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Total Synthesis of the Alkaloid (±)-Metaphanine[1]

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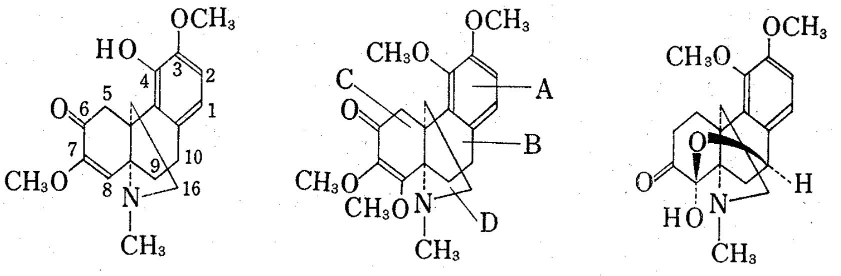
(±)-Metaphanine (**49**), which is a member of hasubanan alkaloids and possesses an intramolecular hemiketal ring, was synthesized.

The keto-lactam (**5**)[3] was derived to the diacetoxy-ketal (**13**) *via* the O-acetyl-keto-lactam (**11**). The compound (**13**) was oxidized to the 10-oxo compound (**16**) which was reduced stereoselectively to the *trans* diol-lactam (**22**), a C_{10}-hydroxy group of which was selectively protected by an acetyl group or by a tetrahydropyranyl group to give the *trans* 10-acetoxy compound (**23**) or the monotetrahydropyranyl ether (**33**), both of which were oxidized and hydrolyzed to provide (±)-7-ethyleneketal-16-oxo-metaphanine (**36**). The selective reduction of the lactam carbonyl group of the compound (**36**) by the Borch's method[4] gave (±)-7-ethyleneketal-metaphanine (**44**) which was hydrolyzed to give (±)-metaphanine (**49**).

Metaphanine is a member of hasubanan alkaloids and its structure has been completely established by Tomita *et al.*[5] Hasubanan alkaloids are classified into three groups, the cepharamine (**1**), hasubanonine (**2**), and metaphanine (**3**) type on the basis of the oxidation stage of the B and C ring of hasubanan skeleton. Among these alkaloids, metaphanine is characteristic in forming an intramolecular hemiketal ring and eight alkaloids of this type have been reported. In previous papers,[3] we have reported total synthesis of (±)-cepharamine and (±)-hasubanonine. Later, we have also presented synthesis of (±)-metaphanine, a representative of the metaphanine type alkaloids, in a preliminary communication[1] and here we wish to give a full detail of synthesis of this alkaloid.



cepharamine (**1**) hasubanonine (**2**) metaphanine (**3**)

Chart 1

On the synthesis of metaphanine, the keto-lactam (**5**) which was a key intermediate of cepharamine and hasubanonine syntheses, was chosen for the starting material. Since an

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[1] A part of this work has been reported in *Tetrahedron Letters*, **1972**, 1393.

[2] Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*

[3] Y. Inubushi, T. Ibuka, and M. Kitano, *Tetrahedron Letters*, **1969**, 1611; *idem*, *Chem. Pharm. Bull.* (Tokyo), **19**, 1820 (1971); T. Ibuka, K. Tanaka, and Y. Inubushi, *Tetrahedron Letters*, **1970**, 4811.

[4] R.F. Borch, *Tetrahedron Letters*, **1968**, 61; R.B. Herbert and C.J. Moody, *Chem. Commun.*, **1970**, 121.

[5] M. Tomita, T. Ibuka, Y. Inubushi, and K. Takeda, *Tetrahedron Letters*, **1964**, 3605; *idem*, *Chem. Pharm. Bull.* (Tokyo), **13**, 695 (1965); *idem*, *ibid.*, **13**, 704 (1965); T. Ibuka, *Yakugaku Zasshi*, **85**, 579 (1965); H.L. deWaal, B.J. Prinsloo, and R.R. Arndt, *Tetrahedron Letters*, **1966**, 6169.

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introduction of an oxygen function at the C_8 position of the keto-lactam (**5**) has been established on the synthesis of (±)-hasubanonine,[3] the problems to be solved are the stereoselective introduction of the C_{10} hydroxy group *trans* to the ethanamine bridge and the selective reduction of the lactam carbonyl group only when both the lactam carbonyl group and the hemiketal ring are present.

We examined first an introduction of a hydroxy group at the C_{10} position of the keto-lactam (**5**).

Introduction of the OR Group at the C_{10} Position of the Keto-lactam (5)[6] and Stereochemistry of the OR Group

The keto-lactam (**5**)[3] or the compound (**6**) which was derived from the keto-nitrile (**4**), was ketalized to the ketal-lactam (**7**) or the acetoxy-ketal-lactam (**8**). These compounds were oxidized with chromic acid, respectively, to give the compound (**9**) or the compound (**10**) which possesses the oxo function at the C_{10} position. The yields of these reactions, however, were poor and irregular. Then, oxidation of the compound having the C_4-acetoxy group in place of the C_4-methoxy group, was examined. As reported in previous papers,[3] oxidation of the O-acetyl-keto-lactam (**11**) with lead tetraacetate-boron trifluoride gave the diacetoxy-ketone (**12**) in high yield whereas no satisfactory result was obtained by the same oxidation reaction of the keto-lactam (**5**) having two methoxy groups on the benzene ring. The diacetoxy-ketone (**12**) was ketalized in the usual manner and the diacetoxy-ketal (**13**) was oxidized with chromic anhydride-acetic acid to provide the 10-oxo-diacetate (**14**), quantitatively, but no C_{10} hydroxy compound was obtained. The infrared (IR) spectrum of this compound revealed a strong absorption band at 1599 cm^{-1} suggesting that the benzylic methylene was oxidized to the keto function. From this result, it is obvious that replacement of the C_4-methoxy group by the acetoxy group is a significant operation not only for oxidation of the benzylic methylene but for an introduction of an acetoxy group at the C_8 position.

Hydrolysis of the 10-oxo-diacetate (**14**) with base provided a sparlingly soluble phenol (**15**), and methylation of this with diazomethane gave a key intermediate of the present synthesis, the 10-oxo compound (**16**), quantitatively, from the diacetoxy-ketal (**13**). For the purpose of formation of a hemiketal ring between two functions at C_8 and C_{10}, the C_{10}-oxo function has to be reduced stereoselectively to the hydroxy group *trans* to the ethanamine bridge. Rapoport, *et al.*[7] reported that oxidation of dihydrodesoxycodeine (**17**) with chromic anhydride-sulfuric acid afforded the *trans* 10-hydroxy compound (**18**) and oxidation of this with manganese dioxide followed by sodium borohydride reduction provided sreteoselectively the *cis* 10-hydroxy compound (**19**), and they also discussed in detail stereochemical outcome of these reactions. Since the compounds in Rapoport's case are basic and the compound in our case has a lactam function, the oxidation and reduction mechanism may be not necessarily the same. Then, we tried sodium borohydride reduction of the 10-oxo compound (**16**) in methanol. The reduction product was acetylated by a conventional method and a detailed examination of the acetylated product revealed that the product is a mixture of two stereoisomeric acetates, the *trans* 10-acetoxy compound (**23**) and the *cis* 10-acetoxy compound (**21**), in a 1/15 ratio. The nuclear magnetic resonance (NMR) spectra of **23** and **21** revealed the signal due to a proton geminal to the C_{10}-acetoxy group at 4.25 τ (q., $J=7$ Hz, $\delta_{AB}=3$ Hz, axial H) and at 3.97 τ (q., $J=3$ Hz, $\delta_{AB}=2$ Hz, equatorial H), respectively. In acetylation reaction of the reduction product mentioned above, the C_8-hydroxy group remained intact because of serious steric hindrance due to the close-neighbouring two tertiary carbons. Then, the solvent effect in sodium borohydride reduction of the 10-oxo compound (**16**) was examined. When iso-propanol or *tert*-butanol containing a small amount of water was employed as a sol-

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6) All compounds in this paper are racemic and some of them are shown by stereostructures antipodal to those of natural alkaloid and its derivatives.

7) H. Rapoport and S. Masamune, *J. Am. Chem. Soc.*, 77, 4330 (1955).

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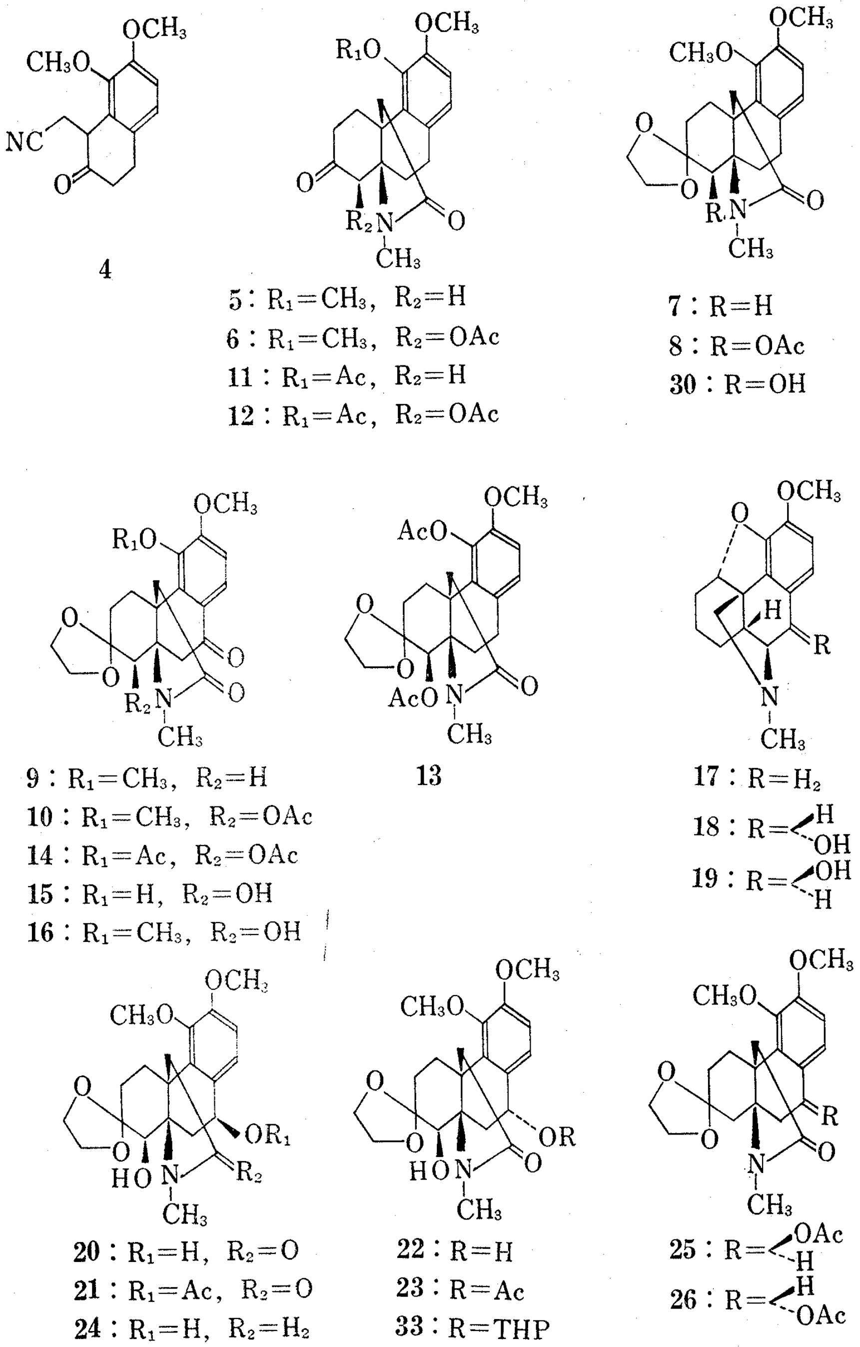

5 : $R_1=CH_3$, $R_2=H$
6 : $R_1=CH_3$, $R_2=OAc$
11 : $R_1=Ac$, $R_2=H$
12 : $R_1=Ac$, $R_2=OAc$

7 : R=H
8 : R=OAc
30 : R=OH

9 : $R_1=CH_3$, $R_2=H$
10 : $R_1=CH_3$, $R_2=OAc$
14 : $R_1=Ac$, $R_2=OAc$
15 : $R_1=H$, $R_2=OH$
16 : $R_1=CH_3$, $R_2=OH$

17 : $R=H_2$
18 : $R=<^{H}_{OH}$
19 : $R=<^{OH}_{H}$

20 : $R_1=H$, $R_2=O$
21 : $R_1=Ac$, $R_2=O$
24 : $R_1=H$, $R_2=H_2$

22 : R=H
23 : R=Ac
33 : R=THP

25 : $R=<^{OAc}_{H}$
26 : $R=<^{H}_{OAc}$

Chart 2

vent, the ratio of the *trans* isomer to the *cis* isomer as their acetates was improved to the 1/5—1/3 ratio, although the reaction required a long time and the yield was reduced. The change in product composition may be attributable to a greater effective size of the reagent by solvation.[8] The other metal hydride reduction of the 10-oxo compound (**16**) using lithium aluminum hydride in ether or sodium dihydro-bis-(2-methoxy-ethoxy) aluminate[9] in benzene, afforded exclusively the *cis* amino-diol (**24**) which was identified with the reduction product of the *cis* diol-lactam (**20**) and the *cis* 10-acetoxy compound (**21**), respectively, with lithium aluminum hydride. Stereochemistry of the C_{10} substituent in the *cis* 10-acetoxy compound

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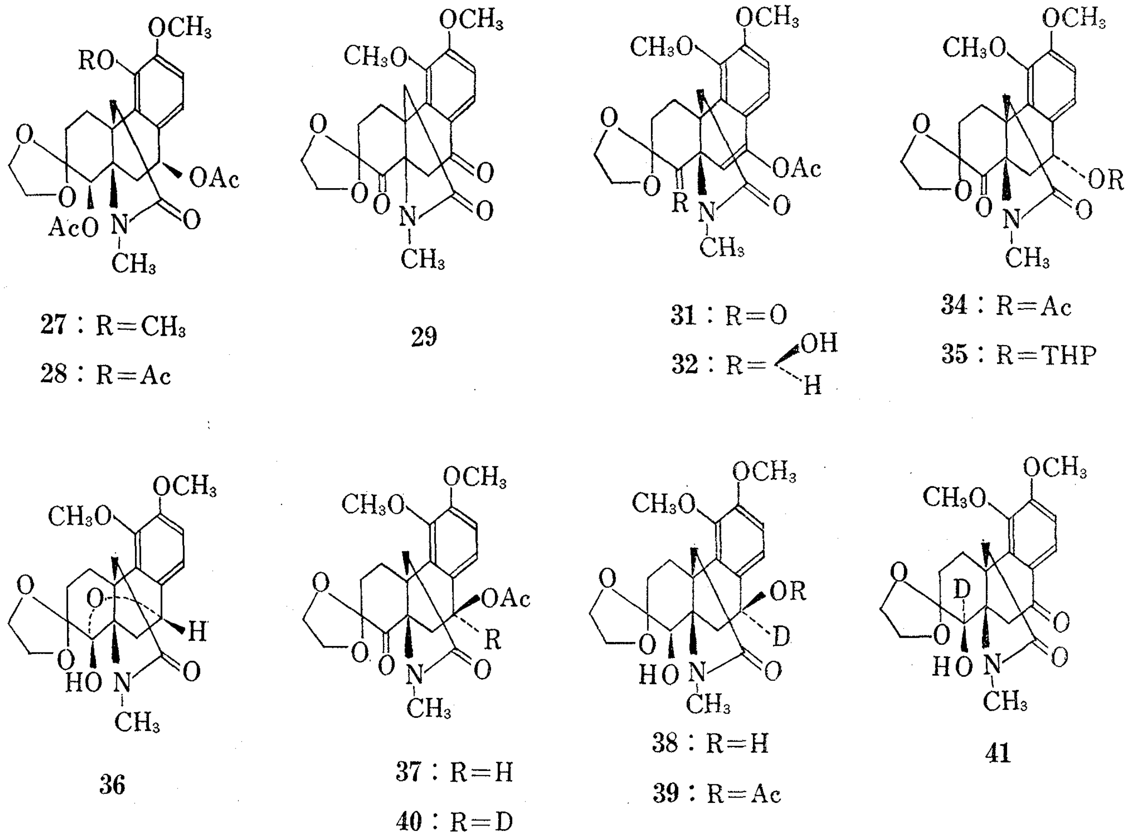
8) H. Hanbenstock and E.L. Eliel, *J. Am. Chem. Soc.*, **84**, 2368 (1962).

9) V. Bazant, M. Čapka, M. Černý, V. Chvalovský, K. Kochloefl, M. Kraus, and J. Malek, *Tetrahedron Letters*, **1968**, 3303.

(**21**), the *trans* 10-acetoxy compound (**23**), and the *cis* amino-diol (**24**) was estimated by comparison of the chemical shift and the coupling constant of the signal due to a proton geminal to the C_{10} substituent with those of the signal concerned in the compounds derived from natural metaphanine in the NMR spectra. This estimation that the C_{10}-acetoxy group of **21** is β-axial and that of **23** is α-equatorial, was supported strongly by chemical evidence as described later.



27 : R=CH_3
28 : R=Ac

29

31 : R=O
32 : R=$<^{OH}_{H}$

34 : R=Ac
35 : R=THP

36

37 : R=H
40 : R=D

38 : R=H
39 : R=Ac

41

Chart 3

The stereochemical factors of the metal hydride reduction which produces preferentially the *cis* C_{10}-hydroxy compounds, were examined. It is easily considered that steric interference between the metal hydride ion and the ethanamine bridge will oppose approach of the metal hydride ion to the carbonyl function from the ethanamine bridge side. However, stereoelectronic factor due to the C_8-hydroxy function other than steric-approach control mentioned above would not be ruled out. Sodium borohydride reduction of the compound (9) which is derived from the O-acetyl-keto-lactam (**11**) by ketalization, oxidation with chromic anhydride, hydrolysis, and methylation with diazomethane or from the ketal-lactam (**7**) by oxidation with chromic anhydride-acetic acid (poor yield) and possesses no oxygen function at the C_8 position, was examined. In this case, acetylation of the reduction product gave a mixture of the *cis* acetate (**25**) and the *trans* acetate (**26**) in a 1/1 ratio. This result suggests that the C_8-hydroxy group is implicated in controlling the steric course of this reduction reaction. It is, however, still equivocal whether the C_8-hydroxy group takes part in the stereochemical control by stereoelectronic manner or through the conformational change of the molecule caused by an introduction of this function. The facts that sodium borohydride reduction of the 10-oxo compound (**16**) possessing the C_8-hydroxy group gives stereoselectively the *cis* C_{10}-hydroxy compound (characterized as its acetate: *vide ante*), and sodium borohydride reduction of the compound (**10**) and the 10-oxo-diacetate (**14**) which possess an acetoxy group at the C_8 position, and acetylation of the reduction products afford stereoselectively the *cis* diacetate (**27**) and the *cis* triacetate (**28**), respectively, and that the conformations of the C_8-hydroxy and the C_8-acetoxy function of these compounds are β-axial as mentioned later, will support the latter argument. Since it was found that the metal hydride reduction of the C_{10}-oxo compounds did not give selectively the *trans* C_{10}-hydroxy compounds although the ratio of the *trans* compounds to the *cis* compounds could be altered to some extent by changing the reaction condition, the other reduction reaction was investigated.

Catalytic reduction of the 10-oxo compound (**16**) and the compound (**9**) gave only the hydrogenolysis products, the compound (**30**) and the ketal-lactam (**7**), respectively, together with the starting material in some extent. Catalytic reduction of the keto-enol-acetate (**31**), which was derived from the 10-oxo compound (**16**) by oxidation with Jones' reagent and by treatment of the resulting diketone (**29**) with iso-propenyl acetate,[10] afforded the hydroxy-enol-acetate (**32**).

Since the conformation of the hydroxy group of the *trans* C_{10}-hydroxy compound was found to be stable equatorial by its NMR spectral examination as mentioned earlier, the product-development control reduction was investigated. Reduction of the 10-oxo compound (**16**) with sodium metal in various alcohols, amyl alcohol, iso-propanol, *tert*-butanol *etc.*, and acetylation of the reduction products afforded the *trans* 10-acetoxy compound (**23**) and the *cis* 10-acetoxy compound (**21**) in a 3—4/1 ratio. Since the total yield of this reduction was 30—65% and irregular, this reduction was also less satisfactory. Next, Meerwein-Ponndorf-Verley reduction[11] of the 10-oxo compound (**16**) using aluminum iso-propoxide in toluene-iso-propanol, was examined and this reduction gave stereoselectively and quantitatively, the desired *trans* diol-lactam (**22**). In this reduction, equilibration of the initially formed products was found to occur. Thus, when the reaction mixture was worked up after 10 hr, the product was found to contain the *trans* diol-lactam (**22**) above 95%, whereas the product contains the *cis* diol-lactam (**20**) approximately above 30%, when the reaction was interrupted after 3 hr.

From the coupling constant of a signal due to a proton geminal to an acetoxy group at the C_{10} position in their NMR spectra, the conformation of the C_{10}-acetoxy group of the *trans* 10-acetoxy compound (**23**) is *quasi* equatorial and that of the *cis* 10-acetoxy compound (**21**) *quasi* axial. The stereostructure of the *trans* diol-lactam (**22**) is now represented by the formula in Fig. 1, when a chair form is supposed for the ring C.

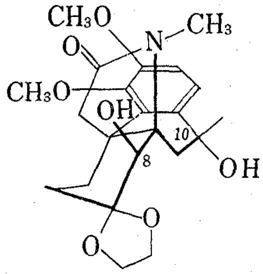


Fig. 1

In order to certify further stereochemistry of the C_{10}-hydroxy group and to put forward the synthetic plan, the intramolecular hemiketal ring formation was examined. On account of serious steric interactions among the atoms around the C_8-hydroxy group as mentioned earlier, the *trans* diol-lactam (**22**) afforded the monoacetate, the *trans* 10-acetoxy compound (**23**), and the monotetrahydropyranyl ether (**33**), respectively, on acetylation and tetrahydropyranylation. These compounds were oxidized with Jones' reagent or Collins' reagent to give the *trans* keto-acetate (**34**) and the *trans* keto-pyranyl ether (**35**), respectively, which were hydrolyzed in an aqueous sodium carbonate solution and an aqueous acetic acid solution, respectively, to give (±)-7-ethyleneketal-16-oxo-metaphanine (**36**), quantitatively, from the *trans* diol-lactam (**22**). Consequently, stereochemistry of the C_{10} OR group in the *trans* diol-lactam (**22**: R=H) and others was firmly established to be *trans* to the ethanamine bridge. The compound (**36**) was identified with a sample derived from natural metaphanine

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[10] R. Deghenghi and C.R. Engel, *J. Am. Chem. Soc.*, **82**, 3201 (1960); R. Villotti, H.J. Ringold, and C. Djerassi, *ibid.*, **82**, 5693 (1960).

[11] A.L. Wilds, "Organic Reactions," Vol. 2, ed. R. Adams, Wiley-Interscience, New York, 1944 p. 178.

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(**3**) by ketalization with boron trifluoride ether complex-ethylene glycol[12] followed by oxidation with potassium permanganate-magnesium sulfate.

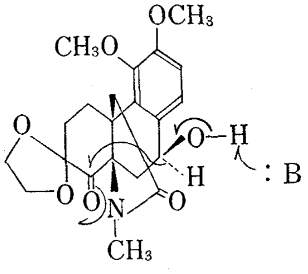

Fig. 2

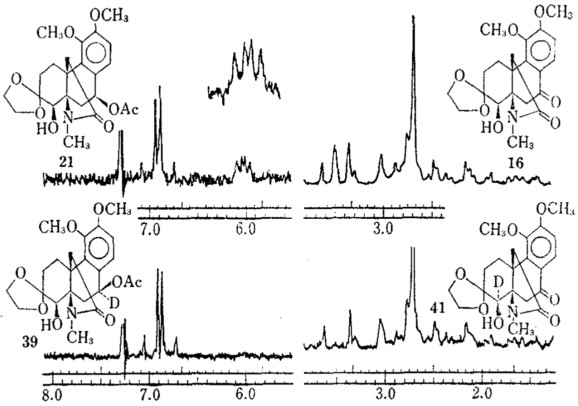

Fig. 3 The NMR Spectra of the Compounds Related to the 1—4 Hydride Shift

On the other hand, acetylation of the *cis* diol-lactam (**20**) gave the monoacetate, the *cis* 10-acetoxy compound (**21**) which was oxidized with Jones' reagent to give the *cis* keto-acetate (**37**). Hydrolysis of this with an aqueous sodium carbonate solution afforded unexpectedly the 10-oxo compound (**16**) in quantitative yield. This result would be explained by assuming the intramolecular 1—4 hydride shift. In order to certify this reaction mechanism and to establish stereochemistry of the oxygen functions at the C_8 and C_{10} position, the following experiments were undertaken. Reduction of the 10-oxo compound (**16**) in methanol with sodium borodeuteride provided the *cis* 10-*d*-diol-lactam (**38**) which on acetylation gave the *cis* 10-*d*-acetoxy compound (**39**). Oxidation of this with Jones' reagent gave the *cis* 10-*d*-acetoxy-ketone (**40**) which was hydrolyzed with an aqueous sodium carbonate solution to afford the 8-*d*-10-oxo compound (**41**) in quantitative yield. This finding indicates that the 1—4 hydride shift as shown in Fig. 2 actually takes place. In the NMR spectrum of 10-oxo compound (**16**), the signal of a proton attached to C_8 appeared at 6.49 τ as a doublet with a coupling constant of 1.5 Hz suggesting that the C_8 equatorial proton couples with the C_6 equatorial proton in a long range interproton coupling (4σ-bond coupling) according to the W rule.[13] The conformation of the C_8-hydroxy group is, therefore, axial. Furthermore, the 10-oxo compound (**16**) and the *cis* amino-diol (**24**) showed a chelated hydroxy band[14] due to the C_8-hydroxy group, and a hemiketal ring formation between the C_8-hydroxy group and the C_{10}-carbonyl function was not observed in the 10-oxo compound (**16**).[15] These findings together with the deuteration experimental result, assign the β-axial conformation to the C_8-hydroxy group and establish firmly stereochemistry of the C_{10} oxygen function which was estimated on the basis of the NMR spectral examination as described earlier.

Synthesis of (±)-Metaphanine (49): Selective Reduction of the Lactam Carbonyl Group

Since stereoselective introduction of the C_{10}-hydroxy group was achieved, the remaining problem is selective reduction of lactam carbonyl function. Lithium aluminum hydride

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[12] C.R. Engel and S. Rakhit, *Can. J. Chem.*, 40, 2153 (1962).

[13] K.B. Wiberg, B.R. Lowry, and B.J. Nist, *J. Am. Chem. Soc.*, 84, 1594 (1962); A. Rassat, C.W. Jefford, J.M. Lehn, and B. Waegell, *Tetrahedron Letters*, 1964, 233; L.M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Edition, Pergamon Press, New York, 1969, pp. 334—341.

[14] M. Tichy, "Advances in Organic Chemistry: Methods and Results," Vol. 5, ed. by R.A. Raphael, E.C. Taylor, and H. Wynberg, Wiley-Interscience, New York, 1965, pp. 161—166.

[15] From inspection of the Dreiding Model, the hemiketal ring formation between the C_8-hydroxy group and the C_{10}-carbonyl function will be possible if the C_8-hydroxy group is α-axial.

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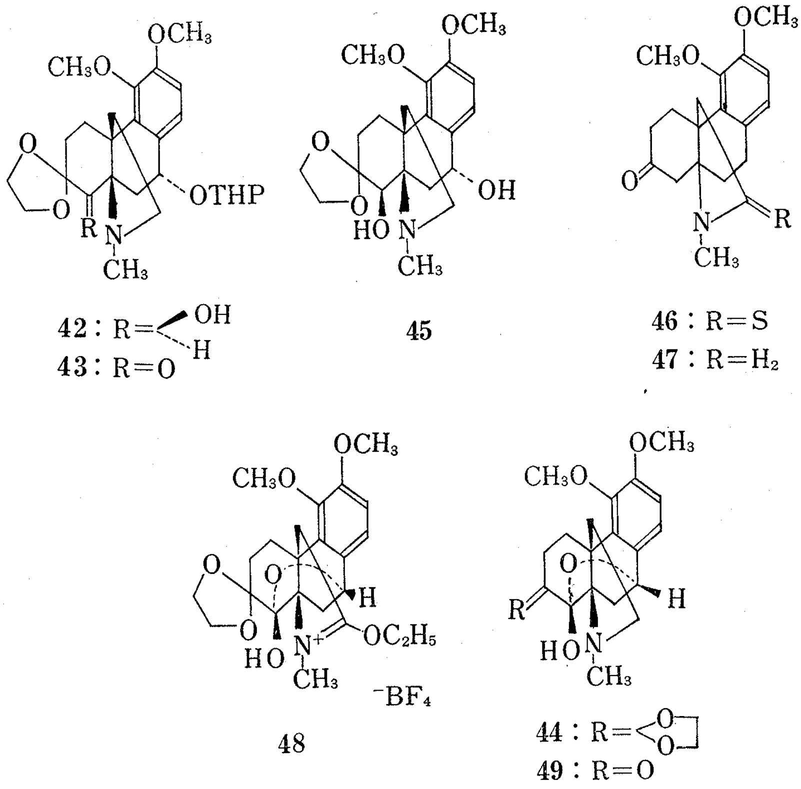
reduction of the monotetrahydropyranyl ether (**33**) gave the amino-alcohol (**42**). Oxidation of the amino-alcohol (**42**) to the keto-amine (**43**) and hydrolysis of the pyranyl ether group will furnish the (**44**) type compound. However, the C_8-hydroxy group seems to be difficult to oxidize because this hydroxy group is crowded and an ethanolamine type hydroxy group. All trials for oxidation of the C_8-hydroxy group with Collins' reagent, NBS,[16] DMSO-acetic anhydride,[17] silver carbonate[18] and by Oppennauer oxidation[19] were unfruitful. Then, the protection of the hemiketal hydroxy group prior to reduction will be properly considered. All trials, however, for the protection of hydroxy group of (±)-7-ethyleneketal-16-oxo-metaphanine (**36**) by methylation, tetrahydropyranylation, and benzylation were failed. Next, lithium aluminum hydride reduction of (±)-7-ethyleneketal-16-oxo-metaphanine (**36**) under mild condition was tried and the desired (±)-7-ethyleneketal-metaphanine (**44**) retaining a hemiketal ring was obtained in 10—20% yield with the *trans* amino-diol (**45**) as the main product. Since the *trans* aminodiol (**45**) was identified with the compound which was obtained from lithium aluminum hydride reduction of the *trans* 10-acetoxy compound (**23**) and from the amino-alcohol (**42**) by hydrolysis with acid, stereochemistry of the C_8-hydroxy group in the *trans* amino-diol (**45**) was assigned to be *β*-axial. Because of poor yield, this procedure was also less satisfactory. The compound (**44**) thus obtained was identified with the compound derived from natural metaphanine.

Then, selective reduction of the lactam carbonyl group was examined. The model compound, the ketal-lactam (**7**), was treated with phosphorus pentasulfide[20] to give the thiolactam



42 : R=<OH, H
43 : R=O
45
46 : R=S
47 : R=H_2
48
44 : R=<O—O (ethylenedioxy)
49 : R=O

Chart 4

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16) L.F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3935, 3938 (1949).
17) J.D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89**, 2416 (1967).
18) H. Rapoport and H.N. Reist, *J. Am. Chem. Soc.*, **77**, 490 (1955); M. Fetizon and M. Golfier, *Compt. Rend.*, **267**, 900 (1968).
19) R.B. Woodward, N.L. Wendler, and F.J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945); H. Rapoport, R. Naumann, E.R. Bissell, and R.M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).
20) M.W. Cronyn, *J. Org. Chem.*, **14**, 1013 (1949); A. Mondon and P.R. Seidel, *Chem. Ber.*, **103**, 1298 (1970).

(**46**) which was desulfurized with Raney nickel to the amine (**47**) in 60% yield. However, no desired product was obtained when this procedure was applied to (±)-7-ethyleneketal-16-oxo-metaphanine (**36**). Next, the Borch's reduction method using the Meerwein reagent and sodium borohydride[4] was applied to the compound (**36**). Thus, treatment of **36** with 1 eq. of triethyloxonium tetrafluoroborate gave the iminoether fluoroborate (**48**) which without isolation was reduced with sodium borohydride to give the desired (±)-7-ethyleneketal-metaphanine (**44**) retaining the hemiketal ring in good yield. Although ethyleneketal group of this compound unexpectedly resisted to hydrolysis, refluxing the compound (**44**) with conc. hydrochloric acid in methanol gave (±)-metaphanine (**49**), mp 205—206°, in *ca.* 55% yield. A sample of this was identified with a sample of natural metaphanine (**3**) in terms of thin–layer chromotography (TLC) behavior, IR, NMR, and mass spectra.

Experimental

All melting points were taken on a Yanagimoto Melting Point Apparatus and were uncorrected. IR spectra were obtained for solutions in chloroform with a Hitachi EPI-S Spectrometer. NMR spectra were measured on a Varian A-60 or HA-100 Spectrometer in deuteriochloroform with tetramethylsilane as an internal standard and chemical shifts were given in τ values. The abbreviations, s, d, t, q, and m in the NMR spectra signify singlet, doublet, triplet, quartet, and multiplet and the coupling constant (J) is measured in Hz. Mass spectra were determined at 80 eV on a Hitachi RMU-6D Spectrometer, and abbreviation M^+ signifies the molecular ion. TLC was performed on Kieselgel G nach Stahl or Aluminiumoxid G nach Stahl using acetone–chloroform (1:4) or benzene–chloroform (1:1) as a developing solvent. Unless otherwise specified, the extracts were dried on anhydrous magnesium sulfate, and column chromatography was effected using Mallinckrodt silicic acid (100 mesh) or Brockmann basic alumina activity II—III. Acetylation was carried out by mixing a substrate with a tenfold amount of pyridine and a fivefold amount of acetic anhydride and allowing the mixture to stand overnight. Identification with an authentic sample was performed by mixed melting point determination and comparison of IR spectra and TLC.

The Compound (**9**)——a) A solution of 1.0 g of the keto-lactam (**5**)[3] 3 ml of ethylene glycol and 15 mg of *p*-toluenesulfonic acid in 50 ml of benzene was refluxed for 15 hr while water was separated with a Dean-Stark type apparatus. To the reaction mixture was added 100 ml of ether and the organic layer was washed with 5% sodium hydroxide solution, water, dried and evaporated under reduced pressure to yield a crystalline solid. Recrystallization from an ether–acetone mixture afforded 1.05 g of the ketal-lactam (**7**) as colorless flakes, mp 177°. The sample of this compound was identified with an authentic sample.[3] To a solution of 700 mg of chromic acid in 20 ml of acetic acid and 3 ml of water was added 720 mg of the ketal-lactam (**7**) and the mixture was stirred for 4 hr at room temperature and poured into 100 ml of ice-water, made alkaline with NH_4OH and extracted with ether. The extract was dried and evaporated to leave a pale yellow oil which was chromatographed over silica gel in chloroform. Elution of the column with the same solvent afforded 200 mg of the compound (**9**) as colorless prisms, mp 215—217° (from acetone–ether). IR ν_{max} cm^{-1}: 1680 and 1590. NMR τ: 7.27 (3H, s., N-Me), 6.05 (10H, s., 2×O-Me, and ethyleneketal H) and 2.66 (2H, q., J=9 Hz, δ_{AB}=42 Hz, aromatic H). *Anal.* Calcd. for $C_{21}H_{25}O_6N$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.02; H, 6.66; N, 3.54.

b) Ketalization of 1.0 g of the O-acetyl-keto-lactam (**11**)[3] was performed by the same manner as described above to give 1.0 g of the compound (**11**: ethyleneketal at C_7). Although this compound had been reported as an oil in a previous paper,[3] it solidified in the present case and recrystallization from a mixture of acetone–ether gave colorless prisms, mp 185°. *Anal.* Calcd. for $C_{22}H_{27}O_6N$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.71; H, 6.58; N, 3.56. To a stirred solution of 480 mg of the compound (**11**: ethyleneketal at C_7) in 15 ml of acetic acid and 2.2 ml of water was added portionwise 350 mg of chromic acid under ice cooling, and the mixture was stirred for 24 hr at room temperature. Work up by the same manner as described above afforded 250 mg of the compound (**14**: R_1=Ac; R_2=H) as colorless prisms. mp 223—225°. IR ν_{max} cm^{-1}: 1772, 1686, 1600, and 1280. NMR τ: 7.65 (3H, s., OAc), 7.72 (3H, s., N-Me), 6.12 (3H, s., O-Me), 6.07 (4H, s., ethyleneketal H) and 2.53 (2H, q., J=9 Hz, δ_{AB}=49 Hz, aromatic H). *Anal.* Calcd. for $C_{22}H_{25}O_7N$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.71; H, 6.17; N, 3.39. A solution of 100 mg of compound (**14**: R_1=Ac; R_2=H) in 5 ml of methanol and 5 ml of 5% aqueous sodium carbonate solution was refluxed for 2 hr. Work up as usual gave 80 mg of a colorless solid of the crude phenolic compound which without purification was methylated with excess diazomethane in a methanol–ether–tetrahydrofuran mixture at 5°. Work up by the usual manner gave a crystalline solid which was recrystallized from ether–acetone to afford 60 mg of **9** as colorless prisms, mp 215°. A sample of this compound was identified with an authentic sample of **9** obtained in a procedure a).

The Compound (**10**)——According to the procedure described above, 120 mg of the compound (**6**)[3] was ketalized to give 116 mg of the acetoxy-ketal-lactam (**8**) as colorless prisms, mp 207°. IR ν_{max} cm^{-1}: 1740,

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1680, and 1210—1240. NMR τ: 7.92 (3H, s., OAc), 7.37 (3H, s., N-Me), 6.18 and 6.09 (each 3H, s., O-Me), 6.02 (4H, m., ethyleneketal H), 5.02 (1H, d., $J=1.5$ Hz, C_8-H) and 3.26 (2H, s., aromatic H). *Anal.* Calcd. for $C_{23}H_{29}O_7N$: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.22; H, 6.88; N, 3.17. Oxidaton of 100 mg of the acetoxy-ketal-lactam (8) with chromic acid-acetic acid was performed by the same manner as described above to give 35 mg of unchanged starting material and 31 mg of the compound (10) (recrystallized from acetone–ether) as colorless prisms, mp 259°. IR ν_{max} cm^{-1}: 1750, 1685, and 1590. NMR τ: 7.93 (3H, s., OAc), 7.44 (3H, s., N-Me), 6.08 and 6.05 (each 3H, s., O-Me), 5.90—6.10 (4H, m., ethyleneketal H), 5.07 (1H, d., $J=1.5$ Hz, C_8-H) and 2.68 (2H, q., $J=9$ Hz, $\delta_{AB}=42$ Hz, aromatic H). *Anal.* Calcd. for $C_{23}H_{27}O_8N$: C, 62.01; H, 6.11; N, 3.14. Found: C, 61.92; H, 6.37; N, 3.16.

The Diacetoxy-ketal (13)——A solution of 4.0 g of the diacetoxy-ketone (12),[3] 10 ml of ethylene glycol, 50 mg of *p*-toluenesulfonic acid in 700 ml of benzene was refluxed while water was separated with a Dean-Stark type apparatus. After 20 hr, the mixture was worked up by the same way as described above for the preparation of the compound (9) to give 6.25 g of a colorless oil. Trituration of this with acetone and recrystallization of the crude crystals from the same solvent afforded 3.27 g of the diacetoxy-ketal (13) as colorless prisms, mp 235—237°. IR ν_{max} cm^{-1}: 1758, 1742, 1680 and 1200—1240. NMR τ: 7.93 and 7.70 (each 3H, s., OAc), 7.38 (3H, s., N-Me), 6.25 (3H, s., O-Me), 6.06 (4H, m., ethyleneketal H), 5.03 (1H, d., $J=1.5$ Hz, C_8-H) and 3.16 (2H, q., $J=9$ Hz, $\delta_{AB}=1$ Hz, aromatic H). *Anal.* Calcd. for $C_{24}H_{29}O_8N$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.76; H, 6.32; N, 3.03. From the mother liquor of recrystallizations, 1.05 g of the starting material (12) was recovered.

Oxidation of the Diacetoxy-ketal (13) **with Chromic Acid**——To the cooled solution of 5.18 g of the diacetoxy-ketal (13) in 150 ml of acetic acid and 22 ml of water was added 3.5 g of chromic acid under stirring. The mixture was stirred for 40 hr at room temperature and was worked up by the same way as described above to yield a crystalline solid. Purification of this material by alumina chromatography and recrystallization of the eluate from acetone–ether gave 5.33 g of the 10-oxo-diacetate (14) as colorless prisms, mp 232—233°. IR ν_{max} cm^{-1}: 1768, 1755, 1690 and 1599. NMR τ: 7.94 and 7.66 (each 3H, s., OAc), 7.44 (3H, s., N-Me), 6.13 (3H, s., O-Me), 6.02 (4H, s., ethyleneketal H), 5.07 (1H, d., $J=1.5$ Hz, C_8-H) and 2.55 (2H, q., $J=9$ Hz, $\delta_{AB}=50$ Hz, aromatic H). *Anal.* Calcd. for $C_{24}H_{27}O_9N$: C, 60.88; H, 5.75; N, 2.96. Found: C, 60.58; H, 5.66; N, 2.84.

The Phenol (15)——A mixture of 1.0 g of the 10-oxo-diacetate (14), 50 ml of 5% aqueous sodium carbonate solution and 50 ml of methanol was refluxed for 2 hr on a water bath under a nitrogen atmosphere and the mixture was made acidic with acetic acid. The mixture was concentrated under reduced pressure, diluted with water and extracted with chloroform. The extract was washed with dil. NH_4OH, water ,dried and evaporated to leave 800 mg of the phenol (15) as a crystalline solid. For analysis, a sample was recrystallized from methanol to give colorless prisms, mp$>$300°. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1662 and 1592. *Anal.* Calcd. for $C_{20}H_{23}O_7N$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.57; H, 6.02; N, 3.38.

The 10-Oxo Compound (16)——To a solution of 450 mg of the phenol (15) in 10 ml of methanol was added excess diazomethane in methanol and the mixture was kept on standing for 65 hr in a refrigerator. Excess diazomethane was decomposed with 5% acetic acid under ice cooling, and the solvent was removed under reduced pressure. The residual oil in benzene was chromatographed on alumina and elution of the column with the same solvent gave a crystalline solid which was recrystallized from ether–acetone to provide 468 mg of the 10-oxo compound (16) as colorless prisms, mp 253—254°. IR ν_{max} cm^{-1}: 3560, 3200—3500, 1682 and 1590. NMR τ: 7.31 (3H, s., N-Me), 6.49 (1H, d., $J=1.5$ Hz, C_8-H), 6.10 and 6.07 (each 3H, s., O-Me) and 2.69 (2H, q., $J=9$ Hz, $\delta_{AB}=22$ Hz, aromatic H). *Anal.* Calcd. for $C_{21}H_{25}O_7N$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.27; H, 6.33; N, 3.24.

The *cis* 10-Acetoxy Compound (21) **and the *trans* 10-Acetoxy Compound** (23)——a) To a stirred solution of 300 mg of the 10-oxo compound (16) in 50 ml of methanol was added 300 mg of sodium borohydride under ice cooling and the mixture was stirred for further 1.5 hr at room temperature. After addition of 10 ml of 5% acetic acid, methanol was evaporated and water was added to the mixture. The aqueous layer was extracted with chloroform and the extract was washed with aqueous sodium bicarbonate solution, water dried and evaporated to yield 300 mg of a mixture of epimeric alcohols as an off-white solid. A part of this mixture was recrystallized twice from acetone–ether to give the pure *cis* diol-lactam (20), as colorless flakes, mp 287—288°. IR ν_{max} cm^{-1}: 3600 and 1678. *Anal.* Calcd. for $C_{21}H_{27}O_7N$: C, 62.21; H, 6.71; N, 3.46. Found: C, 62.07; H, 6.81; N, 3.47. Since this separation of epimeric alcohols was not preparative, 500 mg of the epimeric mixture was acetylated and work up as usual afforded 550 mg of a mixture of acetates as a slightly yellow oil. This oil crystallized on trituration with acetone–ether and recrystallization from ether–acetone gave the pure *cis* 10-acetoxy compound (21) as colorless prisms, mp 235—236°. IR ν_{max} cm^{-1}: 3580, 1726, 1677, and 1200—1250. NMR τ: 7.92 (3H, s., OAc), 7.34 (3H, s., N-Me), 6.16 and 6.08 (each 3H, s., O-Me), 6.48 (1H, d., $J=1.5$ Hz, C_8-H), 3.97 (1H, q., $J=3$ Hz, $\delta_{AB}=2$ Hz, C_{10}-H) and 3.10 (2H, q., $J=9$ Hz, $\delta_{AB}=3$ Hz, aromatic H). *Anal.* Calcd. for $C_{23}H_{29}O_8N$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.64; H, 6.37; N, 3.06. The mother liquor removed the crystalline *cis* 10-acetoxy compound (21) was concentrated and the residue in chloroform was chromatographed on a silica gel column. On elution of the column with the same solvent, the earliest eluate gave 34 mg of the *trans* 10-acetoxy compound (23) which was recrystallized from acetone–ether to afford colorless prisms, mp 138—139°. IR ν_{max} cm^{-1}: 3580, 1730, 1678, and 1200—1250. NMR

τ: 7.72 (3H, s., OAc), 7.12 (3H, s., N-Me), 6.16 and 6.08 (each 3H, s., O-Me), 6.48 (1H, d., $J=1.5$ Hz, C_8-H), 4.25 (1H, q., $J=7$ Hz, $\delta_{AB}=3$ Hz, C_{10}-H) and 3.12 (2H, s., aromatic H). *Anal.* Calcd. for $C_{23}H_{29}O_8N$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.43; H, 6.77; N, 2.88. The following eluate gave an additional 40 mg of the *cis* 10-acetoxy compound (**21**).

b) Sodium borohydride reduction of the 10-oxo compound (**16**: 50 mg) by the procedure a) was modified by using iso-propanol (10 ml) in place of methanol. Acetylation of 60 mg of the reduction product followed by silica gel chromatography afforded 10 mg of the *trans* 10-acetoxy compound (**23**) and 32 mg of *cis* 10-acetoxy compound (**21**) as colorless prisms, respectively. These were identified with the authentic samples, respectively.

c) Sodium borohydride reduction of 50 mg of the 10-oxo compound (**16**) was carried out by using 5 ml of iso-propanol and 5 ml of *tert*-butanol. The reduction product was acetylated and chromatographed on a silica gel column as described above to afford 8 mg of the *trans*-10-acetoxy compound (**23**) and 22 mg of the *cis* 10-acetoxy compound (**21**). These samples were identified with the authentic samples, respectively.

The *cis* Amino-diol (24)——a) To a stirred solution of 58 mg of the 10-oxo compound (**16**) in 1 ml of tetrahydrofuran and 25 ml of dry ether was added portionwise 180 mg of lithium aluminum hydride and the mixture was refluxed for 8 hr with stirring. After excess reagent was decomposed cautiously with water, the mixture was filtered, and the precipitate was washed thoroughly with ether. The filtrate and washings were combined and concentrated to give an oil which was dissolved in 3% acetic acid. The acidic aqueous layer was washed with ether, made alkaline with NH_4OH and extracted with ether. The extract was washed with water, dried and evaporated to leave a colorless oil. Trituration with ether gave a crystalline solid which was recrystallized from ether to yield 25 mg of the *cis* amino-diol (**24**) as colorless prisms, mp 194—195°. IR ν_{max} cm^{-1}: 3550. NMR τ: 7.43 (3H, s., N-Me), 6.45 (1H, d., $J=1.5$ Hz, C_8-H), 6.16 and 6.11 (each 3H, s., O-Me) 6.07 (4H, s., ethyleneketal H), 5.50 (1H, q., $J=2.5$ Hz, $\delta_{AB}=2$ Hz, C_{10}-H) and 3.05 (2H, q., $J=9$ Hz, $\delta_{AB}=6.5$ Hz, aromatic H). *Anal.* Calcd. for $C_{21}H_{29}O_6N$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.19; H, 7.24; N, 3.53.

b) To a solution of 1 ml of sodium dihydro-bis-(2-methoxyethoxy) aluminum hydride (70% in benzene) in 13 ml of dry benzene was added dropwise a solution of 20 mg of 10-oxo compound (**16**) in 7 ml of dry benzene under refluxing and stirring, and the mixture was further refluxed for 2 hr. The reaction mixture was treated with the similar manner as that in the procedure a) and the resulting oil was dissolved in 30 ml of 10% acetic acid. The acidic solution was made alkaline and extracted with chloroform. Evaporation of the solvent left an oil which was purified by chromatography on alumina to provide 7 mg of the *cis* amino-diol (**24**) as colorless prisms. A sample was identical with an authentic sample.

c) The *cis* 10-acetoxy compound (**21**: 55 mg) was reduced with lithium aluminum hydride by the similar manner as that described in the procedure a). Work up of the reaction mixture gave 35 mg of the *cis* amino-diol (**24**) as colorless prisms, a sample of which was identical with an authentic sample.

d) Reduction of the *cis* diol-lactam (**20**: 55 mg) with lithium aluminum hydride was carried out by the similar manner as that described above to provide 25 mg of the *cis* amino-diol (**24**). A sample was identified with an authentic sample.

The *cis* Acetate (25) and the *trans* Acetate (26)——Sodium borohydride (50 mg) reduction of the compound (**9**: 100 mg) was carried out by the similar manner as that employed for the preparation of the *cis* diol-lactam (**20**). The residue (105 mg) from the extract was acetylated to give a mixture of the monoacetates as a colorless oil (120 mg). This oil in chloroform was chromatographed over silica gel and elution of the column with the same solvent provided 38 mg of the *trans* acetate (**26**) as a colorless oil in the earlier eluate. IR ν_{max} cm^{-1}: 1730 and 1680. NMR τ: 7.82 (3H, s., OAc), 7.15 (3H, s., N-Me), 6.15 (3H, s., O-Me), 6.08 (7H, s., O-Me and ethyleneketal H), 4.26 (1H, q., $J=6.5$ Hz, $\delta_{AB}=3$ Hz, C_{10}-H) and 3.10 (2H, q., $J=9$ Hz, $\delta_{AB}=0.5$ Hz, aromatic H). Mass Spectrum *m/e*: 431 (M^+). The following eluate gave 40 mg of a colorless oil which crystallized on trituration with acetone-ether and recrystallization from the same solvent afforded 30 mg of the *cis* acetate (**25**) as colorless prisms, mp 194—196°. IR ν_{max} cm^{-1}: 1729 and 1678. NMR τ: 7.91 (3H, s., OAc), 7.22 (3H, s., N-Me), 6.13 and 6.11 (each 3H, s., O-Me), 6.09 (4H, broad s., ethyleneketal H), 4.00 (1H, q., $J=5$ Hz, $\delta_{AB}=1$ Hz, C_{10}-H), and 3.10 (2H, q., $J=9$ Hz, $\delta_{AB}=1$ Hz, aromatic H). Mass Spectrum *m/e*: 431 (M^+). *Anal.* Calcd. for $C_{23}H_{29}O_7N$: C, 64.02; H, 6.77; N, 3.25. Found: C, 63.87; H, 6.86; N, 3.36.

The *cis* Diacetate (27) and the *cis* Triacetate (28)——Reduction of the compound (**10**: 89 mg) with sodium borohydride (50 mg) was carried out in the similar manner as that previously stated. Work up as usual afforded 90 mg of the crude C_{10}-hydroxy compound (**27**: OH in place of C_{10}-acetoxy group). An analytical sample was obtained by two times recrystallizations from acetone as colorless prisms, mp 271—273°. IR ν_{max} cm^{-1}: 3300—3600, 1742 and 1680. NMR τ: 7.93 (3H, s., OAc), 7.31 (3H, s., N-Me), 6.15 and 6.08 (each 3H, s., O-Me), 5.26 (1H, q., $J=2.5$ Hz, $\delta_{AB}=2$ Hz, C_{10}-H) and 5.08 (1H, d., $J=1.5$ Hz, C_8-H). *Anal.* Calcd. for $C_{23}H_{29}O_8N$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.72; H, 6.50; N, 3.07. The crude C_{10}-hydroxy compound (60 mg) was acetylated in the usual way to give 70 mg of an oil which was subject to chromatography on a silica gel column. The column was eluted with chloroform and the earliest eluate gave 38 mg of the *cis* diacetate (**27**) as colorless prisms (from acetone–ether), mp 231—233°. IR ν_{max} cm^{-1}: 1740—1735, and 1678. NMR τ: 7.95 and 7.91 (each 3H, s., OAc), 7.42 (3H, s., N-Me), 6.14 and 6.07 (each 3H, s., O-Me),

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6.05 (4H, m., ethyleneketal H), 5.11 (1H, d., $J=1.5$ Hz, C_8-H) and 3.96 (1H, q., $J=2.5$ Hz, $\delta_{AB}=3$ Hz, C_{10}-H). *Anal.* Calcd. for $C_{25}H_{31}O_9N$: C, 61.34; H, 6.38; N, 2.86. Found: C, 61.31; H, 6.38; N, 2.85. The column was then eluted with chloroform containng methanol in 1% proportion and 18 mg of unchanged material was recovered. Similar reduction of the 10-oxo-diacetate (**14**: 190 mg) with sodium borohydride provided a crude dihydro compound which was acetylated with acetic anhydride–pyridine at 50—65° for 5 hr. The crude acetate was recrystallized from acetone–ether to give 157 mg of the *cis* triacetate (**28**) as colorless prisms, mp 230°. IR ν_{max} cm^{-1}: 1759, 1745, 1733, 1685, and 1200—1245. NMR τ: 7.96, 7.92, and 7.68 (each 3H, s., OAc), 7.40 (3H, s., N-Me), 6.20 (3H, s., O-Me), 5.10 (1H, d., $J=1.5$ Hz, C_8-H) and 3.95 (1H, q., $J=2$ Hz, $\delta_{AB}=3$ Hz, C_{10}-H). *Anal.* Calcd. for $C_{26}H_{31}O_{10}N$: C, 60.34; H, 6.04; N, 2.71. Found: C, 60.20; H, 6.12; N, 2.73.

The Diketone (**29**)——The 10-oxo compound (**16**: 170 mg) was treated with 0.8 ml of the standard Jones' reagent in 50 ml of acetone at 0° and the mixture was stirred for 1 hr at room temperature. Excess reagent was decomposed by addition of methanol and the mixture was diluted with water and extracted with chloroform. The extract was washed with water and dried. Removal of the solvent yielded 170 mg of a solid which was recrystallized from acetone to afford 165 mg of the diketone (**29**) as colorless prisms, mp 223—225°. IR ν_{max} cm^{-1}: 1732, 1687, and 1587. NMR τ: 7.09 (3H, s., N-Me), 6.08 and 6.05 (each 3H, s., O-Me), 5.80—6.10 (4H, m., ethyleneketal H), and 2.66 (2H, q., $J=9$ Hz, $\delta_{AB}=42$ Hz, aromatic H). *Anal.* Calcd. for $C_{21}H_{23}O_7N$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.76; H, 5.62; N, 3.47. Mass Spectrum *m/e*: 401 (M^+) and 373 (M^+-CO).

Catalytic Reduction of the 10-Oxo Compound (**16**): **The Compound** (**30**)——A solution of 30 mg of the 10-oxo compound (**16**) in 12 ml of acetic acid was hydrogenated at an atmospheric pressure over 30 mg of platinum oxide at room temperature. After 1.5 hr, the mixture was filtered and the filtrate was concentrated under reduced pressure to dryness. The residual oil (35 mg) in chloroform was subject to chromatography over a silica gel column to give 11 mg of the compound (**30**) as colorless flakes (from acetone–methanol), mp 300—305°. Mass Spectrum *m/e*: 389 (M^+). *Anal.* Calcd. for $C_{21}H_{27}O_6N \cdot 1/3H_2O$: C, 63.79; H, 7.05; N, 3.55. Found: C, 63.94; H, 6.87; N, 3.54.

Catalytic Hydrogenation of the Compound (**9**): **The Ketal-lactam** (**7**)——In the same manner as above, 51 mg of the compound (**9**) was hydrogenated at an atmospheric pressure and room temperature to give 23 mg of the keto-lactam (**9**) as colorless flakes (from acetone–ether), mp 177°. A sample was identical with an authentic sample.[3)]

The Keto-enol-acetate (**31**)——A mixture of 60 mg of the diketone (**29**), 5 mg of *p*-toluenesulfonic acid and 5 ml of isopropenyl acetate was refluxed on an oil bath. After 5 hr, the mixture was poured into ice-water and then extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution, water, dried and evaporated under reduced pressure to leave 85 mg of a brown oily gum. This was subject to silica gel chromatography in chloroform to produce 48 mg of the keto-enol-acetate (**31**) as a slightly yellow oil. IR ν_{max} cm^{-1}: 1761, 1734, and 1680. NMR τ: 7.67 (3H, s., OAc), 7.08 (3H, s., N-Me), 6.14 and 6.08 (each 3H, s., O-Me), 5.80—6.10 (4H, m., ethyleneketal H), 4.63 (1H, s., C_9-H) and 3.08 (2H, q., $J=9$ Hz, $\delta_{AB}=5$ Hz, aromatic H). Mass Spectrum *m/e*: 443 (M^+) and 415 (M^+-CO).

Catalytic Hydrogenation of the Keto-enol-acetate (**31**): **The Hydroxy-enol-acetate** (**32**)——A solution of 103 mg of the keto-enol-acetate (**31**) in 10 ml of 95% ethanol was hydrogenated over 20 mg of platinum oxide at an atmospheric pressure and room temperature. After 1 hr, hydrogen uptake ceased and catalyst was removed by filtration, and the filtrate was concentrated to dryness. The residual colorless oil was subject to chromatography on silica gel to give 95 mg of the hydroxy-enol-acetate (**32**) as a colorless oil. IR ν_{max} cm^{-1}: 3550, 1760, and 1674. NMR τ: 7.69 (3H, s., OAc), 7.25 (3H, s., N-Me), 6.30 (1H, d., $J=1.5$ Hz, C_8-H), 6.10 and 6.13 (each 3H, s., O-Me), 6.00 (4H, s., ethyleneketal H), 4.65 (1H, s., C_9-H) and 3.12 (2H, q., $J=9$ Hz, $\delta_{AB}=4$ Hz, aromatic H). Mass Spectrum *m/e*: 445 (M^+).

Reduction of the 10-Oxo Compound (**16**) **in Various Alcohols**——a) To a solution of 40 mg of the 10-oxo compound (**16**) in 10 ml of *n*-amyl alcohol was added portionwise 200 mg of sodium metal for 30 min under refluxing, stirring and a nitrogen atmosphere. The mixture was stirred for further 3 hr and 10% acetic acid was added to the mixture. The mixture was extracted with chloroform and the extract was washed with dil. sodium carbonate solution, water, dried and evaporated to leave 40 mg of a brown solid. Acetylation of this compound gave 58 mg of a yellow oil which was chromatographed over a silica gel column in chloroform. Elution of the column with the same solvent afforded 24 mg of the *trans* 10-acetoxy compound (**23**), mp 138—139°, in the earlier eluate. Continued elution with the same solvent provided 10 mg of the *cis* 10-acetoxy compound (**21**), mp 235—236°. These materials were identified with the authentic samples, respectively.

b) In the same manner as above, 800 mg of sodium metal was added to a solution of 100 mg of the 10-oxo compound (**16**) in 70 ml of dry *tert*-butanol. Work up as usual gave 95 mg of the crude brown oil which was subject to chromatography over a silica gel column. Elution of the column with the same solvent provided 30 mg of unchanged starting material and elution with chloroform containing methanol in 1% proportion gave a mixture of 60 mg of the *cis* diol-lactam (**20**) and the *trans* diol-lactam (**22**). This crude product was acetylated and usual work up gave 70 mg of the residue which was chromatographed on a silica gel column. The similar elution of the column as that in the procedure a) provided 35 mg of the *trans* 10-acetoxy

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compound (23), mp 138°, and 13 mg of the *cis* 10-acetoxy compound (21), mp 234—235°, as colorless prisms, respectively (from acetone–ether). These materials were identified with the authentic samples, respectively.

Meerwein Ponndorf Reduction of the 10-Oxo Compound (16): The *trans* Diol-lactam (22)——a) A mixture of 1.0 g of the 10-oxo compound (16), 8.0 g of aluminum isopropoxide and 36 ml of dry toluene was refluxed under nitrogen. After 8 hr, 36 ml of dry isopropanol was added to the mixture and this mixture was heated on an oil bath, and the resulting acetone was distilled off with isopropanol at the rate of 1—5 drops per min. Throughout the reaction period ,the whole amount of the solvent in the vessel was maintained by addition of isopropanol. Heating was continued until the distillate had shown a negative test for acetone (10 hr). Then, most of remaining isopropanol was distilled under reduced pressure. After cooling, 25 ml of acetic acid was added to the residue under ice cooling and the mixture was diluted with ice-water and extracted with chloroform. The extract was washed with dil. NH_4OH and water, dried and evaporated to leave 920 mg of a off-white solid which was recrystallized from acetone–chloroform to yield 850 mg of the *trans* diol-lactam (22) as colorless flakes, mp>300°. *Anal.* Calcd. for $C_{21}H_{27}O_7N \cdot 1/4H_2O$: C, 61.53; H, 6.76; N, 3.46. Found: C, 61.50; H, 6.60; N, 3.45. Mass Spectrum *m/e*: 405 (M^+). From the mother liquor removed the compound (22), 60 mg of the starting material was recovered. Acetylation of 400 mg of the *trans* diol-lactam (22) by the usual manner afforded 440 mg of the *trans* 10-acetoxy compound (23) which was identical with an authentic sample.

b) The 10-oxo compound (16: 1.0 g) was reduced by the similar manner as described above except shortening heating time for removal of the resulting acetone in 3 hr and the same work up afforded 950 mg of an oil. Acetylation followed by chromatography on a silica gel column in chloroform gave 300 mg of unchanged (16), 300 mg of the *trans* 10-acetoxy compound (23), and 200 mg of the *cis* 10-acetoxy compound (21), respectively. These samples were identical with the authentic samples, respectively.

(±)-7-Ethyleneketal-16-oxo-metaphanine (36)——a) To a solution of 500 mg of the *trans* diol-lactam (22), 5 mg of *p*-toluenesulfonic acid in 190 mg of methylene chloride was added drowise a solution of 1.0 g of 3,4-dihydro-α-pyran in 20 ml of methylene chloride and the mixture was stirred for 15 min. To the mixture was added 100 ml of the saturated aqueous sodium bicarbonate solution and the mixture was stirred for 5 min. The organic layer was washed with water, dried and concentrated to give a crystalline solid. Recrystallization from acetone gave 600 mg of the monotetrahydropyranyl ether (33) as colorless flakes, mp 184—185°. IR ν_{max} cm^{-1}: 3540, 3400, and 1673. Mass Spectrum *m/e*: 489 (M^+). Judging from its NMR spectrum, the product was a mixture of two epimers due to an asymmetric center of the tetrahydropyranyl ether moiety (*ca.* 2: 3). The compound (33) was hydrolyzed with acetic acid as usual and acetylation of the product gave the *trans* 10-acetoxy compound (23) in a quantitative yield. To a solution of 120 mg of the compound (33) in 30 ml of methylene chloride was added 500 mg of Collins bispyridine chromium (VI) oxide reagent at room temperature with stirring. After 17 hr, the mixture was filtered and the precipitate was washed with methylene chloride. The filtrate and washing were combined, washed with water, dil. NH_4OH, water and dried. Removal of the solvent gave a slightly yellow oil which was purified by alumina chromatography in benzene to give 84 mg of the *trans* keto-pyranyl ether (35) as a colorless oil. IR ν_{max} cm^{-1}: 1721 and 1679. Mass Spectrum *m/e*: 487 (M^+). This oil was also proved to be a mixture of two epimers due to an asymmetric center of the pyranyl moiety by its NMR spectrum. A solution of 345 mg of the *trans* keto-pyranyl ether (35) in 45 ml of an acetic acid –water mixture (2: 1) was heated at 50—55° for 4 hr with stirring. The mixture was poured into ice–water and made alkaline with NH_4OH and extracted with chloroform. The extract was washed with water, dried and evaporated to provide 280 mg of a white crystalline solid. Recrystallization from methanol–chloroform gave 265 mg of (±)-7-ethyleneketal-16-oxo-metaphanine (36) as colorless flakes, mp>300°. IR ν_{max} cm^{-1}: 3540 and 1675. Mass Spectrum *m/e*: 403 (M^+). *Anal.* Calcd. for $C_{21}H_{25}O_7N$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.26; H, 6.20; N, 3.38.

b) To a solution of 70 mg of the *trans* 10-acetoxy compound (23) in 20 ml of acetone was added a few drops of the standard Jones' reagent at 0° with stirring and the mixture was then stirred at room temperature for 30 min. Excess reagent was decomposed by addition of methanol and the mixture was poured into ice-water and extracted with chloroform. The extract was washed with water, dried and concentrated to dryness. The residue (70 mg) in chloroform was chromatographed over a silica gel column and the column was eluted with the same solvent. The earlier eluate gave 35 mg of the *trans* keto-acetate (34) as a colorless oil. IR ν_{max} cm^{-1}: 1731 and 1683. NMR τ: 7.95 (3H, s., OAc), 7.16 (3H, s., N-Me), 6.12 and 6.08 (each 3H, s., O-Me), 5.94 (4H, m., ethyleneketal H), 4.23 (1H, q., $J=3.5$ Hz, $\delta_{AB}=3$ Hz, C_{10}-H), and 3.06 (2H, q., $J=9$ Hz, $\delta_{AB}=1$ Hz, aromatic H). Mass Spectrum *m/e*: 445 (M^+). The following eluate afforded 10 mg of the diketone (29) as colorless prisms (from acetone–ether). This was identified with an authentic sample obtained previously. To a solution of 40 mg of the *trans* keto-acetate (34) in 10 ml of methanol was added 8 ml of 5% aqueous sodium carbonate solution and the mixture was heated on a water bath for 4 hr under nitrogen. The reaction mixture was poured into ice-water and made acidic with acetic acid and extracted with chloroform. The extract was washed with dil. NH_4OH, water and dried. The solvent was evaporated and the crystalline residue was recrystallized from acetone to give 31 mg of (±)-7-ethyleneketal-16-oxo-metaphanine (36), a sample of which was identified with an authentic sample obtained in the procedure a).

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7-Ethyleneketal-metaphanine (44: Optically Active Form)——A solution of 300 mg of metaphanine (3) and 2 ml of boron trifluoride etherate in 15 ml of ethylene glycol and 25 ml of methylene chloride was stirred vigorously for 65 hr at room temperature. The mixture was poured into ice-water and then made alkaline with NH_4OH and extracted with chloroform. The extract was washed with water and dried. Removal of the solvent gave 400 mg of an oily residue which was triturated with ether to leave a crystalline solid. Recrystallization from ether–methanol afforded 310 mg of 7-ethyleneketal–metaphanine (**44**: optically active form) as colorless prisms, mp 192—193°. IR ν_{max} cm^{-1}: 3550. NMR τ: 7.38 (3H, s., N-Me), 7.15 (1H, broad s., OH), 6.16 (6H, s., $2\times$O-Me), 6.00 (4H, m., ethyleneketal H), 5.08 (1H, d., J=6.5 Hz, C_{10}-H) and 3.25 (2H, q., J=8 Hz, δ_{AB}=1.5 Hz, aromatic H). *Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.51; H, 6.92; N, 3.63.

7-Ethyleneketal-16-oxo-metaphanine (36: Optically Active Form)——To a stirred solution of 55 mg of 7-ethyleneketal–metaphanine (**44**: optically active form), 70 mg of magnesium sulfate in 15 ml of acetone and 2 ml of water was added dropwise a mixture of 75 mg of potassium permanganate, 5 ml of acetone and 8 ml of water, and the mixture was stirred at room temperature for 4.5 hr. Excess reagent was decomposed by addition of a solution of 150 mg of sodium bisulfite in 20% acetic acid and then acetone was evaporated under reduced pressure. The residue was mixed with water and extracted with chloroform. The extract was washed with water and evaporated to leave a crystalline material. Recrystallization from chloroform–methanol provided 30 mg of 7-ethyleneketal-16-oxo-metaphanine (**36**: optically active form) as colorless needles, mp>300°. IR ν_{max} cm^{-1}: 3540 and 1675. NMR τ: 6.92 (3H, s., N-Me), 6.13 (6H, s., O-Me), 5.80—6.10 (4H, m., ethyleneketal H), 5.08 (1H, d., J=6.5 Hz, C_{10}-H), and 3.21 (2H, s., aromatic H). Mass Spectrum m/e: 403 (M^+). *Anal.* Calcd. for $C_{21}H_{25}O_7N$: C, 61.84; H, 6.30; N, 3.43. Found: C, 61.68; H, 6.18; N, 3.42. A sample was identical with a synthetic sample (36) by comparison of IR (in $CHCl_3$) and mass spectra and TLC behavior. A slight discrepancy in the IR spectrum was observed when measured in Nujol mull.

Oxidation of the *cis* 10-Acetoxy Compound (21) to the *cis* Keto-acetate (37)——To a solution of 50 mg of the *cis* 10-acetoxy compound (21) in 20 ml of acetone was added the standard Jones' reagent in the same manner as described above. Work up of the reaction mixture produced 59 mg of a colorless oil which was chromatographed over a silica gel column in chloroform. Elution with the same solvent gave 31 mg of the *cis* keto-acetate (37) as a colorless oil in the earlier eluate. IR ν_{max} cm^{-1}: 1727 and 1683. NMR τ: 7.89 (3H, s., OAc), 7.20 (3H, s., N-Me), 6.12 and 6.10 (each 3H, s., O-Me), 5.94 (4H, m., ethyleneketal H), 4.11 (1H, q., J=5 Hz, δ_{AB}=3 Hz, C_{10}-H) and 3.09 (2H, s., aromatic H). Mass Spectrum m/e: 445 (M^+). The following eluate gave 8 mg of the diketone (29).

Conversion of the *cis* Keto-acetate (37) to the 10-Oxo Compound (16) by Treatment with the Sodium Carbonate Solution——A solution of 65 mg of the *cis* keto-acetate (37) in 20 ml of methanol and 16 ml of 5% aqueous sodium carbonate solution was refluxed on a water bath for 4 hr. The mixture was cooled and poured into ice-water, and made acidic with acetic acid and extracted with chloroform. The extract was dried and evaporated to produce 58 mg of a colorless oil. Trituration of this oil with acetone–ether gave crystals which were recrystallized from the same solvent to afford 53 mg of the 10-oxo compound (16) as colorless prisms, mp 253—254°. *Anal.* Calcd. for $C_{21}H_{25}O_7N$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.30; H, 6.29; N, 3.40. This material was completely identical with an authentic sample (mixed mp, IR, NMR, and mass spectra).

Conversion of the 10-Oxo Compound (16) to the 8-*d*-10-Oxo Compound (41)——Reduction of 200 mg of the 10-oxo compound (16) with sodium borodeuteride (300 mg) was carried out in the same manner as that previously described for the preparation of the *cis* diol-lactam (20). Recrystallization of a crude crystalline product from acetone–methanol gave 120 mg of the *cis*-10-*d*-diol lactam (38) as colorless prisms, mp 235°. Mass Spectrum m/e: 406 (M^+). Acetylation of 90 mg of the compound (38) afforded 75 mg of the *cis* 10-*d*-acetoxy compound (39) as colorless prisms, mp 233—235°. IR ν_{max} cm^{-1}: 3580, 1731, 1680, and 1205—1280. NMR τ: 7.92 (3H, s., OAc), 7.34 (3H, s., N-Me), 6.16 and 6.08 (each 3H, s., O-Me), 6.01 (4H, s., ethyleneketal H), and 3.10 (2H, q., J=9 Hz, δ_{AB}=3 Hz, aromatic H). Mass Spectrum m/e: 448 (M^+). The *cis* 10-*d*-acetoxy compound (39: 70 mg) was oxidized with Jones' reagent in the same manner as that employed for the preparation of the *cis* keto-acetate (37). Work up of the reaction mixture produced 50 mg of the *cis* 10-*d*-acetoxy-ketone (40) as a colorless oil. IR ν_{max} cm^{-1}: 1728 and 1681. A solution of 50 mg of the *cis* 10-*d*-acetoxy-ketone (40) in 20 ml of methanol was treated with 16 ml of 5% aqueous sodium carbonate solution in the same manner as that employed for the *cis* keto-acetate (37). Work up of the reaction mixture provided 35 mg of the 8-*d*-10-oxo compound (41) as colorless prisms (from acetone–ether), mp 254—255°. IR ν_{max} cm^{-1}: 3560, 3200—3500, 1682 and 1590. NMR τ: 7.31 (3H, s., N-Me), 6.10 and 6.07 (each 3H, s., O-Me), 6.00 (4H, s., ethyleneketal H) and 2.69 (2H, q., J=9 Hz, δ_{AB}=22 Hz, aromatic H). Mass Spectrum m/e: 404 (M^+).

Reduction of the Monotetrahydropyranyl Ether (33) with Lithium Aluminum Hydride to the Amino-alcohol (42)——Reduction of the monotetrahydropyranyl ether (33: 230 mg) with lithium aluminum hydride (200 mg) was achieved in the same manner as that previously described for the preparation of the compound (24) and work up of the reaction mixture produced 234 mg of a colorless oil as a basic substance. Purification of this material by alumina chromatography in benzene gave 137 mg of the amino-alcohol (42) as a colorless oil. Judging from its NMR spectrum, this oil was found to be a mixture of epimers due to an asym-

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metric center of the tetrahydropyranyl moiety in a 3: 2 ratio. IR ν_{max} cm^{-1}: 3540. Mass Spectrum *m/e*: 475 (M$^+$).

Reduction of (±)-7-Ethyleneketal-16-oxo-metaphanine (36) with Lithium Aluminum Hydride to the *trans* Amino-diol (45) and (±)-7-Ethyleneketal-metaphanine (44)——To a stirred solution of 116 mg of (±)-7-ethyleneketal-16-oxo-metaphanine (36) in 200 ml of dry ether was added portionwise 100 mg of lithium aluminum hydride which was previously exposed to air for 1 day, and the mixture was refluxed for 7 hr with stirring. Work up in the similar manner as that described before afforded 65 mg of a basic substance and 32 mg of a neutral substance as a colorless oil. From the neutral fraction, 10 mg of the starting material (36) was recovered as colorless flakes. The basic substance in benzene was subject to chromatography over an alumina column and elution of the column with benzene–chloroform (3: 1) gave 21 mg of (±)-7-ethyleneketal-metaphanine (44) in the earlier eluate as colorless prisms (from acetone–ether), mp 215°. IR ν_{max} cm^{-1}: 3550. NMR τ: 7.38 (3H, s., N-Me), 7.15 (1H, broad, OH), 6.16 (6H, s., 2×O-Me), 6.00 (4H, m., ethyleneketal H), 5.08 (1H, d., J=6.5 Hz, C_{10}-H), and 3.25 (2H, q., J=8 Hz, δ_{AB}=1.5 Hz, aromatic H). *Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.50; H, 6.95; N, 3.54. The IR and NMR spectra and TLC behavior of this material were completely identical with those of 7-ethyleneketal-metaphanine derived from natural metaphanine (3). Continued elution of the column with benzene–chloroform (1: 2) produced a crystalline solid. Recrystallization from ether–acetone afforded 35 mg of the *trans* amino-diol (45) as colorless prisms, mp 127—129°. IR ν_{max} cm^{-1}: 3550. NMR τ: 7.47 (3H, s., N-Me), 6.45 (1H, d., J=1.5 Hz, C_8-H), 6.16 and 6.13 (each 3H, s., O-Me), 6.05 (4H, s., ethyleneketal H), 5.26 (1H, q., J=6.5 Hz, δ_{AB}=3 Hz, C_{10}-H) and 2.92 (2H, q., J=9 Hz, δ_{AB}=19.5 Hz, aromatic H). *Anal.* Calcd. for $C_{21}H_{29}O_6N$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.28; H, 7.77; N, 3.48.

The *trans* Amino-diol (45) from the *trans* 10-Acetoxy Compound (23)——The *trans* 10-acetoxy compound (23: 75 mg) was reduced with lithium aluminum hydride in the same manner as that described before to yield 50 mg of the *trans* amino-diol (45) as colorless prisms (from acetone–ether), mp 127°. This material was completely identical with an authentic sample (mixed mp and IR and NMR spectra and TLC behavior).

Hydrolysis of the Amino-alcohol (42) to the *trans* Amino-diol (45)——A solution of 54 mg of the amino-alcohol (42) in 9 ml of acetic acid–water (2: 1) was heated at 60° with stirring for 5 hr. The mixture was poured into ice-water and extracted with chloroform. The aqueous layer was made alkaline with NH_4OH and extracted with ether and dried. Removal of the solvent afforded a crystalline solid which was recrystallized from ether to give 35 mg of the *trans* amino-diol (45) as colorless prisms, mp 128°. A sample was identical with an authentic specimen.

The Thiolactam (46)——To a solution of 100 mg of the ketal-lactam (7) in 20 ml of dry benzene was added 80 mg of phosphorus pentasulfide and the mixture was refluxed for 2 hr with stirring. To the cooled reaction mixture was added 5% sodium hydroxide solution and the mixture was stirred for 30 min at room temperature and extracted with chloroform. The extract was washed with water, dried and evaporated to produce 75 mg of an oil. Chromatography on silica gel and recrystallization of the crystalline eluate from acetone–ether afforded 20 mg of the thiolactam (46) as slightly yellow flakes, mp 193—195°. IR ν_{max} cm^{-1}: 1719 and 1490. NMR τ: 6.82 (3H, s., N-Me), 6.15 and 6.08 (each 3H, s., O-Me), and 3.20 (2H, s., aromatic H). *Anal.* Calcd. for $C_{19}H_{23}O_3NS \cdot 1/3H_2O$: C, 64.94; H, 6.80. Found: C, 64.99; H, 6.86. Mass Spectrum *m/e*: 345 (M$^+$), 347 (M$^+$+2).

Raney Nickel Reduction of the Thiolactam (46): The Amine (47)——To a solution of 15 mg of the thiolactam (46) in 25 ml of 95% ethanol was added 1.50 g of Raney nickel (W-2) and the mixture was refluxed for 8 hr with stirring. The mixture was cooled, filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform and extracted with 3% acetic acid. The aqueous extract was made alkaline with NH_4OH and extracted with ether. The extract was dried and evaporated to leave a colorless oil which on trituration with ether gave a crystalline solid. Recrystallization from ether gave 10 mg of the amine (47) as colorless prisms, mp 114°. IR ν_{max} cm^{-1}: 1706. NMR τ: 7.77 (3H, s., N-Me), 6.10 and 6.01 (each 3H, s., O-Me) and 3.22 (2H, s., aromatic H). *Anal.* Calcd. for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.18; H, 8.08; N, 4.46.

Treatment of (±)-7-Ethyleneketal-16-oxo-metaphanine (36) with Meerwein Reagent followed by Sodium Borohydride Reduction: (±)-7-Ethyleneketal-metaphanine (44)——A solution of 55 mg of triethyloxonium fluoborate and 100 mg of (±)-ethyleneketal-16-oxo-metaphanine (36) in 15 ml of dry methylene chloride was stirred at room temperature. After 22 hr, methylene chloride was removed under reduced pressure at 10° and the residue was dissolved in 10 ml of 95% ethanol. To this solution was added portionwise 25 mg of sodium borohydride under stirring at 0° and stirring was further continued for 22 hr at room temperature. The mixture was poured into ice-water and extracted with chloroform. The chloroform extract was reextracted with 3% acetic acid and the aqueous layer was made alkaline with NH_4OH and extracted with ether. The ether extract was washed with water, dried and evaporated to give a crystalline solid. Recrystallization from a cooled acetone–ether mixture provided 48 mg of (±)-7-ethyleneketal-metaphanine (44) as colorless prisms, mp 215°. A sample was identical with an authentic sample. On the other hand, the chloroform extract, from which the basic substance was removed by shaking with 3% acetic acid, was washed with dil. NH_4OH, water and dried. Removal of the solvent left 28 mg of the starting material (36) as colorless flakes.

Deketalization of (±)-7-Ethyleneketal-metaphanine (44): (±)-Metaphanine (49)——A mixture of 32 mg

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of **44**, 9 ml of methanol and 4 ml of conc. hydrochloric acid was refluxed on a water bath for 2 hr. After removal of methanol under reduced pressure, the residue was diluted with water and made alkaline with NH_4OH and then extracted with chloroform. The extract was washed with water, dried and evaporated to give 34 mg of a residue which in chloroform was chromatographed over a silica gel column. Elution of the column with the same solvent and recrystallization of the eluate from an ether–methanol mixture gave 15 mg of (±)-metaphanine (**49**) as colorless prisms, mp 205—206°. IR ν_{max} cm^{-1}:3480 and 1730. NMR τ: 7.43 (3H, s., N-Me), 6.14 (6H, s., 2×O-Me), 4.97 (1H, d., $J=6.5$ Hz, C_{10}-H), 3.18 (2H, q., $J=8.1$ Hz, $\delta_{AB}=1.5$ Hz, aromatic H). Mass Spectrum *m/e*: 345 (M^+). *Anal.* Calcd. for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.87; H, 6.76; N, 4.11. Continued elution of the column with chloroform–methanol (50: 1) afforded 8 mg of unchanged starting material (**44**).

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