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Structure of Stepinonine,[1] a New Dimeric Benzylisoquinoline-2-phenyl-s-homotetrahydroisoquinoline Alkaloid

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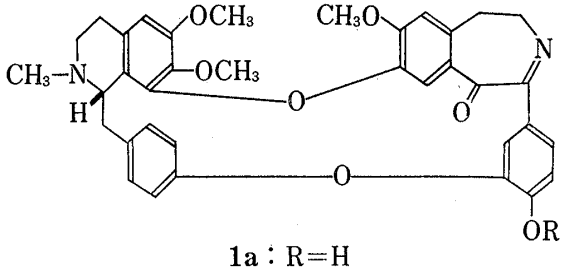
Structure of stepinonine (**1a**), isolated from *Stephania japonica* Miers grown in Formosa, was established through the reductive fission (Chart 2) of N,O-dimethyltetrahydrostepinonine (**4**) with sodium in liquid ammonia, oxidation of O-ethyl-N-methyltetrahydrostepinonine (**16**) with $KMnO_4$ (Chart 5), and the reductive fission of the deuterated product (**18**) derived from stepinonine (Chart 6). Syntheses of the 3-benzazepine derivatives, (**15 a,b,c**) and mass spectrometric fragmentation of these compounds were also presented.

Stephania japonica Miers has proved to be a rich source of alkaloids. Twelve alkaloids belonging to the aporphine, dibenz(d, f)azonine, bisbenzylisoquinoline, protoberberine, and hasubanan types, have been isolated and their structures have been established. In 1963, Tomita, *et al.*[3] isolated a new phenolic base, to which the tentative name, the Base-B, was given, from this plant grown in Formosa. Later, the complete structure of this base which is now designated as stepinonine, was presented in a preliminary communication.[1] We wish to give here a full detail of structure elucidation of stepinonine (**1a**).



1a : R=H
1b : R=$COCH_3$

Chart 1

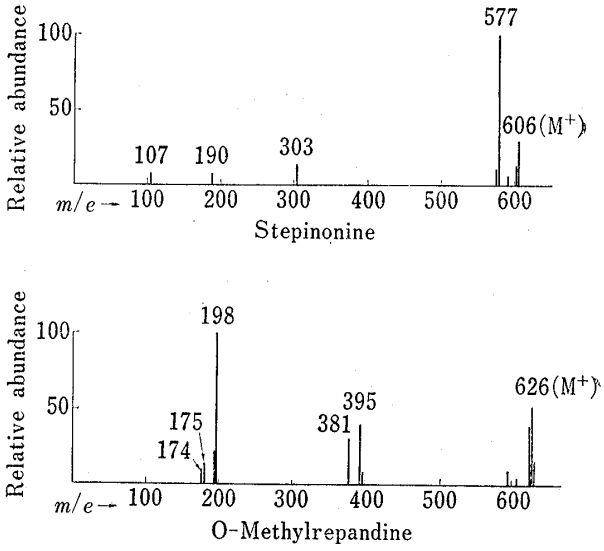


Fig. 1. Mass Spectra of Stepinonine (1a) and O-Methylrepandine

Stepinonine (**1a**) [yellow crystals, mp 244—245° or 280° (dimorphisms)] has the composition $C_{36}H_{34}O_7N_2$. The presence of the carbonyl function and the hydroxyl group was suggested by its infrared (IR) spectrum, and the nuclear magnetic resonance (NMR) spectrum showed the presence of three methoxyl groups, one N-methyl group (7.46 τ) and ten aromatic protons. The mass fragmentation pattern of this base (Fig. 1) is entirely different from

1) A preliminary communication of this work appeared in *Tetrahedron Letters*, **1972**, 4001.
2) Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*
3) M. Tomita and T. Ibuka, *Yakugaku Zasshi*, **83**, 996 (1963).

those of common bisbenzylisoquinoline alkaloids,[4] *e.g.*, O-methylrepandine[4a] (Fig. 1), suggesting a new type carbon skeleton of stepinonine. Acetylation of stepinonine gave the mono-acetate (**1b**), the IR spectrum of which revealed a band due to a phenolic acetate (1767 cm^{-1}) and no hydroxyl band. Sodium borohydride reduction of stepinonine afforded tetrahydrostepinonine (**2**) which showed no carbonyl band in the IR spectrum and an increment of integral value corresponding to four protons compared with stepinonine in the NMR spectrum. N-Methylation of tetrahydrostepinonine (**2**) gave N-methyltetrahydrostepinonine (**3**). These results suggest the presence of an imino ketone group. The NMR spectrum of **3** revealed the N-methyl signals corresponding to two N-methyl groups at 7.40 τ and 7.84 τ and the chemical shift of the signal which is assigned to the newly introduced N-methyl group appeared abnormally in high field compared with that of the N-methyl signal of common tetrahydroisoquinoline alkaloids. This finding suggests also a new type carbon skeleton of stepinonine. O-Methylation of **3** resulted in N,O-dimethyltetrahydrostepinonine (**4**) which was subjected to the reductive fission with sodium in liquid ammonia to provide two kinds of

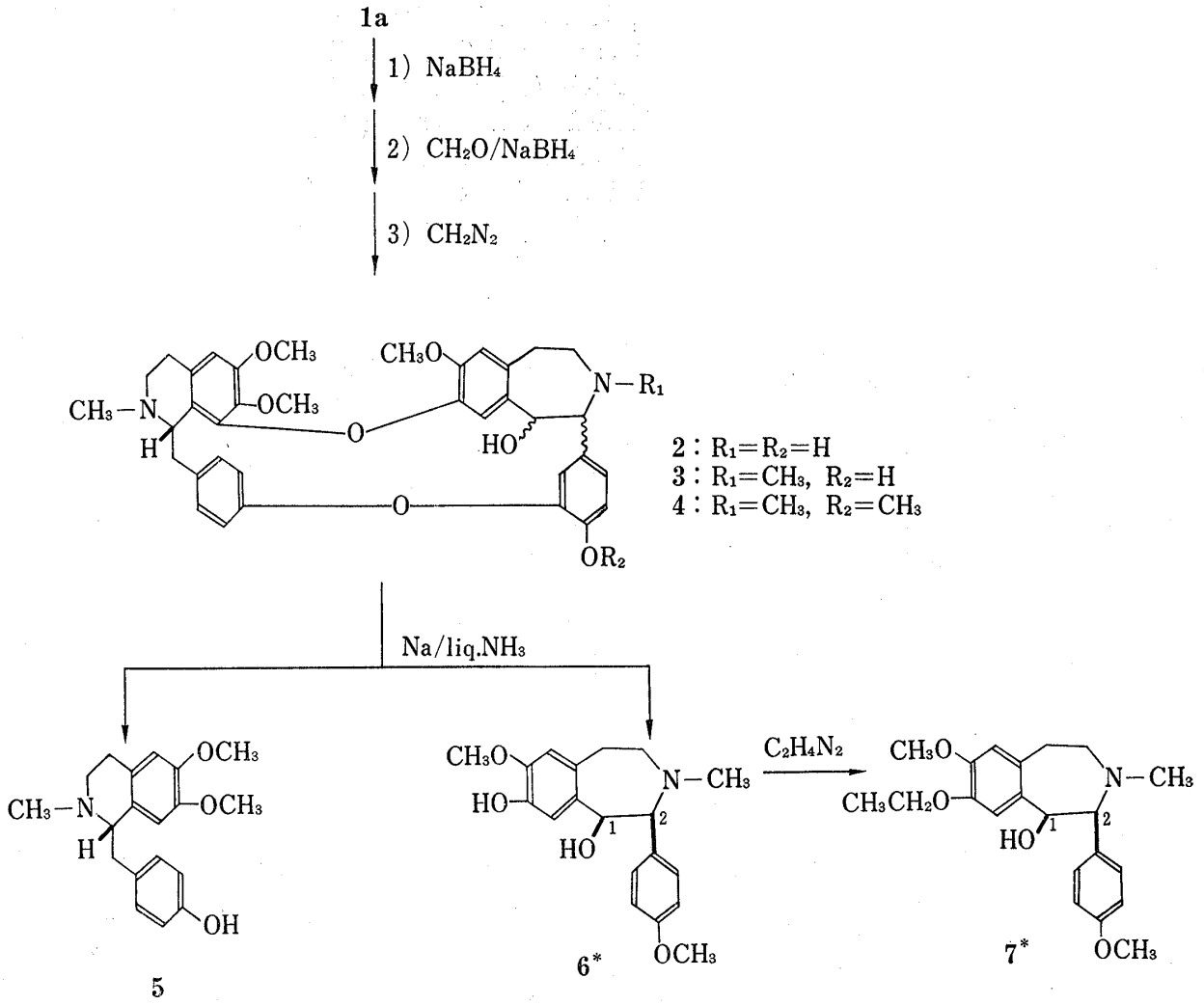


Chart 2. The Stereochemistry of the Compound marked with the Asterisk Indicates the Relative Configuration

4) *a*) M. Tomita, T. Kikuchi, K. Fujitani, A. Kato, H. Furukawa, Y. Aoyagi, T. Ibuka, and M. Kitano, *Tetrahedron Letters*, **1966**, 857; *b*) D.C. Dejongh, S.R. Shrander, and M.P. Cava, *J. Amer. Chem. Soc.*, **88**, 1052 (1966); *c*) J. Baldas, Q.N. Porter, I.R.C. Bick, and M.J. Vernengo, *Tetrahedron Letters*, **1966**, 2059; *d*) M. Tomita, H. Furukawa, T. Kikuchi, A. Kato, and T. Ibuka, *Chem. Pharm. Bull.* (Tokyo), **14**, 232 (1966).

phenolic bases (**5**) and (**6**). Then, the compound (**5**) was proved to be identical with an authentic sample of S-armepavine[5] by comparison of IR, NMR spectra, specific rotation, and by mixed melting point determination. The other phenolic base (**6**) was ethylated with diazoethane to give the O-ethylated compound (**7**) which showed an entirely different mass fragmentation pattern from that of benzylisoquinoline type alkaloids,[4] and a signal due to an N-methyl group appeared in high field (7.88 τ) in the NMR spectrum. One of the authors has reported synthesis of 7,8-dimethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol and some spectroscopic properties of this compound.[6] From comparing these spectral data with those of the compound (**7**), the same carbon skeleton was assumed for these two compounds. The coupling constant between the C_1 and C_2 proton (*ca.* 1 Hz) in the NMR spectrum of the compound (**7**) suggested the *cis* relationship of the C_1–OH and the C_2-phenyl group.[6]

In order to establish the structure of the degradation product (**7**), syntheses of the **7** type compounds were tried through an unambiguous synthetic route[6] as shown in Chart 3. Since the degradation product (**7**) possesses two methoxyl groups and one ethoxyl group in the molecule, three possible structures, **15a**, **15b**, and **15c** for the compound (**7**) should be considered. We started first synthesis of the compound (**15a**) as follows. The Friedel-Crafts reaction of methyl 3,4-dimethoxyphenylacetate[7] (**8a**) and *p*-ethoxyphenylacetic acid (**9a**) under the presence of $ZrCl_4$ as a catalyst afforded the keto-ester (**10a**) which was brominated to give the keto-bromide (**11a**). Treatment of **11a** with monomethylamine, followed by reduction with sodium borohydride provided the ring closure product, the *trans* lactam-alcohol (**12a**). The *trans* relationship of the hydroxyl group and the phenyl group in **12a**

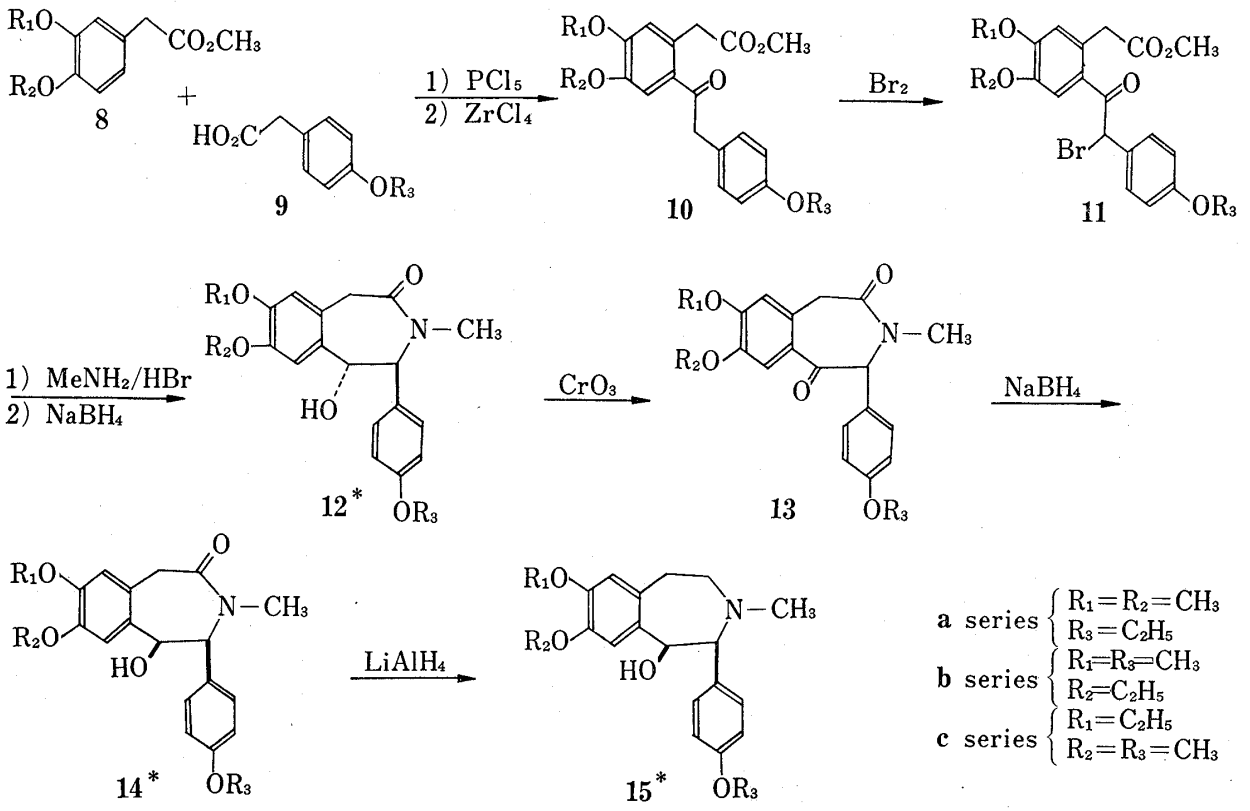


Chart 3. The Stereochemistry of the Compounds marked with the Asterisk Indicates the Relative Configuration

5) M. Tomita and E. Fujita, *Pharm. Bull.* (Japan), **1**, 101 (1953).
6) Y. Inubushi, T. Harayama, and K. Takeshima, *Chem. Pharm. Bull.* (Tokyo), **20**, 689 (1972).
7) B.C. Pal, *J. Sci. Ind., Research* (India), **17A**, 270 (1958).

was estimated from the coupling constant (8 Hz) of the C_1 and C_2 proton signals.[6] Since the configuration of C_1 and C_2 of the degradation product (**7**) has been assumed to be *cis*, the compound (**12a**) should be converted to its *cis* isomer.[6] Thus, the lactam-alcohol (**12a**) was oxidized with Jones' reagent to give the keto-lactam (**13a**). Reduction of **13a** with sodium borohydride gave stereoselectively the *cis* lactam-alcohol (**14a**). The coupling constant of signals due to the C_1 and C_2 protons was observed as 3 Hz, suggesting the *cis* relationship of the C_1–OH and the C_2–phenyl group in **14a**. Lithium aluminum hydride reduction of **14a** gave the compound (**15a**)[8] in which the coupling constant concerned was observed as 1 Hz. The NMR spectra of the compound (**15a**) and the compound (**7**) were identical but slight differences were observed in the finger print region of their IR spectra.

Next, we tried to synthesize the structure isomer (**15b**). The compound (**15b**) was synthesized from methyl 3-methoxy-4-ethoxyphenylacetate (**8b**)[9] and *p*-methoxyphenylacetic acid (**9b**) in a similar manner as described above. By comparison of their IR and NMR spectra, the compound (**15b**) and the degradation product (**7**) were proved to be identical. As mentioned before, the compound (**15a**) and (**7**) showed only slight differences in their IR spectra. Therefore, in order to support the identity of the compound (**7**) with (**15b**), synthesis of the other isomer (**15c**) was preferable. The compound (**15c**) was synthesized from the compound (**8c**)[9] and the compound (**9c**) in a similar manner as described above. Then, spectral properties of these three isomers were examined. In the NMR spectral comparison, the compound (**15a**) and (**15b**) could not be differentiated but the compound (**15c**) could be distinguished from other two isomers, (**15a**) and (**15b**). In the IR spectral comparison, slight differences among three isomers were observed in the finger print region but more definitive evidence for the distinction was required. Then, mass spectra of these compounds were examined. In the mass spectrum of the compound (**15a**) possessing an ethoxyl group at the $C_{4'}$ position, showed two fragment ions at *m/e* 135 and *m/e* 164, whereas the spectra of the compound (**15b**) and (**15c**) possessing a methoxyl group at the $C_{4'}$ position exhibited two fragment ions at *m/e* 121 and *m/e* 150. Šantavý, *et al.*[10] have proposed two different types of mass spectrometric fragmentation of rhoeadine type alkaloids, [the route (a) and the route (b)], which possess the 3-benzazepine skeleton as shown in Chart 4. Although these alkaloids contain a six membered acetal ring (the ring D), the synthetic compounds contain no acetal ring. Therefore, the fragmentation sequence of synthetic compounds will be analogous to the route (b) in rhoeadine alkaloids as shown in Chart 4. Thus, these three structure isomers can be distinguished conclusively from one another by comparison of their IR, NMR and Mass spectra. Furtheremore, the mass spectrum of the degradation product (**6**) showed two characteristic fragment ions at *m/e* 121 and *m/e* 150 indicating that the compound (**6**) possesses a methoxyl group at $C_{4'}$ position. Consequently, it is obvious that the compound (**7**) can be represented by the structure **15b**. Since structures of the compound (**6**) and (**7**) are now established, it is evident that the stepinonine molecule is composed of the armepavine moiety and the 3-benzazepine moiety.

In order to establish the position of a phenolic hydroxyl group and the linking fashion connecting two moieties in the stepinonine molecule, the following experiments were undertaken.

O-Ethylation of **3** with diazoethane gave O-ethyl-N-methyltetrahydrostepinonine (**16**) which was oxidized with $KMnO_4$ to provide the ethoxydiphenyl ether dicarboxylic acid (**17**). This acid was identified with an authentic sample[11] by direct comparison. Stepinonine,

8) Lithium aluminum hydride reduction of the compound (**13a**) gave the *cis* amino-alcohol (**15a**) to some extent but this reduction reaction was not stereoselective.
9) E.R. Shepard and J.F. North, *J. Amer. Chem. Soc.*, **72**, 4364 (1950).
10) F. Šantavý, T.L. Kaul, L. Hruban, L. Dolejs, V. Hanus, and K. Blaha, *Collection Czech. Chem. Communs.*, **30**, 3479 (1965); J. Slavik, L. Dolejs, K. Vokac, and V. Hanus, *ibid.*, **30**, 2864 (1965).
11) M. Tomita and T. Ibuka, *Yakugaku Zasshi*, **83**, 940 (1963).

therefore, is built up of the armepavine (**5**) and the 3-benzazepine moiety which are linked through two diphenyl ether linkages in the "head to head" and "tail to tail" fashion and the position of a phenolic hydroxyl group is situated in the $C_{4'}$ position of the 3-benzazepine moiety.

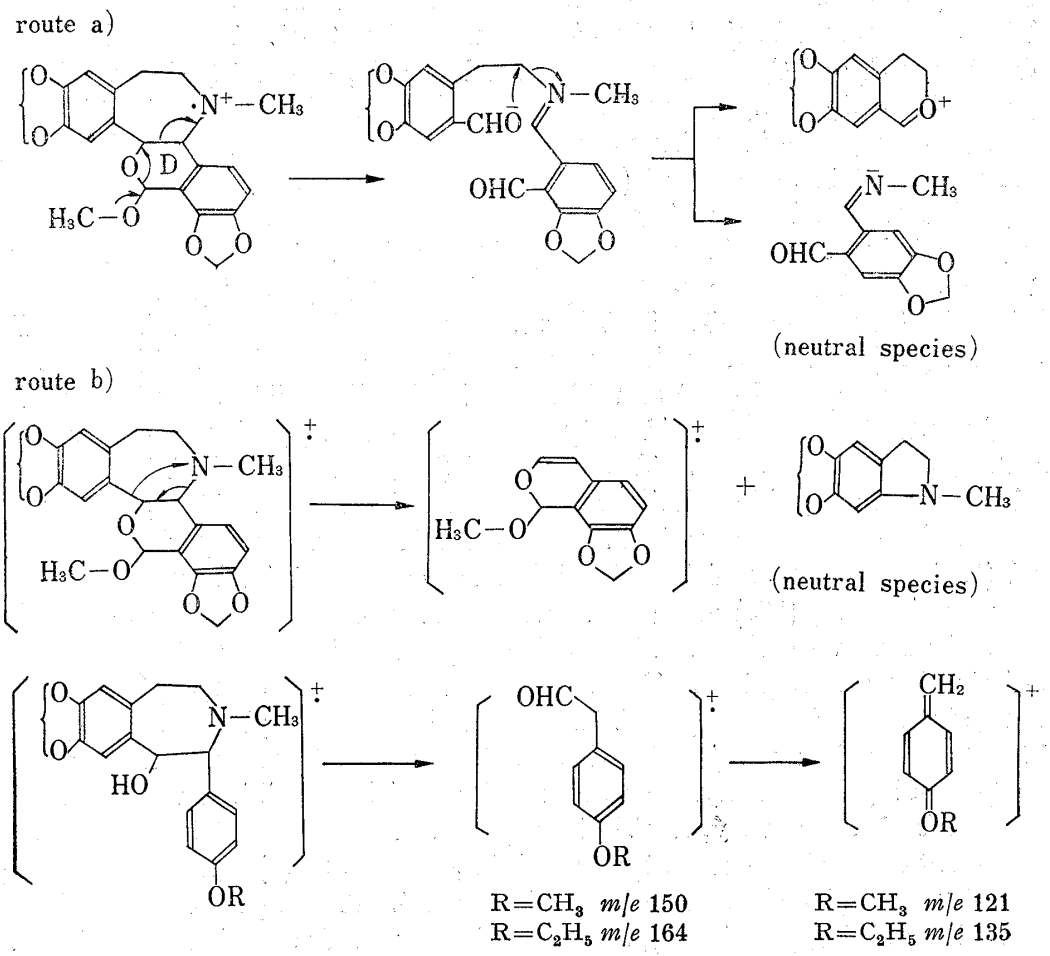


Chart 4

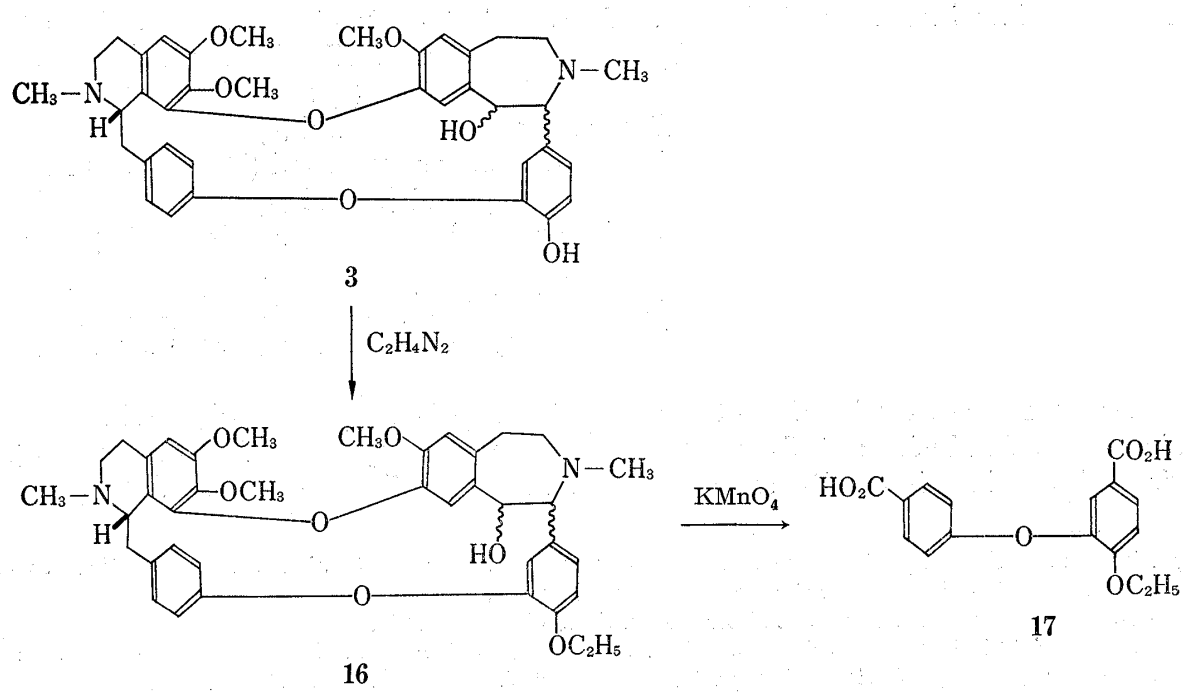


Chart 5

The attached position of a diphenyl ether linkage at the armepavine moiety (C_5 or C_8) was established as follows. Treatment of the nonphenolic base (**16**) with C_2H_5OD–D_2O–DCl at 125—130° for 100 hr[12] provided the deuterated product (**18**) which was subjected to the reductive fission with sodium in liquid ammonia to give two phenolic compounds, (**19**) and (**20**). One **19** was identified with an authentic sample of S-[5-D]-armepavine.[12] The other phenolic base (**20**) was methylated with diazomethane to derive the compound (**21**), the structure of which was certified by comparison with a sample of 7,8-dimethoxy-4'-ethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol (**15a**: racemate) synthesized through an unequivocal synthetic route.[6] The mass spectra of the compound (**20**) and (**21**) indicated that the exchange of an aromatic proton for deuterium did not take place at the C ring but did occur at the A ring. However, the exchange position of deuterium on the A ring is not established. From these experimental results, it is evident that the armepavine moiety and the 3-benzazepine moiety must link at the C_8 position of the former with the oxygen function at the C_8 position of the latter.

Stepinonine, therefore, must have the structure (**1a**) and is the first example of the alkaloid possessing this type of the dimeric structure.

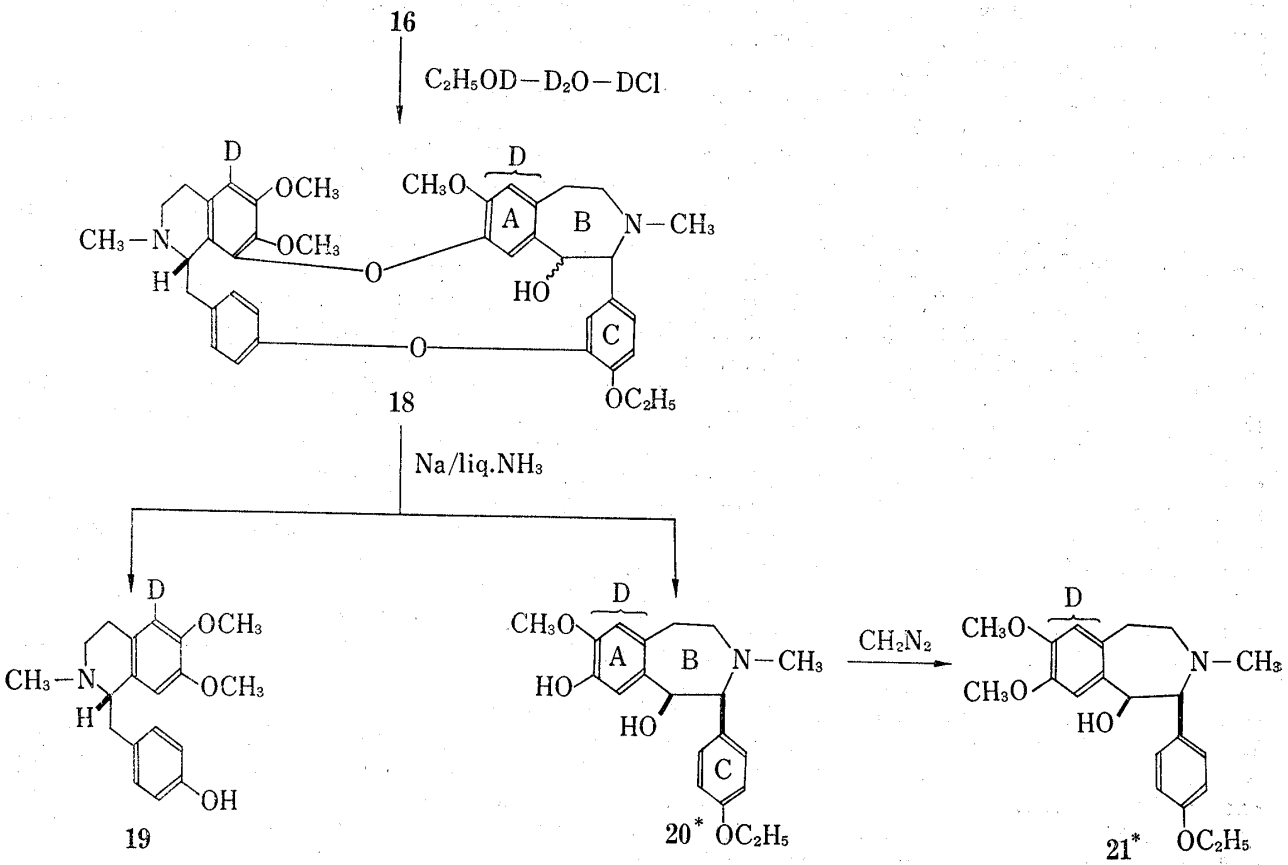


Chart 6. The Stereochemistry of the Compounds marked with the Asterisk Indicates the Relative Configuration

Experimental

All melting points were measured on a Yanagimoto Melting Point Apparatus and were uncorrected. Unless otherwise stated, IR spectra were measured for solutions in chloroform with a Hitachi EPI-S Spectrometer. Measurements of NMR spectra were made for deuteriochloroform solutions on a Varian A-60 Spectrometer with tetramethylsilane as an internal standard, and chemical shifts were given in τ values. Mass spectra were taken on a Hitachi Mass Spectrometer Model RMU-6D.

12) Y. Inubushi, T. Kikuchi, T. Ibuka, and I. Saji, *Tetrahedron Letters*, **1972**, 423.

Stepinonine (1a)[3]——Stepinonine crystallized from a mixture of acetone and MeOH to give yellow prisms, mp 244—245° or 280° (dimorphisms). $[\alpha]_D^{30}$ −28° (c=1.0, pyridine). IR ν_{max} cm^{-1}: 3500 (OH) and 1663 (C=O). NMR: 2.63—4.40 (10H, aromatic protons), 6.04, 6.15, and 6.63 (each 3H, s., OCH_3), 7.46 (3H, s., N-CH_3). *Anal.* Calcd. for $C_{36}H_{34}O_7N_2$: C, 71.27; H, 5.65; N, 4.62. Found: C, 71.16; H, 5.87; N, 4.30. Stepinonine Hydrobromide, mp>300°. *Anal.* Calcd. for $C_{36}H_{34}O_7N_2 \cdot 2HBr \cdot 2H_2O$: C, 53.74; H, 5.02; N, 3.48. Found: C, 53.67; H, 5.02; N, 3.67. Stepinonine Oxalate, mp 208—210°. (decomp. with efferv.) (from C_2H_5OH: H_2O=2: 1). *Anal.* Calcd. for $C_{36}H_{34}O_7N_2 \cdot 2(COOH)_2 \cdot 1 \cdot 1/2H_2O$: C, 59.05; H, 5.08; N, 3.45. Found: C, 58.97; H, 5.22; N, 3.74.

Stepinonine Mono-acetate (1b)——To a solution of 41 mg of stepinonine (**1a**) in 4 ml of pyridine was added 1 ml of Ac_2O and the mixture was kept on standing for 2 days. Excess Ac_2O and pyridine was evaporated under reduced pressure and the residue was mixed with aqueous 1% NH_4OH and the mixture was extracted with ether. After drying over anhyd. Na_2SO_4, the solvent was removed and the crystalline residue was recrystallized from EtOH–ether to leave colorless prisms, mp 157°. $[\alpha]_D^{20}$ −12° (c=0.5, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1}: 1767 (OAc), 1662 (C=O). NMR: 2.63—4.40 (10H, aromatic protons), 6.02, 6.14, and 6.61 (each 3H, s., OCH_3). *Anal.* Calcd. for $C_{38}H_{36}O_8N_2 \cdot 1/2\ H_2O$: C, 69.39; H, 5.68. Found: C, 69.54; H, 6.26.

Tetrahydrostepinonine (2)——To a suspension of 50 mg of stepinonine (**1a**) in 15 ml of aqueous 95% MeOH was added 50 mg of $NaBH_4$ under stirring. The mixture became temporarily homogeous and then the crystalline substances were deposited. Stirring was continued for 5 hr and excess $NaBH_4$ was decomposed by addition of 3% AcOH. The solvent was removed and the residue was mixed with aqueous ammonia and the alkaline mixture was extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. Na_2SO_4. The solvent was removed to leave 48 mg of colorless needles (**2**), mp 173—174° (from $CHCl_3$). $[\alpha]_D^{29}$ +102° (c=1.0, $CHCl_3$). IR ν_{max} cm^{-1}: 3500 (OH). *Anal.* Calcd. for $C_{36}H_{38}O_7N_2 \cdot H_2O$: C, 68.77; H, 6.41. Found C, 68.85; H, 6.28.

N-Methyltetrahydrostepinonine (3)——To a solution of 50 mg of tetrahydrostepinonine (**2**) in 10 ml of MeOH was added 2 ml of 37% formaldehyde and the mixture was allowed to stand for 5 hr at room temperature. To this mixture was then added excess $NaBH_4$, and the mixture was stirred for several hr at room tenperature. After excess $NaBH_4$ was decomposed with 3% AcOH, the solvent was removed under reduced pressure. The residue was made alkaline with 3% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. Na_2SO_4 and evaporated to leave 46 mg of colorless oil. When triturated with acetone–C_6H_6, the residue was solidified and recrystallization from acetone–C_6H_6 gave colorless needles (**3**), mp 164°. $[\alpha]_D^{25}$ +102° (c=1.0, $CHCl_3$). IR ν_{max} cm^{-1}: 3500 (OH). NMR ($CDCl_3$/pyridine=2/1): 6.32, 6.60 and 6.82 (each 3H, s., OCH_3), 7.40 and 7.84 (each 3H, s., N-CH_3). *Anal.* Calcd. for $C_{37}H_{40}O_7N_2$: C, 71.13; H, 6.45. Found: C, 71.37; H, 6.65. Mass Spectrum m/e: 624 (M^+).

N,O-Dimethyltetrahydrostepinonine (4)——To a solution of 20 mg of N-methyltetrahydrostepinonine (**3**) in 10 ml of MeOH was added an ethereal diazomethane solution prepared from 3 g of nitrosomethylurea. The reaction mixture was kept on standing for 2 days and the solvent was evaporated. The residue was dissolved in 5% AcOH and the acidic solution was washed three times with ether. The aqueous layer was made alkaline with NH_4OH and extracted with ether. The ether extract was successively washed with aqueous 5% NaOH solution and water, dried and evaporated. The crystalline residue was recrystallized from MeOH–ether to give 12 mg of colorless prisms (**4**), mp 261—262° (decomp.). IR ν_{max} cm^{-1}: 3500 (OH). NMR: 6.12, 6.27, 6.55, and 6.82 (each 3H, s., OCH_3), 7.43 and 7.90 (each 3H, s., N-CH_3), 7.65 (1H, broad, OH). *Anal.* Calcd. for $C_{38}H_{42}O_7N_2$: C, 71.45; H, 6.63. Found: C, 71.46; H, 6.93.

Reductive Fission of N,O-Dimethyltetrahydrostepinonine (4) with Sodium in Liquid Ammonia——To a mixture of 200 ml of liquid ammonia and 50 ml of ether kept at −45° was added one after other a solution of 190 mg of N,O-dimethyltetrahydrostepinonine (**4**) in 50 ml of dry toluene and 0.4 g of sodium for 4 hr. Liquid ammonia was evaporated and the residue was extracted with 5% HCl. The aqueous acidic layer was made alkaline with 3% NaOH and the alkaline solution was made ammonia alkaline with NH_4Cl and extracted with ether. The ethereal extract was washed with water, dried and evaporated to leave 115 mg of red-yellowish oil. When triturated with MeOH, crystals came out. Crystals were separated by filtration and crystals deposited further from the mother liquor were separated as little as possible. Recrystallizations of crystals from MeOH–ether gave 35 mg of colorless prisms (**6**), mp 204°. $[\alpha]_D^{19}$ +20° (c=0.5, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3320 (OH). *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04. Found: C, 69.00; H, 7.31. Mass Spectrum m/e: 329 (M^+), 150 and 121. On the other hand, a solution of excess oxalic acid in ethanol was added to the mother liquor (virtually one spot on TLC, silica gel) freed from crystals. The crystalline oxalate was collected by filtration and recrystallization from ethanol gave 60 mg of colorless needles, mp 210—212°. The free base from this salt was obtained in the usual way and recrystallizations from ether–acetone gave 35 mg of colorless rods (**5**), mp 142—144°, $[\alpha]_D^{24}$ +117° (c=1.0, $CHCl_3$). A sample of this compound (**5**) was identified with an authentic sample of (S)-armepavine[5] by comparison of IR and NMR spectra.

The Compound (7)——To a solution of 9 mg of the compound (**6**) in 7 ml of MeOH was added an ethereal diazoethane solution prepared from 1 g of nitrosoethylurea and the reaction mixture was kept on standing for 4 days. The solvent was evaporated and the residue was dissolved in 10 ml of 1% HCl and the acidic solution was washed with ether, made alkaline with a NaOH solution and extracted with ether. The extract was dried over $MgSO_4$ and evaporated to leave 7 mg of colorless oil (**7**) which was purified through an alumina

column. The oil showed one spot on TLC (Al_2O_3–$CHCl_3$). IR ν_{max} cm^{-1}: 3310 (OH). NMR: 2.68—3.34 (6H, aromatic protons), 5.33 (1H, d,. J=1 Hz, C_1–H), 6.14 and 6.22 (each 3H, s., OCH_3), 6.58 (1H, d., J= 1 Hz, C_2–H), 7.88 (3H, s., N–CH_3), 8.60 (3H, t., J=7 Hz, OCH_2CH_3). Mass Spectrum *m/e*: 357 (M^+), 150 and 121. This oil was identified with a sample of synthetic compound (**15b**), the picrate of which gave correct analytical data, by comparison of IR and NMR spectra (*vide infra*).

The Keto-ester (10a)——To a solution of 3 g of *p*-ethoxyphenylacetic acid (**9a**) in 50 ml of CH_2Cl_2 was added 4.5 g of PCl_5 under ice-cooling. After the mixture was stirred for 1.5 hr, 3.0 g of $ZrCl_4$ was added, and the mixture was stirred for 30 min. To the mixture was added 2.1 g of methyl 3,4-dimethoxyphenyl acetate (**8a**). After being kept on standing overnight, the mixture was poured into ice water, made alkaline with an aq. Na_2CO_3 solution, and extracted with CH_2Cl_2. The extract was successively washed with an aq. $NaHCO_3$ solution, water, and dried over anhyd. K_2CO_3 and evaporated. When triturated with ether, the residue was solidified and recrystallizations from acetone–ether gave 2.56 g of colorless needles (**10a**), mp 125°, in 69% yield. IR ν_{max} cm^{-1}: 1730 (COOMe) and 1670 (C=O). NMR: 2.63—3.29 (6H, aromatic protons), 6.10, 6.15 and 6.33 (each 3H, s., OCH_3) and 8.62 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.43; H, 6.50.

The Keto-ester (10b)——The compound (**10b**) was synthesized from 3.0 g of *p*-methoxyphenylacetic acid (**9b**) and 2.4 g of methyl 3-methoxy-4-ethoxyphenylacetate (**8b**) in a similar manner as described above. The compound (**10b**: 2.3 g) was obtained as colorless rods, mp 88° in 60% yield. IR ν_{max} cm^{-1}: 1730 (COOMe) and 1670 (C=O). NMR: 2.60—3.26 (6H, aromatic protons), 6.10, 6.22 and 6.32 (each 3H, s., OCH_3) and 8.56 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.46; H, 6.38.

The Keto-ester (10c)——The compound (**10c**) was synthesized from 0.5 g of *p*-methoxyphenylacetic acid (**9c**) and 0.45 g of methyl 3-ethoxy-4-methoxyphenylacetate (**8c**) in a similar manner as above. The compound (**10c**: 0.5 g) was obtained as colorless needles, mp 125—126° in 67% yield. IR ν_{max} cm^{-1}: 1730 (COOMe) and 1670 (C=O). NMR: 2.60—3.27 (6H, aromatic protons), 6.13, 6.22, and 6.33 (each 3H, s., OCH_3), 8.52 (3H, t., J=7.5 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.52; H, 6.50.

The Keto-bromide (11a)——To a solution of 3.72 g of the keto-ester (**10a**) in 20 ml of $CHCl_3$ was added 1.6 g of bromine under ice-cooling and stirring at room temperature. Stirring was continued for 3 hr and throughout all reaction period, the flask was shielded from the light. The reaction mixture was successively washed with an aq. $NaHSO_3$ solution and water, and the organic solvent was evaporated under reduced pressure. When triturated with ether, the residue gave the crude keto-bromide (**11a**: 3.0 g) as crystals, mp 101—102°. IR ν_{max} cm^{-1}: 1731 (COOMe) and 1682 (C·Br·C=O). NMR: 2.48—3.25 (6H, aromatic protons), 3.70 (1H, s., CH·Br), 6.10, 6.20, and 6.32 (each 3H, s., OCH_3), 8.61 (3H, t., J=7 Hz, OCH_2CH_3). Mass Spectrum *m/e*: 451 (M^+). Because of its labile nature, the crude crystals were used for the further synthetic step.

The Keto-bromide (11b)——The keto-bromide (**11b**) was synthesized from 0.5 g of the keto-ester (**10b**) and 0.22 g of bromine in a similar manner as that in the synthesis of the compound (**11a**). The crude keto-bromide (**11b**: 0.5 g) was obtained as crystals, mp 103—105°. IR ν_{max} cm^{-1}: 1730 (COOMe) and 1680 (C–Br–C=O). NMR: 2.48—3.25 (6H, aromatic protons), 3.71 (1H, s., CH·Br), 6.10, 6.20, and 6.31 (each 3H, s., OCH_3), 8.59 (3H, t., J=7 Hz, OCH_2CH_3). Mass Spectrum *m/e*: 451 (M^+). Because of its labile nature, the crude keto-bromide (**11b**) was used for the next synthetic step.

The Keto-bromide (11c)——The keto-ester (**11c**) was synthesized from 0.5 g of the keto-ester in a similar manner as described above. The crude keto-bromide (**11c**: 0.44 g) was obtained as crystals, mp 102—107°. IR ν_{max} cm^{-1}: 1730 (COOMe) and 1680 (C·Br·C=O). Mass Spectrum *m/e*: 451 (M^+). Since the crude compound was too labile to further purification, the crude crystals were employed for the next synthetic step.

The Lactam-alcohol (12a: *trans* Isomer)——To a solution of 1 g of the crude keto-bromide (**11a**) in 50 ml of dioxane was added a solution of 67 mg of $MeNH_2$ in a small amount of dioxane after the atmosphere had been replaced with N_2. The reaction mixture was kept on standing overnight and made acidic by addition of one drop of 48% HBr solution. The organic solvent was removed under 60° *in vacuo* and the residue was dissolved in aqueous MeOH solution. To this solution was added portionwise 2 g of $NaBH_4$ under cooling and the mixture was stirred for 1.5 hr. Then, the solvent was removed, and the residue was mixed with water, and extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. K_2CO_3 and evaporated. When triturated with acetone–ether, the residue was solidified. Recrystallization from ether gave 0.28 g of colorless prisms, mp 182—184°, (**12a**: *trans* isomer). IR ν_{max} cm^{-1}: 3400 (OH) and 1620 (CO·N). NMR: 2.75—3.33 (6H, aromatic protons), 4.88 (1H, d.d., J=5 Hz, J=8 Hz, C_1–H), 5.64 (1H, d., J=8 Hz, C_2–H), 6.16 (6H, s., 2×OCH_3) and 7.05 (1H, d., J=5 Hz, This signal disappeared, when treated with D_2O). *Anal.* Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78. Found: C, 67.65; H, 6.97.

The Lactam-alcohol (12b: *trans* Isomer)——To a solution of 0.76 g of the keto-bromide (**11b**) in 20 ml of dioxane was added a solution of excess $MeNH_2$ (about 10 times of mol. equivalent*) in a small amount of dioxane, after the atmosphere had been replaced with N_2. The reaction mixture was heated at 80—90° for 10 min, made acidic with 48% HBr solution and evaporated under reduced pressure. The residue was dissolved in MeOH and excess $NaBH_4$ (*ca.* 1.5 g)* was added to this solution. After the reaction mixture was kept on standing overnight and worked up in a similar manner as that in the case of the compound

(12a). Recrystallizations from acetone–ether gave 0.39 g of colorless needles, mp 194—196° (12b: *trans* isomer). IR ν_{max} cm^{-1}: 3380 (OH) and 1625 (CO–N). NMR: 2.75—3.31 (6H, aromatic protons), 4.88 (1H, d., J=8 Hz, C_1–H), 5.59 (1H, d., J=8 Hz, C_2–H), 6.15 and 6.20 (each 3H, s., OCH_3), 7.02 (1H, broad s., OH), 7.28 (3H, s., N–CH_3) and 8.60 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{25}O_5N \cdot 1/3H_2O$: C, 66.79; H, 6.83. Found: C, 66.96; H, 6.71. Mass Spectrum *m/e*: 371 (M^+). (* In this case, excess $MeNH_2$ and excess $NaBH_4$ were employed and the reaction mixture was heated for a short time. A good yield of (12b) was obtained compared with that in the case of synthesis of the compound (12a).)

The Lactam-alcohol (12c: *trans* Isomer)——The lactam-alcohol (12c: *trans* isomer) was synthesized from 2.0 g of the crude keto-bromide (11c) in a similar manner as that in the compound (12b: *trans* isomer). Recrystallizations of the crude product from acetone–ether gave 0.53 g of colorless prisms (12c), mp 195—198°. IR ν_{max} cm^{-1}: 3370 (OH) and 1620 (CO–N). NMR: 2.20—3.32 (6H, m., aromatic protons), 4.89 (1H, d., J=8 Hz, C_1–H), 5.60 (1H, d., J=8 Hz, C_2–H), 6.17 and 6.20 (each 3H, s., OCH_3), 7.02 (1H, broad s., OH), 7.29 (3H, s., N–CH_3) and 8.55 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{25}O_5N \cdot 1/2H_2O$: C, 66.37; H, 6.89. Found: C, 66.26; H, 6.61.

The Keto-lactam (13a)——To a solution of 50 mg of the lactam-alcohol (12a: *trans* isomer) in 10 ml of acetone was added 5 drops of Jones' reagent under ice-cooling. The reaction mixture was stirred for 15 min and excess reagent was decomposed with MeOH. The mixture was filtered and the residue was washed with water several times. The filtrate and washings were combined and evaporated under reduced pressure. The residue was mixed with a small amount of water and extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. K_2CO_3 and evaporated to leave an oil. This oil in $CHCl_3$ was chromatographed on an alumina column and the eluate was recrystallized from acetone–ether to give 38 mg of colorless prisms, (13a), mp 142—146°, in 60% yield. IR ν_{max} cm^{-1}: 1652 (CO). NMR: 2.23—3.36 (6H, aromatic protons), 4.58 (1H, s., C_2–H), 6.03 and 6.08 (each 3H, s., OCH_3), 6.70 (3H, s., N–CH_3), 8.59 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{23}O_5N$: C, 68.28; H, 6.28. Found: C, 68.33; H, 6.41.

The Keto-lactam (13b)——To a solution of 25 mg of the lactam-alcohol (12b: *trans* isomer) in 7 ml of acetone was added 3 drops of Jones' reagent under cooling. The reaction mixture was worked up in a similar manner as above to give 19 mg of colorless oil (13b). IR ν_{max} cm^{-1}: 1652 (CO). NMR: 2.21—3.38 (6H, aromatic protons), 4.60 (1H, s., C_2–H), 6.10 and 6.20 (each 3H, s., OCH_3), 6.71 (3H, s., N–CH_3) and 8.51 (3H, t., J=7 Hz, OCH_2CH_3) Mass Spectrum *m/e*: 369 (M^+).

The Keto-lactam (13c)——To a solution of 300 mg of the lactam-alcohol (12c: *trans* isomer) in 40 ml of acetone was added 1 ml of Jones' reagent under ice-cooling. The reaction mixture was worked up in a similar manner as above to give 180 mg of colorless prisms (13c), mp 152°, from acetone–ether, in 61% yield. IR ν_{max} cm^{-1}: 1652 (CO). NMR: 2.23—3.40 (6H, aromatic protons), 4.60 (1H, t., J=1 Hz, C_2–H), 6.04 and 6.20 (each 3H, s., OCH_3), 6.70 (3H, s., N–CH_3), 8.52 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{23}O_5N \cdot 1/2H_2O$: C, 66.72; H, 6.40. Found: C, 66.93; H, 6.11.

The Lactam-alcohol (14a: *cis* Isomer)——To a solution of 1.0 g of the keto-lactam (13a) in 50 ml of MeOH was added portionwise 0.1 g of $NaBH_4$ under stirring and ice-cooling. The reaction mixture was kept on standing overnight at room temperature and the solvent was evaporated under reduced pressure. The residue was mixed with a small amount of water and extracted with $CHCl_3$. The extract was washed with water, dried over anhyd. K_2CO_3 and evaporated. When triturated with acetone–ether, the residue was solidified. Recrystallization from acetone–ether gave 68 mg of colorless prisms (14a), mp 172—174°, in 67% yield. IR ν_{max} cm^{-1}: 3350 (OH) and 1610 (CO–N). NMR: 2.95—3.41 (6H, aromatic protons), 4.50 (1H, d.d., J=3 Hz, J=7 Hz, C_1–H: This signal changed to a doublet (J=3 Hz) by treatment with D_2O), 5.17 (1H, d., J=3 Hz, C_2–H), 6.13 and 6.31 (each 3H, s., OCH_3), 6.97 (1H, d., J=7 Hz, OH; This signal disappeared when treated with D_2O), 7.30 (3H, s., N–CH_3) and 8.60 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78. Found: C, 67.60; H, 6.76.

The Lactam-alcohol (14b: *cis* Isomer)——To a solution of 50 mg of the keto-lactam (13b) in 10 ml of MeOH was added portionwise 150 mg of $NaBH_4$ under cooling and stirring, and stirring was continued for 1.5 hr. The reaction mixture was worked up in a similar manner as above to give 33 mg of colorless prisms (14b), mp 166—168° (from acetone–ether) in 66% yield. IR ν_{max} cm^{-1}: 3390 (OH) and 1615 (CO–N). NMR: 2.95—3.43 (6H, aromatic protons), 4.51 (1H, broad s., C_1–H: This signal changed to a doublet (J=3 Hz), when treated with D_2O), 5.15 (1H, d., J=3 Hz, C_2–H), 6.14 and 6.23 (each 3H, s., OCH_3), 7.29 (3H, s., N–CH_3) and 8.71 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{25}O_5N \cdot 1/3H_2O$: C, 66.79; H, 6.83. Found: C, 66.98; H, 6.73. Mass Spectrum *m/e*: 371 (M^+).

The Lactam-alcohol (14c: *cis* Isomer)——To a solution of 50 mg of the keto-lactam (13c) in 10 ml of MeOH was added portionwise 0.13 g of $NaBH_4$ and stirring was continued for 1.5 hr. The reaction mixture was worked up in a similar manner as above to give 33 mg of colorless prisms (14c), mp 165—167° (from acetone–ether) in 66% yield. IR ν_{max} cm^{-1}: 3360 (OH) and 1615 (CO–N). NMR: 2.97—3.46 (6H, aromatic protons), 4.53 (1H, d., J=3 Hz, C_1–H), 5.18 (1H, d., J=3 Hz, C_2–H), 6.24 and 6.32 (each 3H, s., OCH_3), 7.30 (3H, s., N–CH_3) and 8.55 (3H, t., J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{21}H_{25}O_5N \cdot 1/2H_2O$: C, 66.37; H, 6.90. Found: C, 66.28; H, 6.97.

The Amino-alcohol (15a: *cis* Isomer): 7,8-Dimethoxy-4′-ethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol——A solution of 0.21 g of the lactam-alcohol (14a: *cis* isomer) in 3 ml of tetrahydro-

furan was diluted with 60 ml of ether. To this solution was added portionwise 0.2 g of $LiAlH_4$ and the reaction was refluxed for 20 hr. Excess $LiAlH_4$ was decomposed with wet ether and the reaction mixture was filtered. The residue was washed with ether. The filtrate and washings were conbined and evaporated. The residue was dissolved in 40 ml of ether and extracted with 5% AcOH. The aqueous acidic solution was made alkaline with ammonia and extracted with $CHCl_3$. The extract was washed with water and the solvent was evaporated to leave 0.18 g of yellow oil. This oil in $CHCl_3$ was chromatographed on a silica gel column to give 0.1 g of colorless oil (**15a**: *cis* isomer). IR ν_{max} cm^{-1}: 3320 (OH). NMR: 2.77—3.35 (6H, aromatic protons), 5.31 (1H, d., $J=1$ Hz, C_1–H), 6.14 and 6.21 (each 3H, s., OCH_3), 6.58 (1H, d., $J=1$ Hz, C_2–H), 7.89 (3H, s., N–CH_3) and 8.60 (3H, t., $J=7$ Hz, OCH_2CH_3). Mass Spectrum *m/e*: 357 (M^+), 164 and 135. The picrate, yellow prisms, has mp 112—116° (from acetone). *Anal.* Calcd. for $C_{27}H_{30}O_{11}N_4$: C, 55.29; H, 5.16. Found: C, 55.35; H, 5.14.

The Amino-alcohol (15b: *cis* Isomer): 7,4′-Dimethoxy-8-ethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol——To a suspension of 80 mg of the lactam-alcohol (**14b**: *cis* isomer) in 3 ml of tetrahydrofuran and 30 ml of ether was added 80 mg of $LiAlH_4$. The reaction mixture was worked up in a similar manner as above to give 60 mg of colorless oil (**15b**: *cis* isomer). IR ν_{max} cm^{-1}: 3310 (OH). NMR: 2.68—3.34 (6H, aromatic protons), 5.33 (1H, d., $J=1$ Hz, C_1–H), 6.14 and 6.22 (each 3H, s., OCH_3), 6.58 (1H, d., $J=1$ Hz, C_2–H), 7.88 (3H, s., N–CH_3) and 8.60 (3H, t., $J=7$ Hz, OCH_2CH_3). Mass Spectrum *m/e*: 357 (M^+), 150 and 121. The picrate, yellow plates (from acetone) melted at 138—140°. *Anal.* Calcd. for $C_{27}H_{30}O_{11}N_4 \cdot 1/2H_2O$: C, 54.46; H, 5.25. Found: C, 54.40; H, 5.33.

The Amino-alcohol (15c: *cis* Isomer): 8,4′-Dimethoxy-7-ethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol——To a suspension of 200 mg of the lactam-alcohol (**14c**: *cis* isomer) in 3 ml of tetrahydrofuran and 60 ml of ether was added 200 mg of $LiAlH_4$. The reaction mixture was worked up in a similar manner as above to give 120 mg of colorless oil (**15c**: *cis* isomer). IR ν_{max} cm^{-1}: 3350 (OH). NMR 2.67—3.32 (6H, aromatic protons), 5.30 (1H, d., $J=1$ Hz, C_1–H), 6.20 (6H, s., $2\times OCH_3$), 6.63 (1H, d., $J=1$ Hz, C_2–H), 7.87 (3H, s., N–CH_3) and 8.54 (3H, t., $J=7$ Hz, OCH_2CH_3). Mass Spectrum *m/e*: 357 (M^+), 150 and 121. The picrate, yellow prisms (from acetone) melted at 208—211°. *Anal.* Calcd. for $C_{27}H_{30}O_{11}N_4$: C, 55.29; H, 5.16. Found: C, 55.18; H, 5.04.

O-Ethyl-N-methyltetrahydrostepinonine (16)——To a solution of 670 mg of N-methyltetrahydrostepinonine (**3**) in 45 ml of EtOH was added an ethereal diazoethane solution prepared from 5 g of nitrosoethylurea. The reaction mixture was kept on standing for 1 day and excess diazoethane was decomposed with 3% AcOH. The solvent was evaporated and the residue was dissolved in AcOH solution. After washing with ether, the acidic solution was made alkaline with an aqueous 5% NaOH solution, and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated. The residue in $CHCl_3$ was purified through an alumina column. Recrystallizations of a crystalline mass from MeOH gave 450 mg of colorless prisms (**16**), mp 255—260° (decomp.). IR ν_{max} cm^{-1}: 3510 (OH). NMR: 2.63—3.72 (10H, aromatic protons), 6.24, 6.54 and 6.80 (each 3H, s., OCH_3), 7.40 and 7.89 (each 3H, s., N–CH_3), 8.57 (3H, t., $J=7$ Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{39}H_{44}O_7N_2 \cdot H_2O$: C, 69.83; H, 6.69. Found: C, 70.03; H, 6.66.

Oxidation of O-Ethyl-N-methyltetrahydrostepinonine (16) with $KMnO_4$——To a solution of 160 mg of O-ethyl-N-methyltetrahydrostepinonine (**16**) in 5 ml of MeOH was added five drops of CH_3I and the mixture was kept on standing for 1 day. The solvent was evaporated. To a solution of the residue in 5 ml of acetone was added dropwise 150 ml of a saturated solution of $KMnO_4$ in water under stirring at 60—65° for 5 hr. The reaction mixture was kept on standing for 1 day at room temperature under stirring. Excess $KMnO_4$ was decomposed with $NaHSO_3$ and 5% HCl solution. The reaction mixture was concentrated under reduced pressure and extracted with AcOEt. The extract was reextracted with 5% Na_2CO_3 solution. The alkaline solution was made acidic with 5% HCl and extracted with AcOEt. The aqueous layer was then continuously extracted with AcOEt. The combined AcOEt extracts were dried over $MgSO_4$ and evaporated to leave a solid mass. Recrystallizations from MeOH gave 10 mg of colorless prisms (**17**), mp 276—281°. IR ν_{max} cm^{-1}: 1675 (CO) and 1160 (–O–). A sample of **17** was identified with an authentic sample[11] by mixed melting point determination.

Reductive Fission of the Deuterated Compound (18) with Sodium in Liquid Ammonia——A suspension of 390 mg of O-ethyl-N-methyltetrahydrostepinonine (**16**) in 3 ml of 5% DCl, in D_2O, 20 ml of D_2O, and 2 ml of EtOD was heated at 125—130° for 100 hr in a sealed tube. The organic solvent was removed and the remaining solution was made alkaline with an aqueous NaOH solution and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated. When triturated with acetone–ether, the residue was crystallized. Recrystallization from the same solvent gave 270 mg of the deuterated compound (**18**). IR ν_{max} cm^{-1}: 3500 (OH). NMR: 2.63—3.72 (8.5 H, aromatic protons; Compared with the compound (**16**), a signal at 3.64 disappeared and integrated intensity of a signal at 3.50 is reduced to one-half), 6.25, 6.55, and 6.81 (each 3H, s., OCH_3), 7.41 and 7.90 (each 3H, s., N–CH_3), and 8.58 (3H, t., $J=7$ Hz, OCH_2CH_3). To a solution of 250 mg of the compound (**18**) in 200 ml of liquid ammonia and 40 ml of ether kept at −70° was added portionwise 0.6 g of sodium until the blue color of the reaction mixture had been maintained. The mixture was stirred further for 5.5 hr and evaporated at room temperature. The residue was dissolved in an aqueous 5% NaOH solution. The NaOH alkaline solution was made ammonia alkaline with NH_4Cl and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4

and evaporated to leave 200 mg of an oil. This oil was treated with the same manner as described in the reductive fission of the compound (**4**) with sodium in liquid ammonia (*vide ante*). The compound (**19**) was obtained as colorless prisms, mp 134—137° (60 mg; from acetone–ether) which were identified with an authentic sample of S-[5-D]-armepavine.[12] The compound (**20**) was obtained as colorless prisms, mp 181—184° (30 mg: from acetone–ether). NMR 2.70—3.55 (5.5H, aromatic protons), 5.48 (1H, s., C_1–H), 6.13 (3H, s., OCH_3), 6.57 (1H, s., C_2–H), 7.87 (3H, s., N–CH_3), and 8.60 (3H, t., $J=7$ Hz, OCH_2CH_3). Mass Spectrum *m/e*: 343 (M^+), 344 (M^++1), 164 and 135.

The Compound (**21**)——To a solution of 12 mg of the compound (**20**) in 60 ml of MeOH was added an ethereal diazomethane solution prepared from 5 g of nitrosomethylurea. The mixture was kept on standing for 2 days. The organic solvent was evaporated, and the residue was mixed with a 5% NaOH solution and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$ and evaporated to leave 5 mg of an oil (**21**). Mass Spectrum *m/e*: 357 (M^+), 358 (M^++1), 164 and 135. A sample of this oil was identified with a sample of the compound (**15a**: racemate), the picrate of which gave correct analytical data, by comparison of IR and NMR spectra (*vide ante*).