Chem. Pharm. Bull. 23(1) 133—138 (1975)

UDC 547.94.04 : 581.192

Chemical Conversion of Stepinonine to Bisbenzylisoquinoline Alkaloids

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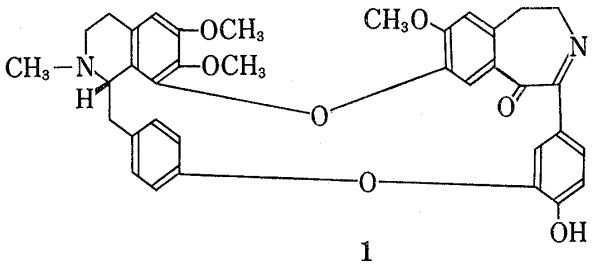
(Received June 26, 1974)

Stepinonine (**1**) was chemically converted to O-methylrepandine (**2**) and O-methyloxyacanthine (**3**) *via* N,O-dimethyltetrahydrostepinonine (**17**) which was subjected to oxidation with Jones' reagent, followed by reduction with Zn–AcOH and $NaBH_4$.

In previous papers,[2] we have reported that stepinonine (**1**), isolated from *Stephania japonica* Miers, is a new dimeric benzylisoquinoline-2-phenyl-s-homotetrahydroisoquinoline alkaloid. The chemical conversion of stepinonine to bisbenzylisoquinoline alkaloids will be significant in respect to support the previous structure assignment of stepinonine and to suggest the biogenetic relationship of these alkaloids. The essential part of this study is the conversion of the 3-benzazepine moiety of stepinonine to the benzylisoquinoline moiety. From this point of view, an attempt was made first to convert chemically the tetrahydro-2-phenyl-3-benzazepine-1-ol derivative to the benzylisoquinoline alkaloid as a model experiment. Then, N,O-dimethyltetrahydrostepinonine was converted to O-methylrepandine (**2**)[3] and O-methyloxyacanthine (**3**).[4]



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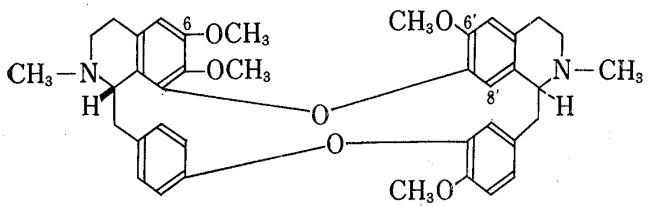

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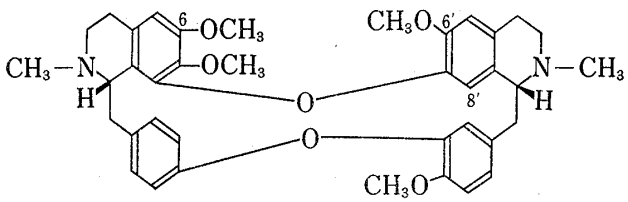

3

Chart 1

On the chemical conversion of the 3-benzazepine derivative, Šantavý, *et al.*[5] have reported the conversion of rhoeageninediol (**4**) into coptisine (**5**). There has been, however, no instance of chemical conversion of the 3-benzazepine derivative to the benzylisoquinoline derivative.

1) Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*
2) *a*) T. Ibuka, T. Konoshima, and Y. Inubushi, *Tetrahedron Letters*, **1972**, 4001; *b*) *Idem, Chem. Pharm. Bull.* (Tokyo), **23**, 114 (1975).
3) M. Tomita and E. Fujita, *Pharm. Bull.* (Japan), **1**, 101 (1953); I.R.C. Bick, W.I. Taylor, and A.R. Todd, *J. Chem. Soc.*, **1953**, 695.
4) M. Tomita and J. Kunitomo, *J. Pharm. Soc. Japan*, **82**, 741 (1962); T. Kugo, M. Tanaka, and T. Sagae, *ibid.*, **80**, 1425 (1960).
5) A. Kasek, V. Simanek, and F. Šantavý, *Tetrahedron Letters*, **1963**, 4549.

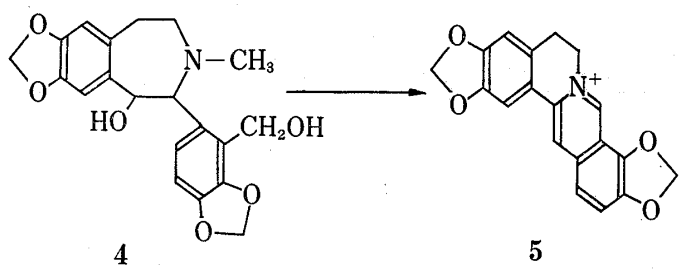

Chart 2

The compound **12** and **13**, which are stereoisomeric with respect to the relative configuration of the C_1 and C_2 substituents, were chosen as the starting materials in the model experiments. These compounds were synthesized in analogy with the previously reported synthetic manner.[2b,6] Thus, Friedel-Crafts reaction of methyl 3,4-dimethoxyphenylacetate (**6**) with *p*-methoxyphenylacetic acid (**7**) gave the keto-ester (**8**) in 71% yield. Bromination of **8** with bromine gave the keto-bromide (**9**). Treatment of **9** with monomethylamine, followed by sodium borohydride reduction provided the lactam-alcohol (**10**). Lithium aluminum hydride reduction of **10** gave the amino-alcohol (**12**). That the relative configuration of the C_1–OH and the C_2–Ph of **12** is *trans*, was estimated by the nuclear magnetic resonance (NMR) spectral inspection (The coupling constant of signals due to the C_1 and C_2 protons was observed as 7 Hz,[2b,6]). On the other hand, oxidation of the compound (**10**) with Jones' reagent gave the keto-lactam (**11**) which was reduced with lithium aluminum hydride to provide the amino-alcohol (**13**). That the relative configuration of the C_1–OH and the C_2–Ph of **13** is *cis*, was estimated by the NMR spectral inspection (The coupling constant of signals due to the C_1 and C_2 protons was observed as 1 Hz.[2b,6]).

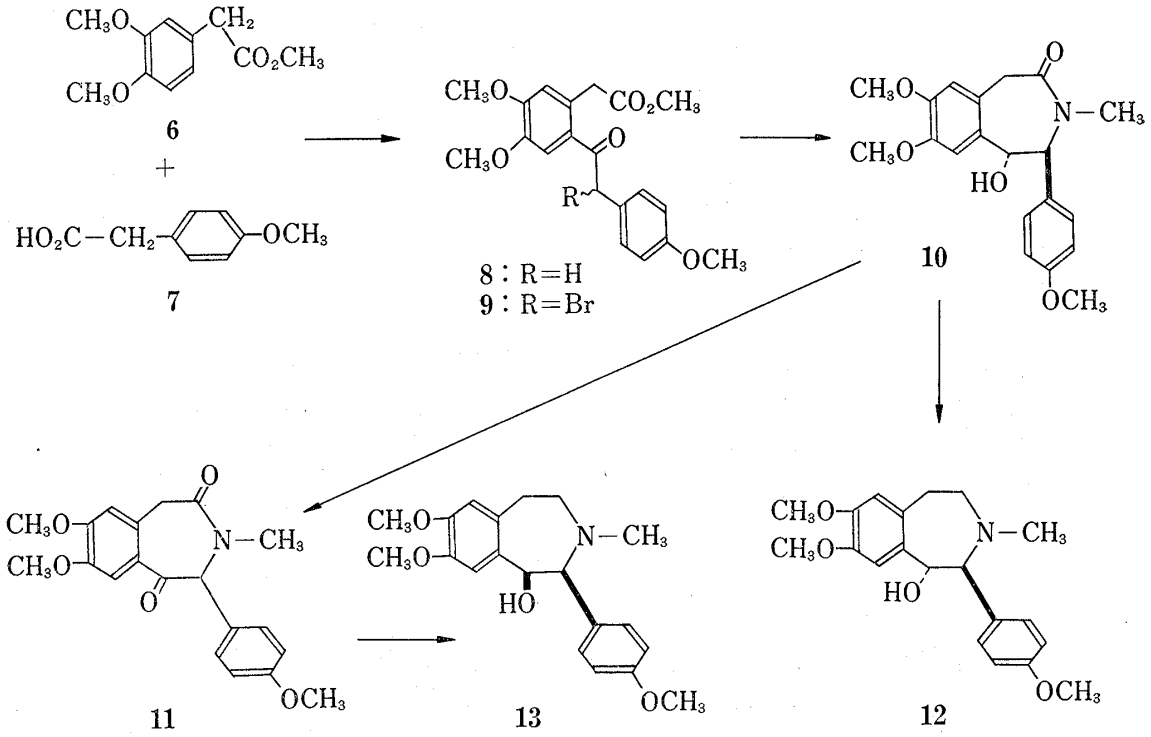

Chart 3

Several experiments for the chemical conversion of these compounds, **12** and **13**, were tried but all trials were unsuccessful.

Then, the procedure that reduction of the 1-oxo-3-benzazepine derivative with Zn–AcOH may result in the benzylisoquinoline derivative through the ring opening, followed by the

6) Y. Inubushi, T. Harayama, and K. Takeshima, *Chem. Pharm. Bull.* (Tokyo), **20**, 689 (1972).

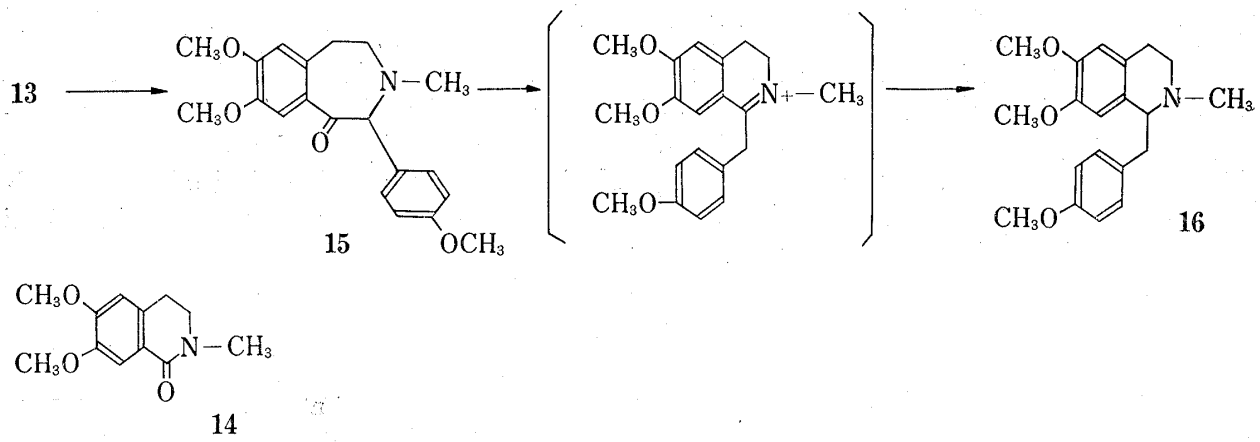

Chart 4

recyclization, was proposed for the present conversion. For this purpose, oxidation of a hydroxyl group of **12** or **13** to the oxo function is required.

Oxidation of **12** with MnO_2 was first examined but in this case, the only isolated product was 6,7-dimethoxyhydrastine (**14**).[7] Oppenauer oxidation of **12** was also unfruitful. Oxidation of **12** with Jones' reagent under cooling and for a short reaction period was successfully carried out to give the desired 1-oxo compound (**15**). Then, reduction of **15** with Zn–AcOH was tried. Since the reduction product is soluble in an aqueous ammonia solution, the product was assumed to be a quaternary base which is formed by recyclization of the ring-opening product. The product without purification was reduced with $NaBH_4$ to give the compound (**16**) although the yield was rather low. The compound (**16**) was identified with an authentic sample of *dl*-N,O,O-trimethylcoclaurine. Since the supposed quaternary intermediate (Chart 4) should be reduced with Zn–AcOH, it is uncertain which reagent, either Zn–AcOH or $NaBH_4$, reduced virtually the intermediate.[8]

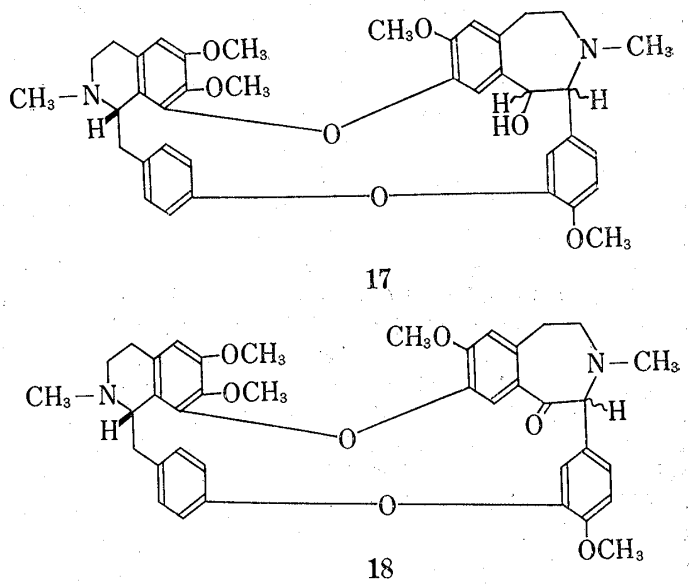

Chart 5

Then, the conversion of stepinonine to the bisbenzylisoquinoline alkaloids through the analogous procedure as described above was tried. N,O-Dimethyltetrahydrostepinonine (**17**)[2b] was oxidized with Jones' reagent to the compound (**18**) which was reduced successively with Zn–AcOH and $NaBH_4$. It has been reported that O-methylrepandine (**2**) and O-methyloxyacanthine (**3**) can be clearly discriminated from each other by NMR spectral comparison.[9] Thus, a signal due to an O-methyl group at C_6 appears around 6.4 τ in the oxyacanthine series, whereas this signal in the repandine series appears around 6.6 τ. Furthermore, a signal due

7) H. Irie, S. Tani, and H. Yamane, *J. Chem. Soc.*, **1972**, 2986.
8) M. Tomita and Y. Watanabe, *Pharm. Bull.* (Japan), **4**, 124; H. Furukawa, *Yakugaku Zasshi*, **86**, 253 (1966).
9) Celebration Publication for the Retirement of Professor Masao Tomita, 1926—1967, Hirokawa Publishing Co., Tokyo, Japan, 1967, p. 45.

to an aromatic proton at C_8' in the oxyacanthine series appears in rather high field (4.5 τ) and in the repandine series, no signal is observed in this region. The signal pattern due to O-methyl groups in these alkaloids can be also utilized for the discrimination of two types of alkaloids. The reduction product from **18** was assumed to be a mixture of O-methylrepandine (**2**) and O-methyloxyacanthine (**3**) in a ratio of 2/1 by NMR spectral inspection. The preparative thin-layer chromatography (TLC) of the mixture described above gave O-methylrepandine (**2**) and O-methyloxyacanthine (**3**) in the pure state which were identified with authentic specimens, respectively.

Experimental

Melting points were determined with a microscopic hot-stage apparatus. Unless otherwise stated, NMR spectra were taken with a Varian A-60 spectrometer for solutions in $CDCl_3$ with tetramethylsilane as an internal reference, and chemical shifts were given in τ values. IR spectra were measured for solutions in $CHCl_3$ with a Hitachi EPI-S Spectrometer. Mass spectra were taken on a Hitachi Mass Spectrometer Model RMU-6D.

The Keto-ester (8)——To a solution of 1 g of *p*-methoxyphenylacetic acid in 15 ml of CH_2Cl_2 was gradually added 1.5 g of PCl_5 in a small portion, and the reaction mixture was stirred for 1 hr at room temperature. To this mixture was added gradually 1 g of $ZrCl_4$ under ice-cooling. After the mixture was stirred for further 0.5 hr, 0.8 g of methyl 3,4-dimethoxyphenylacetate (**6**) was added to the mixture. The mixture was stirred overnight at room temperature, poured into ice-water, made alkaline with an aq. Na_2CO_3 solution and extracted with CH_2Cl_2. The extract was washed successively with a 5% $NaHCO_3$ solution, water and dried over anhyd. K_2CO_3. The solvent was removed to leave 0.95 g of an oil. When triturated with ether, the oil was solidified. Recrystallization from ether gave 0.75 g of colorless needles (**8**), mp 97—100°, in 71% yield. IR ν_{max} cm^{-1}: 1730 (ester) and 1670 (ketone). NMR: 6.33, 6.23, 6.14, and 6.10 (each 3H, s., OCH_3). *Anal.* Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.00; H, 6.06.

The Lactam-alcohol (10)——To a solution of 1 g of the keto-ester (**8**) in $CHCl_3$ was added dropwise an equimolar bromine solution in $CHCl_3$ and the mixture was stirred for 3.5 hr. After reddish-brown color of bromine had faded, the mixture was washed successively with an aqueous $NaHSO_3$ solution, water and evaporated. When triturated with ether, the residue (300 mg: the keto-bromide; **9**) was solidified. IR ν_{max} cm^{-1}: 1735 (ester) and 1685 (ketone). Because of its labile nature, the crude crystals were employed for the next synthetic step. To a solution of 0.1 g of the keto-bromide (**9**) in 8 ml of dioxane was added a solution of excess $MeNH_2$[10] (above ten times of molar equivalent) in dioxane and the mixture was warmed at 60° for 5 min. The crystalline precipitates deposited. The mixture was made acidic with 48% HBr and the solvent was evaporated under reduced pressure below 60°. The residue was dissolved in a mixture of MeOH–water and 1.5 g[10] of $NaBH_4$ was added to the solution. The reaction mixture was stirred for 2.5 hr under cooling and MeOH was removed. The concentrated solution was poured into ice-water and extracted with $CHCl_3$. The solvent was evaporated and the residue was solidified on standing. Recrystallization from a mixture of acetone and ether gave 50 mg of colorless prisms (**10**), mp 217—218°, in 60% yield. IR ν_{max} cm^{-1}: 3400 (OH) and 1625 (lactam CO). NMR: 7.27 (3H, s., N–CH_3), 6.19 (3H, s., OCH_3), 6.15 (6H, s., 2×OCH_3), 5.62 (1H, d., J=8 Hz, C_2–H), 4.87 (1H, d., J=8 Hz, C_1–H), and 2.85—3.30 (6H, m,. aromatic protons). *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 66.95; H, 6.42. Found: C, 67.21; H, 6.49.

The Keto-lactam (11)——To a suspension of 2.5 g of the lactam-alcohol (**10**) in acetone was added dropwise Jones' reagent under cooling and the reaction mixture was stirred for 30 min, after the red-brownish color of reagent had been maintained. Excess reagent was decomposed with MeOH and the reaction mixture was filtered and the precipitates were washed thoroughly with $CHCl_3$. The filtrate and washings were combined and evaporated. The residue was mixed with a small amount of water and extracted with $CHCl_3$. The extract was washed with water and evaporated. When triturated with a mixture of acetone and ether, the residue was solidified and recrystallization from acetone–ether gave 1.5 g of colorless prisms (**11**), mp 156—158°, in 60% yield. IR ν_{max} cm^{-1}: 1655 (ketone and lactam CO). NMR: 6.71 (3H, s., N–CH_3), 6.21, 6.09 and 6.05 (each 3H, s., OCH_3), 4.60 (1H, s., C_2–H), 3.35—2.80 (5H, m., aromatic protons), and 2.25 (1H, s., aromatic proton). *Anal.* Calcd. for $C_{20}H_{21}O_5N$: C, 67.34; H, 5.96. Found: C, 67.59; H, 5.96.

The Amino-alcohol: 4′,7,8-Trimethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol (12: *trans* Isomer)——To a suspension of 0.5 g of the lactam-alcohol (**10**) in 50 ml of anhyd. ether was added 0.5 g of $LiAlH_4$ and the reaction mixture was refluxed for 18 hr. Excess reagent was decomposed with wet ether

10) A good yield of **10** was obtained when excess $MeNH_2$ was used and the reaction mixture was warmed for a short period, and when the reaction mixture was acidified with HBr immediately after the crystalline precipitates deposited. In this case, excess $NaBH_4$ was also needed.

and filtered. The residue was washed thoroughly with ether, and the filtrate and washings were combined. The solvent was removed and the residue was dissolved in ether. The ether solution was extracted with 5% AcOH, and the acidic solution was made alkaline with ammonia and extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. K_2CO_3 and evaporated. The residue in $CHCl_3$ was chromatographed on a silica gel column. Elution of the column with the same solvent left 300 mg of a colorless oil (**12**: *trans*) in 62% yield, which revealed one spot on TLC (silica gel G according to Stahl, solvent, $CHCl_3$/acetone=1/1). IR ν_{max} cm^{-1}: 3400 (OH). NMR: 7.80 (3H, s., N–CH_3), 6.30 (1H, d., J=7 Hz, C_2–H), 6.23, 6.19, and 6.10 (each 3H, s., OCH_3), 5.25 (1H, d., J=7 Hz, C_1–H) and 2.85—3.35 (6H, m., aromatic protons). Mass Spectrum *m/e*: 343 (M^+), 150, and 121.

The Amino-alcohol: 4′,7,8-Trimethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol (**13**: ***cis***)——To a suspension of 1 g of the keto-lactam (**11**) in 50 ml of anhyd. ether was added 1 g of $LiAlH_4$. The mixture was refluxed for 15 hr and excess hydride was decomposed with wet ether. The mixture was filtered and the residue was washed thoroughly with ether. The filtrate and washings were combined and evaporated. The residue was dissolved in a small amount of ether, and the ether solution was extracted with 5% AcOH. The acidic solution was made alkaline with ammonia and extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. K_2CO_3 and evaporated to leave 0.8 g of an oil. This oil in $CHCl_3$ was chromatographed on a silica gel column and elution of the column with the same solvent gave 0.5 g of colorless oil (**13**: *cis*) which showed one spot on TLC (silica gel G, $CHCl_3$/acetone=1/1). IR ν_{max} cm^{-1}: 3400 (OH). NMR: 7.88 (3H, s., N–CH_3), 6.60 (1H, d., J=1 Hz, C_2–H), 6.19 (6H, s., 2×OCH_3), 6.11 (3H, s., OCH_3), 5.32 (1H, d., J=1 Hz, C_1–H), 2.65—3.35 (6H, m., aromatic protons). Picrate, yellow prisms, mp 133—135° (from acetone). *Anal.* Calcd. for $C_{26}H_{28}O_{11}N_4 \cdot 1/2H_2O$: C, 53.70; H, 5.03. Found: C, 53.80; H, 5.18.

Oxidation of the Amino-alcohol (**12**: ***trans***) **with MnO_2: 6,7-Dimethoxyhydrastine** (**14**)——To a solution of 250 mg of the amino-alcohol (**12**: *trans*) in $CHCl_3$ was added 2 g of MnO_2. The mixture was stirred for 18 hr at room temperature and filtered. The filtrate was washed with water, and evaporated to leave 120 mg of an oil. This oil in $CHCl_3$ was chromatographed on a silica gel column and elution of the column with the same solvent gave 16 mg of crystals (**14**), mp 121—122° (from acetone–ether). IR ν_{max} cm^{-1}: 1640 (lactam CO). NMR: 6.85 (3H, s., N–CH_3), 6.07 (6H, s., 2×OCH_3), 3.35 (1H, s., aromatic proton), and 2.46 (1H, s., aromatic proton). Mass Spectrum *m/e*: 221 (M^+). *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83. Found: C, 64.86; H, 6.72. All these data of the compound (**14**) were identical with those of 6,7-dimethoxyhydrastine.[7]

The 1-Oxo-3-benzazepine Derivative (**15**)——To a solution of 100 mg of the amino-alcohol (**13**) in a small amount of acetone was added 5 drops of Jones' reagent under ice-cooling and stirring. Stirring was continued 10 min and excess reagent was decomposed with MeOH. The mixture was filtered and the residue was washed thoroughly with acetone. The filtrate and washings were combined, evaporated and dissolved in HCl solution. The acidic solution was washed with ether, made alkaline with aqueous ammonia and extracted with ether. The extract was washed with water, dried over anhyd. $MgSO_4$ and evaporated to leave 45 mg of a yellow oil. This oil in $CHCl_3$ was chromatographed on a silica gel column and elution of the column with the same solvent gave 38 mg of a colorless oil in 40% yield. IR ν_{max} cm^{-1}: 1669 (CO). NMR: 7.56 (3H, s., N–CH_3), 6.22, 6.15, and 6.09 (each 3H, s., OCH_3) 5.47 (1H, s., CO–CH–C_6H_5) and 2.69—3.33 (6H, m., aromatic protons). Mass Spectrum *m/e*: 341 (M^+).

Reduction of the 1-Oxo-3-benzazepine Derivative (**15**) **with Zn-AcOH**: **(±)-N,O,O-Trimethylcoclaurine** (**16**)——To a solution of 45 mg of the 1-oxo-3-benzazepine derivative (**15**) in 2 ml of AcOH was added 100 mg of Zn powder and the reaction mixture was stirred at 90—100° for 8 hr. AcOH was evaporated and the residue was dissolved in a small amount of water, made alkaline with ammonia and extracted with ether. Evaporation of the ether extract left a slight amount of the residue. On the other hand, the alkaline aqueous solution was concentrated under reduced pressure. The residue was dissolved in aqueous MeOH. To the solution was added 100 mg of $NaBH_4$ under cooling and the mixture was stirred for 5 hr at the same temperature above. The solvent was removed and a small amount of water was added to the residue. The aqueous salution was made alkaline and extracted with $CHCl_3$. The extract was evaporated to leave 10 mg of a yellow oil. This oil in benzene was chromatographed on an alumina column to give 3 mg of an oil which was identified with an authentic sample of N,O,O-trimethylcoclaurine by comparison of IR spectra. Oxalate, mp 157°, colorless needles from acetone. Mass Spectrum *m/e*: 327 (M^+), 207, 206, 190, and 176.

Oxidation of N,O-Dimethyltetrahydrostepinonine (**17**) **with Jones' Reagent: The Compound** (**18**)——To a solution of 30 mg of N,O-dimethyltetrahydrostepinonine (**17**) in a small amount of acetone was added a few drops of Jones' reagent under ice-cooling and the reaction mixture was stirred for 15 min. Excess reagent was decomposed with MeOH and the mixture was filtered. The residue was thoroughly washed with acetone. The filtrate and washings were combined and evaporated. The residue was mixed with an aq. ammonia solution and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated to leave 28 mg of a yellow oil. This oil in $CHCl_3$ was chromatographed on an alumina column to give 19 mg of a colorless oil in 67% yield. IR ν_{max} cm^{-1}: 1678 (CO). NMR: 7.83 and 7.42 (each 3H, s., N–CH_3), 6.60, 6.46, 6.21, and 6.10 (each 3H, s., OCH_3), 6.05 (1H, s., CO–CH–C_6H_5), and 2.65—3.60 (10H, m., aromatic protons). Mass Spectrum *m/e*: 636 (M^+).

Reduction of the Compound (18) with Zn-AcOH: O-Methylrepandine (2) and O-Methyloxyacanthine (3)——To a solution of 240 mg of the compound (18) in 15 ml AcOH was added excess Zn powder and the reaction mixture was stirred for 7 hr at 100—110°. The mixture was filtered and the filtrate was washed with ether. The acidic aqueous solution was made alkaline with ammonia and extracted with ether. The extract was evaporated to leave 150 mg of a yellow oil. This oil without purification was dissolved in MeOH. To this solution was added 100 mg of $NaBH_4$ and the mixture was stirred for 3 hr. The solvent was removed and the residue was mixed with a small amount of an aqueous ammonia solution and extracted with $CHCl_3$. The extract was evaporated to leave 130 mg of a yellow oil. This oil was subjected to the preparative TLC (silica gel GF: developed by $CHCl_3$–acetone–MeOH (4: 4: 1) and two kinds of pure oil (each 10 mg) were obtained. One is crystallized from MeOH to give colorless prisms (2), mp 206—208°, which was identified with an authentic sample of O-methylrepandine by mixed melting point determination. The other did not crystallize but its picrate formed yellow prisms, mp 179—182°, which was identified with an authentic sample of O-methyloxyacanthine picrate by mixed melting point determination.

Acknowledgement The authors are indebted to Dr. K. Kitamura, and Mrs. M. Wobe for NMR spectrum measurements and to Dr. K. Hashimoto, Mr. A. Kato, and Miss M. Fujioka for mass spectrum measurements. Thanks are also to the members of the Analysis Center of our Faculty.