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# STRUCTURE OF METAPHANINE

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METAPHANINE, a non phenolic alkaloid, was first isolated from Stephania japonica Miers (Menispermaceae) by Kondo et al.[1] in 1924 and thereafter the empirical formula, $C_{19}H_{23}O_5N$, was given correctly by Takeda[2] in 1960. The authors wish to report the complete structure of metaphanine on the basis of the following evidences.

Metaphanine (I), m.p. 232°, $C_{19}H_{23}O_5N$*1, Pka'*2: 6.03, contains one N-$CH_3$ group (NMR*3 $\tau$: 7.43(3H)), two $OCH_3$ groups (NMR. $\tau$: 6.14(6H)), one OH group (IR $\nu_{max.}^{CHCl_3}$: 3480 $cm^{-1}$(OH)),

*1 All compounds given by formulae in this communication gave correct elementary analysis.

*2 Unless otherwise stated, all NMR. spectra were taken on Varian Associates A-60 recording spectrometer operated at 60 Mc. in $CDCl_3$ with $SiMe_4$ as internal standard.

*3 All Pka' values were determined in 80% aq. methylcellosolve.

one carbonyl group (IR $\nu_{max.}^{KBr}$: 1730 $cm^{-1}$) and two aromatic hydrogens (NMR. $\tau$: 3.23(1H, doublet, J = 8.1 cps) and 3.30(1H, doublet, J = 8.1 cps)). Therefore, the rational formula, $C_{15}H_{13}.(CO).(OCH_3)_2.(N\text{-}CH_3).(OH).(\text{-}O\text{-})$ was given for metaphanine and metaphanine should be a pentacyclic alkaloid.

Acetolysis of metaphanine (I) with acetic anhydride in a sealed tube gave a neutral compound (IIa), m.p. 150°, $C_{20}H_{18}O_6$; $C_{14}H_6.(OAc)_2.(OCH_3)_2$, NMR. $\tau$($CCl_4$): $OCH_3 \times 2$, 6.06(3H), 6.10(3H); $OCOCH_3 \times 2$, 7.62(3H), 7.75(3H), IR $\nu_{max.}^{KBr}$: 1775 $cm^{-1}$(OAc), UV $\lambda_{max.}^{EtOH}$ $m\mu$(log $\varepsilon$): 232(4.41), 257(4.77), 281(4.19), 306(4.11), 312(4.12), 343(3.39), 361(3.32). Hydrolysis of (IIa) with methanolic-KOH followed by methylation with methyliodide gave 3,4,7,8-tetramethoxyphenanthrene (IIb), m.p. 63-65°, NMR. $\tau$($CCl_4$): $OCH_3 \times 4$, 6.05(6H), 6.09(3H), 6.15(3H); (IIb) picrate, m.p. 147-148°, $C_{24}H_{21}O_{11}N_3$. (IIb) and (IIb) picrate were identified with authentic samples[3] by mixed melting point determinations and comparison of their IR spectra. Hydrolysis of (IIa) with ethanolic-KOH followed by ethylation with ethyliodide gave 3,4-dimethoxy-7,8-diethoxyphenanthrene (IIc), m.p. 63-64°, NMR. $\tau$($CCl_4$): $OCH_3 \times 2$, 6.06(3H), 6.14(3H); $OCH_2CH_3 \times 2$, 8.52(3H), 8.54(3H). (IIc)picrate, m.p. 144-145°, $C_{26}H_{25}O_{11}N_3$, was identified with an authentic sample[*4] by direct comparison.

On catalytic hydrogenation over $PtO_2$ in acetic acid metaphanine (I) absorbed one mole of hydrogen to afford dihydrometaphanine (IIIa), m.p. 211°, $C_{19}H_{25}O_5N$, $[\alpha]_D^{20}$: +72° ($CHCl_3$),

[*4] M. Tomita and T. Ibuka, unpublished results.

Pkā: 6.76. The absence of carbonyl absorption band in its IR spectrum indicated that the $>C=O$ group was reduced to a $>C<^{OH}_{H}$ group. NMR spectrum (in dimethylsulfoxide[4]) of (IIIa) showed two OH signals, one is tertiary O$\underline{H}$ (4,76$\tau$: 1H, singlet) and the other is secondary O$\underline{H}$ (5.88$\tau$: 1H, doublet, J=6.5 cps), and both signals disappeared on the addition of $D_2O$.

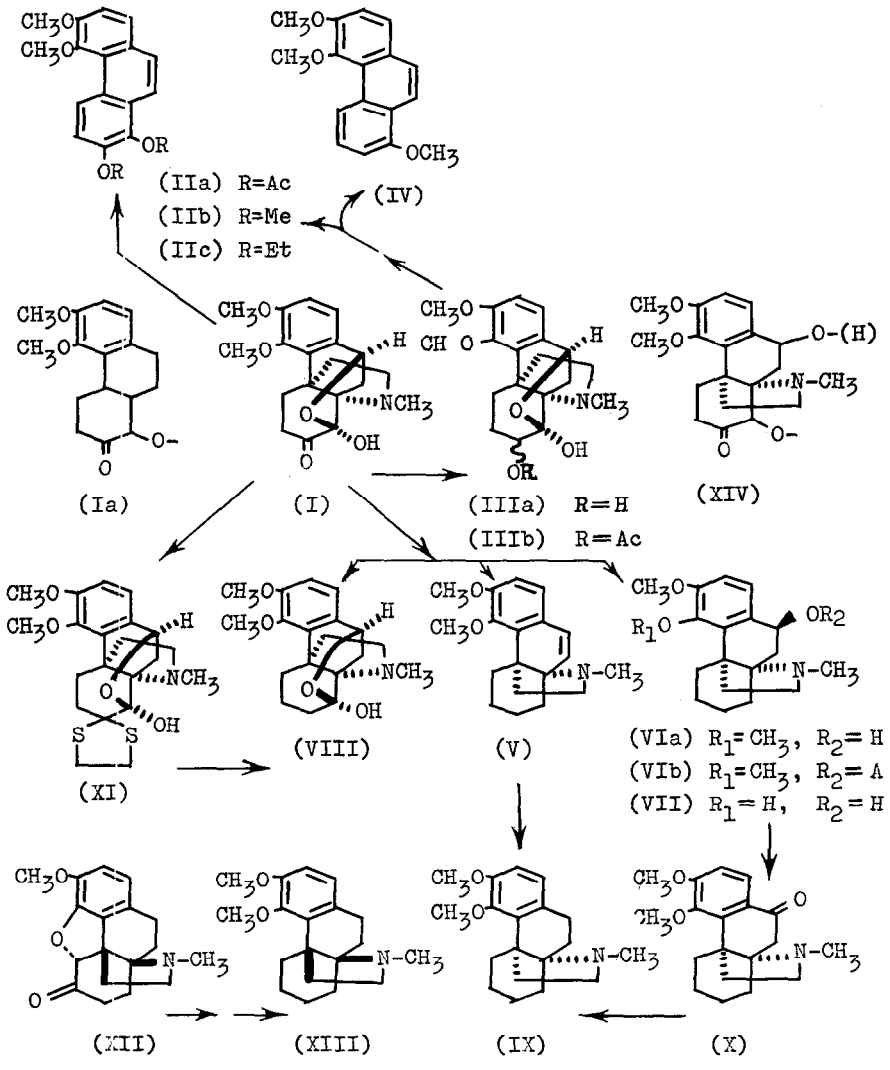
Treatment of (IIIa) with $Ac_2O$-pyridine gave monoacetyldihydrometaphanine (IIIb), m.p. 221°, $C_{21}H_{27}O_6N.{}^1/_2.H_2O$, $[\alpha]_D^{15}$: +35 ($CHCl_3$), Pkā: 6.15, $IR\nu_{max.}^{Nujol}$: 1730 (OAc), 3450 $cm^{-1}$ (OH), NMR.$\tau$: $OCH_3 \times 2$, 6.15(3H), 6.16(3H); $\dot{N}$-$CH_3$, 7.40(3H); $OCO\underline{CH_3}$, 7.90(3H); $>C<^{OAc}_{\underline{H}}$, 4.88(1H, quartet, $J_A$=5 cps, $J_B$=11 cps).

It has been well known that on the acetolysis of morphine-sinomenine series alkaloids oxygen atoms of carbonyl group or ether linkage remain as acetoxyl groups on the derived phenanthrene nucleus, whereas alcoholic hydroxyl groups are eliminated by dehydration in the course of the aromatization process[5,6].

Acetolysis of (IIIa) with acetic anhydride followed by hydrolysis and methylation gave 3,4,7,8-tetramethoxyphenanthrene (IIb) in 33% yield, and 3,4,8-trimethoxyphenanthrene (IV) in 65% yield, respectively. (IV), m.p. 136°, $C_{17}H_{16}O_3$ and (IV)picrate m.p. 128-129°, $C_{23}H_{19}O_{10}N_3$ were identified with authentic samples prepared by Pshorr's method.[7]

The above experimental results suggested that the partial structure (Ia) might be present in the metaphanine molecule, if no rearrangement took place during the acetolysis process.

Huang-Minlon reduction of metaphanine (I) under mild condition, recommended by Gates[8], gave four deoxo derivatives.


(IIa) R=Ac
(IIb) R=Me
(IIc) R=Et
(IV)
(Ia)
(I)
(IIIa) R=H
(IIIb) R=Ac
(XIV)
(XI)
(VIII)
(V)
(VIa) R1=CH3, R2=H
(VIb) R1=CH3, R2=Ac
(VII) R1=H, R2=H
(XII)
(XIII)
(IX)
(X)

namely, deoxometaphanine-A (V), -B (VIa), -C (VII) and -D (VIII).

Deoxometaphanine-A (V), NMR.$\tau$: olefinic H×2, 3.49(1H, doublet, J=10cps), 4.35(1H, doublet, J=10 cps); (V) perchlorate, m.p. 229-230°, (decomp.), $C_{19}H_{25}O_2N.HClO_4$, $[\alpha]_D^{14}$: +250°(MeOH), UV $\lambda_{max.}^{EtOH}$ mμ(log ε): 217(4.32), 274(4.13), 280(4.11), 296(3.73), 310(3.66). Catalytic hydrogenation of (V) over $PtO_2$ dihydrodeoxometaphanine-A (IX); (IX) hydrobromide, m.p. 270-271°(decomp.) $C_{19}H_{27}O_2N.HBr$, $[\alpha]_D^{24}$: +37°(MeOH).

Deoxometaphanine-B (VIa) showed the presence of a hydroxyl group at 3400 $cm^{-1}$ in the IR spectrum and a signal attritutable to $>C<^{\underline{OH}}_{\underline{H}}$ hydrogen at 5.22 (1H, triplet) in the NMR. spectrum. (VIa) perchlorate, m.p.226-227°(decomp.), $C_{19}H_{27}O_3N.HClO_4$. Acetylation of (VIa) with $Ac_2O$-pyridine gave acetyldeoxometaphanine-B (VIb), IR$\nu_{max.}^{CHCl_3}$: 1730 $cm^{-1}$(OAc), NMR.$\tau$: $OCOCH_3$, 7.84 (3H); $>C<^{\underline{OAc}}_{\underline{H}}$, 3.97(1H, triplet). Reduction of (VIb) with lithium aluminium hydride regenerated the original deoxometaphanine-B (VIa). Oxidation of (VIa) with activated manganese dioxide in chloroform gave dehydrodeoxometaphanine-B (X), m.p. 143-144°, $C_{19}H_{25}O_3N$, $[\alpha]_D^{23}$: -44°($CHCl_3$), IR$\nu_{max.}^{CHCl_3}$: 1678 $cm^{-1}$ (conj. CO), UV $\lambda_{max.}^{EtOH}$ mμ(log ε):230(4.24), 275(3.93), 285-310 (shoulder; 3.09-3.60). Huang-Minlon reduction of (X) gave dihydrodeoxometaphanine-A(IX).

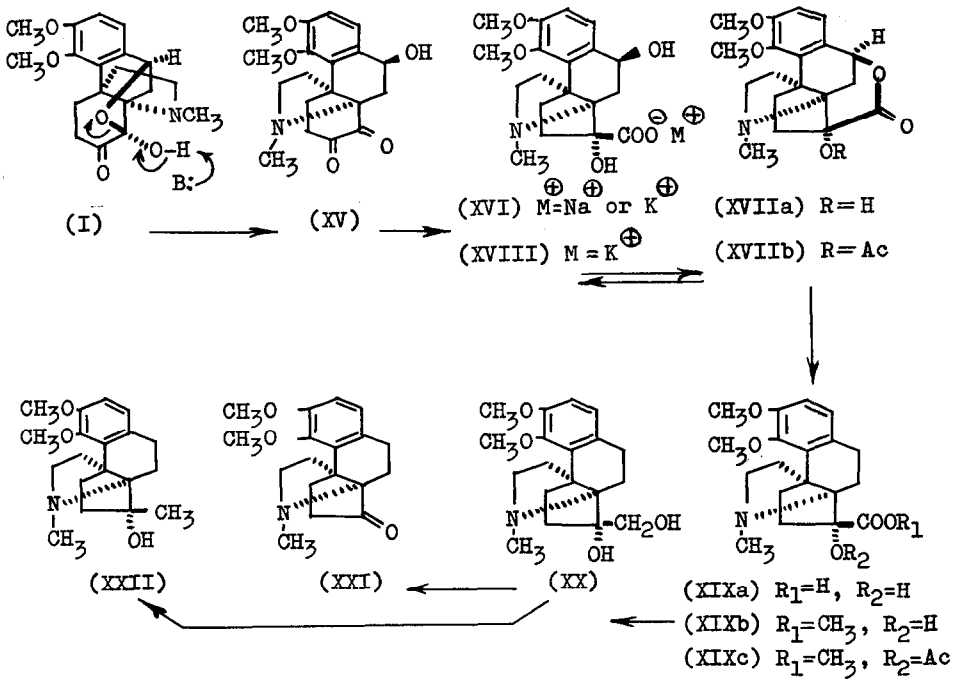
Deoxometaphanine-C (VII), IR$\nu_{max.}^{CHCl_3}$: 3500-3400 $cm^{-1}$(OH), gave strong blue coloration with 2,6-dichloroquinone-4-chloroimide and showed the presence of only one $OCH_3$ group at 6.17 $\tau$ (3H) in the NMR. spectrum. Methylation of (VII) with diazomethane was failed but with Rodionov reagent[9] gave (VIa).

Deoxometaphanine-D (VIII), m.p. 249-250°, $C_{19}H_{25}O_4N$, $[\alpha]_D^{22}$: +68°($CHCl_3$), IR $\nu_{max.}^{CHCl_3}$: 3500-3300 $cm^{-1}$(OH) was also obtainable by Raney-W-2 Nickel reduction of metaphanine thioketal (XI), m.p. 238-239°, $C_{21}H_{27}O_4NS_2$ which in turn is derived from metaphanine.

Direct proof of the structure (including the absolute configuration) of dihydrodeoxometaphanine-A (IX) was achieved by comparison of (IX) and its hydrobromide with authentic samples of the compound (XIII)[10] and its hydrobromide, m.p. 270-271°(decomp.), $[\alpha]_D$: -42°(MeOH) which were synthesized from dihydroindolinecodeinone (XII).[11]

On the basis of the above results, metaphanine should have the partial structure of (XIV).

Treatment of metaphanine (I) with aq.-MeOH-KOH or -NaOH under room temperature caused the benzilic acid rearrangement producing a $\alpha$-hydroxycarboxylic acid derivative (XVI) via a $\alpha$-diketone intermediate (XV) which could not be isolated. Treatment of (XVI) with dil. hydrochloric acid afforded a lactone (XVIIa), m.p. 71-72°, $C_{19}H_{23}O_5N.CH_3OH$(methanol adduct), NMR.$\tau$: $>C<^{\underline{H}}_{OCO-}$, 4.60 (1H, quartet, $J_A$=4 cps, $J_B$=2.5 cps). Hydrolysis of (XVIIa) with 1% MeOH-KOH gave a potassium carboxylate (XVIII), which showed a carboxylate band at 1572 $cm^{-1}$ in the IR spectrum. Treatment of (XVIII) with dil. mineral acid gave the original lactone (XVIIa) in quantitative yield. Acetylation of the lactone (XVIIa) with $Ac_2O$-pyridine gave a lactone acetate (XVIIb), m.p. 205°, $C_{21}H_{25}O_6N$, IR $\nu_{max.}^{CHCl_3}$: 1730 $cm^{-1}$ ( OAc and $\delta$-lactone), NMR.$\tau$: 7.83(3H, $OCOCH_3$); 4.52(1H, quartet, $>C<^{\underline{H}}_{OCO}$, $J_A$=4.5 cps, $J_B$=2 cps).




Hydrogenolysis of the lactone (XVIIa) over $PtO_2$ gave an amino-acid (XIXa), m.p. 176-177°, $C_{19}H_{25}O_5N.2H_2O$, IR$\nu_{max.}^{Nujol}$: 1594 $cm^{-1}$ ($COO^-$); (XIXa) hydrochloride, m.p. 233-235°(decomp.), $C_{19}H_{25}O_5N.HCl.^1/_2.H_2O$, IR$\nu_{max.}^{Nujol}$: 1700(COOH), 2300-2750 $cm^{-1}(\overset{+}{N}\text{-H})$. Methylation of (XIXa) hydrochloride with diazomethane gave an amino-acid methylester (XIXb), m.p. 143°, $C_{20}H_{27}O_5N$, IR$\nu_{max.}^{CHCl_3}$: 1728 ($COOCH_3$), 3300-3100 $cm^{-1}$(OH), NMR.$\tau$: $OCH_3 \times 3$, 6.07(3H), 6.17(3H), 6.28(3H); O<u>H</u>, 4.18(1H, singlet), which on treatment with

$Ac_2O$-pyridine gave an acetylmethylester (XIXc), IR $\nu_{max.}^{CHCl_3}$: 1733 (OAc, $COOCH_3$), NMR. $\tau$: $OCH_3 \times 3$, 6.11(3H), 6.18(3H), 6.30(3H); N-$CH_3$, 7.41(3H); $OCOCH_3$, 7.87(3H). Reduction of (XIXb) or (XIXc) with lithium aluminium hydride gave a diol (XX), m.p. 174°, $C_{19}H_{27}O_4N$. Tosylation of (XX) with tosylchloride-pyridine followed by reduction with lithium aluminium hydride afforded a compound (XXII), m.p. 122°, $C_{19}H_{27}O_3N$, NMR. $\tau$: 8.81 (-C(HO)=C-$CH_3$, 3H, singlet). Periodate oxidation of (XX) gave a five membered ketone (XXI), IR $\nu_{max.}^{CHCl_3}$: 1730 $cm^{-1}$. This result indicated that the diol (XX) contains a >C(OH)-$CH_2$OH system in the molecule.

It was reported that the Veratrum alkaloids (protoverine[12], zygadenine[13], germine[14], cevine[12] etc.,) containing α-ketolhemiketal grouping in the molecule are stable to acid treatment and hemiketal hydroxyl group resists to acetylation under usual condition.

In tha same manner, α-diketone monohemiketal grouping in metaphanine (I) and the α-ketolhemiketal grouping in dihydrometaphanine (IIIa) were stable to acids and each hemiketal hydroxyl group resisted to acetylation under usual condition.

Oxidation of monoacetyldihydrometaphanine (IIIb) with $KMnO_4$ in acetone-magnesium sulfate buffer gave γ-lactam (XXIII) as major product, m.p. 244-245°, $C_{21}H_{25}O_7N$, IR $\nu_{max.}^{CHCl_3}$: 3500-3350 $cm^{-1}$ (OH), 1730(OAc), 1683 $cm^{-1}$ (γ-lactam), NMR. $\tau$: 5.99(1H, OH), 5.14(1H, triplet, >C(OAc)-H), 6.13(6H, $OCH_3 \times 2$), 6.91(3H, $NCH_3$),

7.90(3H, $OCOCH_3$), 5.04(1H, $>C<^{O-}_{H}$, doublet[*5], J=6.5 cps).

Treatment of (IIIa) or (IIIb) with $LiAlH_4$ caused the reductive fission of the hemiketal ether bridge to afford a triol (XXIVa), m.p. 161-162°, $C_{19}H_{27}O_5N$, $[\alpha]_D^{26}$: +4° ($CHCl_3$). This triol was also obtainable by reduction with $LiAlH_4$ of the γ-lactam (XXIII). Acetylation of (XXIVa) with $Ac_2O$-pyridine gave a triol triacetate (XXIVb), m.p. 100-104°, $C_{25}H_{33}O_8N$, IR $\nu_{max.}^{CHCl_3}$: 1730 $cm^{-1}$(OAc), which on reduction with $LiAlH_4$ gave the original triol (XXIVa). Treatment of (XXIVa) with dil. perchloric acid under mild condition caused dehydration producing an olefinic compound (XXV), m.p. 143°, $C_{19}H_{25}O_4N$, UV $\lambda_{max.}^{EtOH}$ mμ (log ε): 216 (4.37), 271(4.12), 300(3.56), 310(3.44). Catalytic hydrogenation of (XXV) over Pd-C afforded a diol (XXVIa), m.p. 161-162°, $C_{19}H_{27}O_4N$, NMR. τ (in dimethylsulfoxide): 5.44(1H, $>C<^{OH}_{H}$, doublet, J=4.5 cps), 5.72(1H, $>C<^{H}_{OH}$, doublet, J=4.5 cps). This diol was also prepared from the triol (XXIVa) by catalytic hydrogenolysis over $PtO_2$ in acetic acid. Acetylation of (XXVIa) with $Ac_2O$-pyridine afforded a diacetate (XXVIb), m.p. 140°,

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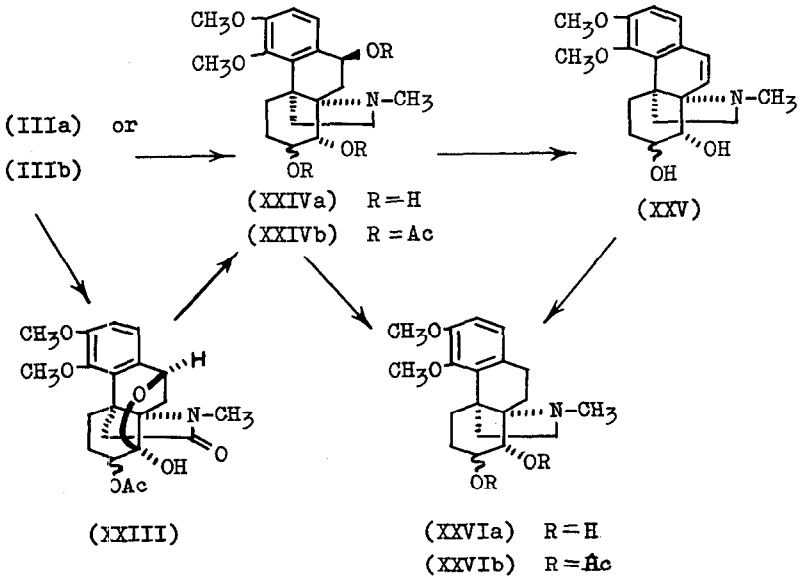
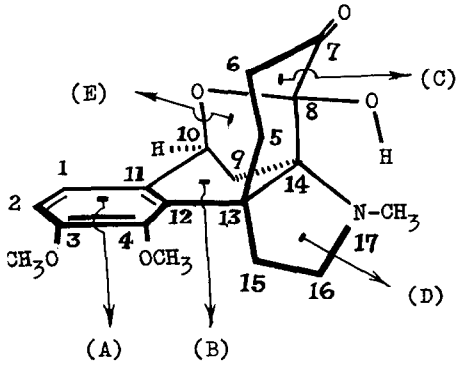
*5 The Dreiding model of metaphanine (I) showed that the dihedral angle between the $C_{10}$-H bond and one of two C-H bonds attaching to $C_9$ atom is almost 90°, and this situation is altered when the hemiketal bridge is cleaved. In accordance with these observations the signal attributable to $C_{10}$-H appeared as doublet in the (I) type compounds, as triplet in the (VIa) type compounds and as quartet in the (XVIIa) type compounds.


(IIIa) or
(IIIb)
(XXIVa) R=H
(XXIVb) R=Ac
(XXV)
(XXIII)
(XXVIa) R=H
(XXVIb) R=Ac


(A)
(B)
(C)
(D)
(E)

(XXVII)

$C_{23}H_{31}O_6N$, IR$\nu_{max.}^{CHCl_3}$: 1730 $cm^{-1}$(OAc), NMR.$\tau$: 4.72(2H, unresolved multiplet, $>C<_{H}^{OAc}$ x 2); 7.90, 8.06(6H, OAc x 2).

From these degradative and spectroscopic evidences described above, it can be concluded that the structure (I) must be allocated to metaphanine. In metaphanine (I), dihydrometaphanine (IIIa) and monoacetyldihydrometaphanine (IIIb) the existence of strong hydrogen bonding between the hemiketal hydroxyl group at C-8 and nitrogen atom was shown by their Pkā values and their IR spectra, and the 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 as that of an ethanamine bridge. Consequently the absolute stereostructure of metaphanine (I) must be represented by the perspective formula (XXVII).*6

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*6 Ring C may take either chair or boat form conformation, but we now depicted only chair form.

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