35 mg.), pyridine (0.5 ml.) and Ac_2O (1 ml.) was allowed to stand overnight at room temperature. The excess reagents were removed *in vacuo*. The residue was made alkaline with dil. NH_4OH and extracted with ether. The ether extract was washed, dried over Na_2SO_4 and evaporated. Recrystallization from MeOH gave a diol diacetate (XX) as colorless needles, m.p. 140°. Yield, 31 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (OAc). NMR τ ($CDCl_3$): benzene protons, 3.22 (2H); $>C<^{\underline{H}}_{OAc}\times 2$, 4.72 (2H, unresolved multiplet); $OCH_3\times 2$, 6.16 (3H), 6.20 (3H); N-CH_3, 7.52 (3H); $OCOCH_3\times 2$, 7.90 (3H), 8.06 (3H). *Anal.* Calcd. for $C_{23}H_{31}O_6N$: C, 66.16; H, 7.48. Found: C, 66.36; H, 7.56.

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Summary

Metaphanine was shown to be an alkaloid derived from a new ring system "hasubanan." Degradative and spectroscopic evidence established metaphanine as I. The absolute configuration of this alkaloid was established as shown by the perspective formula (XXI).

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