Studies on the Syntheses of Heterocyclic Compounds. 715.[1] Stevens Rearrangement of *cis*-and *trans*-Berbine Methiodides by Sodium Bis(2-methoxyethoxy)aluminum Hydride

Tetsuji Kametani,* Shyh-Pyng Huang, Chizuko Koseki, Masataka Ihara, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Received April 27, 1977

Refluxing the *cis*- and *trans*-berbine methiodides in the presence of sodium bis(2-methoxyethoxy)aluminum hydride in dioxane gave rise to Stevens rearrangement to afford the spirobenzylisoquinolines and the 8-methylberbines. Studies using deuterium labeled substrates or optically active compounds have made clear the following matters. Quasi-axially oriented hydrogens at the C_8 and C_{14} positions of berbine methiodides were independently abstracted by the complex hydride. The *trans*-quinolizidinium methiodides gave the spirobenzylisoquinolines with retention of the stereochemistry at the C_8 and C_{14} positions and the 8-methylberbines with inversion at the C_8 position. On the other hand, the cis methiodides yielded the spirobenzylisoquinolines with retention at the C_8 and inversion at the C_{14} position, and the 8-methylberbines with retention at the C_8 position.

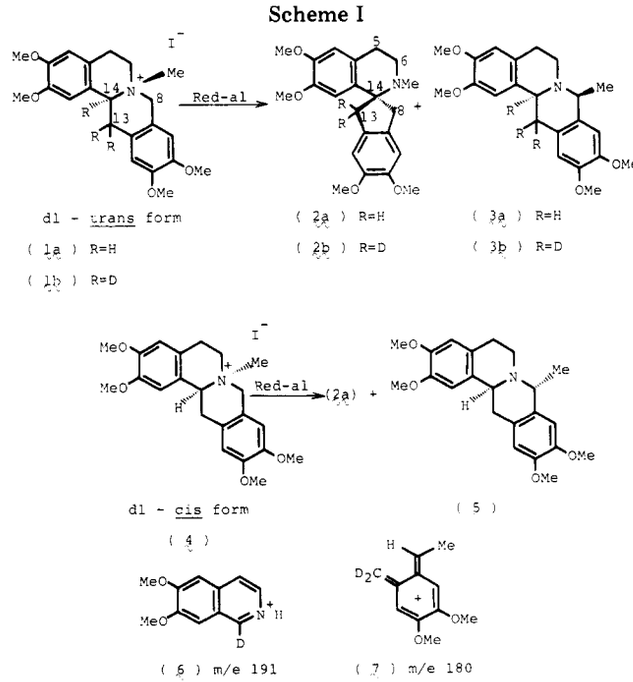
In the course of our investigation of the hydrogenolysis with sodium bis(2-methoxyethoxy)aluminum hydride (Red-al),[2] we found the Stevens type rearrangement of berbine methiodides yielding spirobenzylisoquinolines and 8-methylberbines.[3] The rearrangement of quaternary berbines to spirobenzylisoquinolines with strong bases has already been reported by two other groups.[4,5] Radical anion intermediate has been suggested for Stevens rearrangement.[6] Furthermore, the retention of the stereochemistry on the migrating group during the rearrangement was known.[3,7] However, the stereochemistry at the carbon anion formed has not yet been studied. It was hoped that the Stevens reaction of the quaternary quinolizidine would reveal the stereochemical requirement for the rearrangement. Therefore, we studied the relationship between the configuration of the quinolizidinium salt and the stereochemistry of the products and here wish to report our interesting findings.

(±)-Xylopinine was heated with methyl iodide in methanol to give a mixture of the methiodides, which were separated into the trans (**1a**) and cis (**4**) methiodides applying low solubility of the trans isomer in chloroform. The stereochemistry was determined by the comparison of the NMR spectra in Me_2SO-d_6;[3] the chemical shift of an *N*-methyl group of the quaternary trans isomer (**1a**) appeared at a higher field (δ 2.85) than that of the cis one (**4**) (δ 3.20). Refluxing the trans methiodide (**1**) with an excess of sodium bis(2-methoxyethoxy)aluminum hydride in dioxane for 24 h under nitrogen gave the spirobenzylisoquinoline (**2a**) in 77% yield and (±)-coralydine (**3a**)[8,9] in 6% yield. On the other hand, the cis isomer (**4**) yielded the spirobenzylisoquinoline (**2a**) in 51% yield and (±)-*O*-methylcorytenchirine (**5**)[9] in 20% yield under the same reaction conditions as above. These facts supported that the quaternary *N*-methyl groups shifted to the same side at the C_8 position to give the 8-methylberbines.

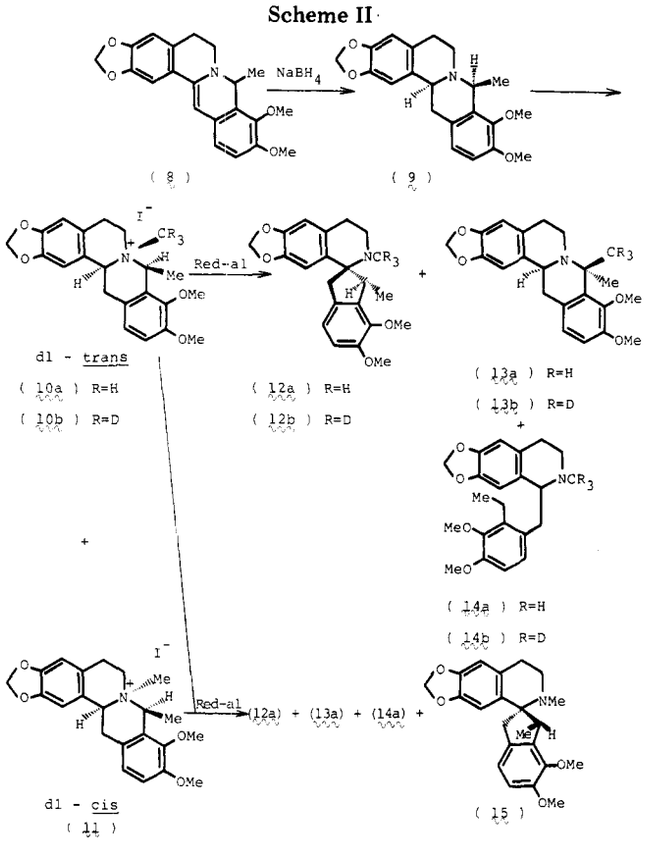
It was assumed that the anion first formed at the C_{14} position abstracted the α-hydrogen at the C_8 position and the anion at the C_8 position resulted in Stevens rearrangement yielding the 8-methylberbines. In order to examine this assumption the reaction of (±)-*trans*-[13,13,14-$^2H_3$]xylopinine methiodide (**1b**) was carried out under the same reaction conditions as above. This trideuterated compound (**1b**) was prepared from the corresponding free base.[10] Coralydine (**3b**) formed in 22.5% yield by the above reaction carried three deuterium atoms. The same spectrum showed a new parent ion at *m/e* 372, three mass units higher than that corresponding to the undeuterated authentic sample (**3a**), and the intensity was found to be more than 95% of trideuterio compound. Furthermore, the isoquinolinium ion (**6**) appeared at *m/e* 191, while the ion (**7**) formed by retro-Diels–Alder fragmentation was observed at *m/e* 180 as a base peak. The 13,13-dideuteriospirobenzylisoquinoline (**2b**) was obtained in 47% yield. The poorer yield of **2b** compared with the case of the nonlabeled compound would be partly due to the isotope effect of the deuterium at the C_{14} position. It was thus made clear that the anions were formed independently at the C_8 and C_{14} positions by the attack of the complex hydride.

Then, we presumed that abstraction of the quasi-axially oriented α hydrogen at the C_8 position of the trans isomer (**1a** and **1b**), followed by an inversion and an attack of the resulting anion at the C_8 position to the quaternary *N*-methyl group, gave the 8-methylberbine (**3a** and **3b**), since the antarafacial shift of the methyl group could not be expected. In order to clarify this assumption, the Stevens-type rearrangements of the trans [N-CD_3]methiodide (**10b**) of the 8β-methylberbine (**9**) and the trans methiodide (**18**) of the 8β-ethylberbine (**17**) were undertaken. (±)-8β-Methylcanadine (**9**), which was synthesized by reduction of the 8-methyldihydroberberine (**8**)[11] with sodium borohydride, was converted, on heating with methyl iodide in acetonitrile, into a 5:4 mixture of the trans (**10a**) and cis (**11**) methiodides. The trans methiodide (**10a**) showed the *N*-methyl group at δ 2.76 as a singlet and the 8-methyl group at δ 1.93 as a doublet with

Scheme I



Scheme II



J = 8 Hz, while the N-methyl and the 8-methyl groups of the cis isomer (**11**) appeared respectively at δ 3.15 as a singlet and δ 1.67 as a doublet with J = 8 Hz in the NMR spectra in Me_2SO-d_6. The trans one (**10a**), which was isolated as a pure form by recrystallization from methanol, was heated with the complex hydride under the same conditions as above for 24 h to furnish the spirobenzylisoquinoline (**12a**) in 9.4% yield, the 8,8-dimethylberbine (**13a**) in 22.5% yield, and 1-(2-ethyl-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (**14a**) in 15% yield. The methyl group at the C_8 position of the spirobenzylisoquinoline (**12a**) was observed at δ 1.30 as a doublet with J = 7 Hz indicating that the methyl group exists syn to the nitrogen atom.[3] The structures of **13a** and **14a** were confirmed by analyses of the NMR and mass spectra. Then the trans [N-CD_3]methiodide (**10b**) was treated under the same conditions. The NMR spectrum ($CDCl_3$) of the 8,8-dimethylberbine (**13b**), which was formed together with **12b** and **14b**, exhibited one quaternary methyl group at δ 1.52 with a disappearance of the other methyl group, which was observed at δ 1.72 in that of the undeuterated sample (**13a**). The α-methyl group, oriented quasi-axially at the C_8 position of **13a**, was expected to resonate at a higher field than the β-methyl group oriented quasi-equatorially.[9] The above finding thus indicated the inversion of the stereochemistry at the C_8 position during the shift of the quaternary N-methyl group to the carbon at the C_8 position in the trans methiodides.

The above fact was further supported by the reaction of the methiodides (**18** and **19**) of the 8β-ethylberbines, which were prepared as follows. Sodium borohydride reduction of the sulfate (**16**)[12] in methanol yielded stereoselectively the 8β-ethylberbine (**17**), which was alternatively synthesized by photocyclization[13] of the enamide (**25**), followed by reduction with sodium borohydride of **26**, debenzylation of **27**, and methylation with diazomethane of the resulting phenol (**28**). The above enamide (**25**) obtained by condensation of the dihydroisoquinoline (**24**) hydrochloride with propionic anhydride in pyridine showed two maxima due to absorptions at 330 and 293 nm with log ϵ 4.14 and 3.97, respectively, indicating the Z form.[14]

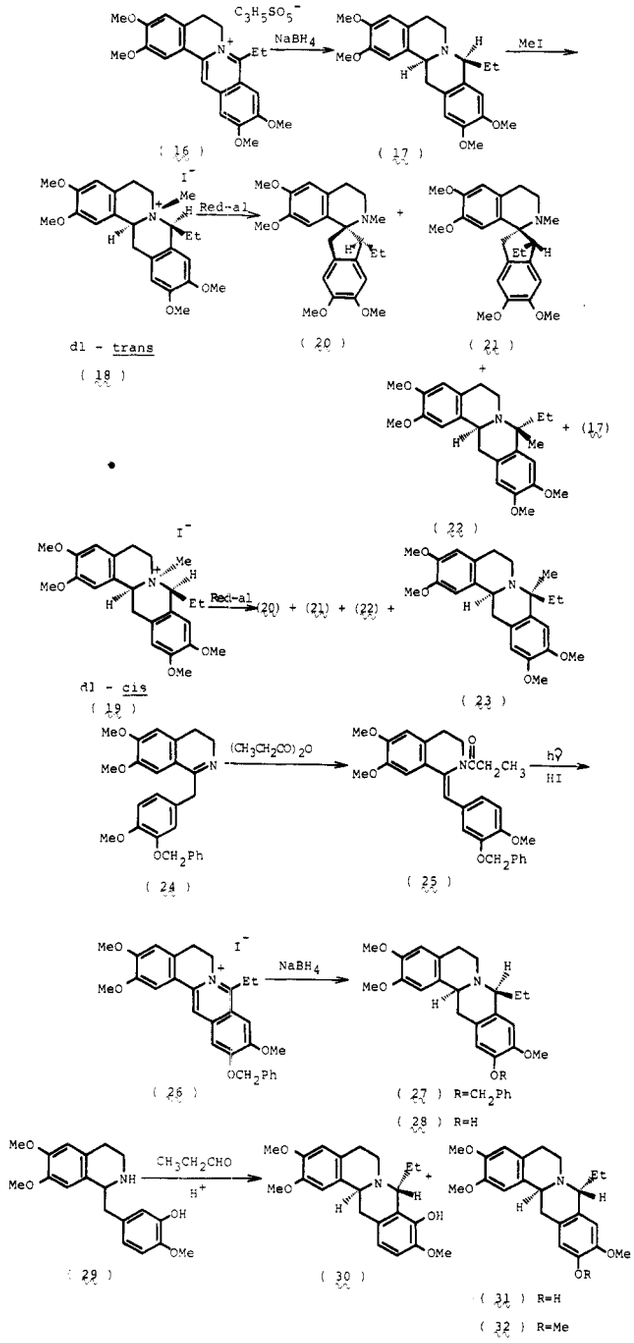
The stereochemistry of **17** was confirmed by the spectral comparison with the stereoisomer (**32**) synthesized as follows. Mannich reaction of the phenolic isoquinoline (**29**) hydrochloride with propionaldehyde in acetic acid gave a separable mixture of two positional isomers (**30** and **31**). The former compound (**30**), obtained in 47.8% yield, showed two aromatic protons at δ 6.48 and 6.77 with ortho coupling constant having J = 10 Hz in the NMR spectrum measured in Me_2SO-d_6 and a positive Gibbs indophenol test.[15] The latter (**31**), which was gained in 22.7% yield and showed a negative Gibbs indophenol test,[15] was transformed into **32** by a treatment with diazomethane. The above three compounds (**30**, **31**, and **32**) exhibited no *trans*-quinolizidine bands in their IR spectra ($CHCl_3$) and the hydrogen of the C_{14} position at δ ca. 4.2 as a triplet, while **17** and **28** showed *trans*-quinolizidine bands at 2700–2800 cm^{-1} and the angular proton signal at a higher field than δ 3.8, which indicated the hydrogens at the C_8 and C_{14} positions of the compounds **17** and **28** to be cis to each other.[9]

Treatment of **17** with methyl iodide in acetonitrile for 3 days at room temperature afforded a mixture of the methiodides, recrystallization of which from methanol easily separated the trans (**18**) and cis (**19**) isomers in 41.6 and 50.5% yields, respectively. The former (**18**) showed the quaternary N-methyl group at δ 2.77, whereas the latter (**19**) exhibited it at δ 3.57 in the NMR spectra ($CDCl_3$).[3] Treatment of the trans methiodide (**18**) with the complex hydride for 24 h gave the spirobenzylisoquinolines (**20**), the 8α-ethyl-8β-methylberbine (**22**), and the N-demethylated product (**17**) in 31, 15.2, and 9.1% yield, respectively, in addition to a trace amount of the stereoisomer (**21**) of **20**. On the other hand, the cis isomer (**19**) afforded **21** and the stereoisomer (**23**) of **22** in 20.3 and 17.2% yield, respectively, together with a trace amount of **20** and **22**. The quaternary methyl group of **22** was observed at a more deshielded field at δ 1.52 than that of **23** at δ 1.37, supporting that the compound **22** has a quasi-equatorially oriented β-methyl group as shown in the structural formula. It was therefore revealed that the quasi-axially oriented α hydrogen at the C_8 position of the trans methiodides was attacked by the complex hydride and the resulting anion gave the 8-methylberbines with the inversion of the stereochemistry at the C_8 position, while the cis methiodides gave the 8-methylberbines without inversion.

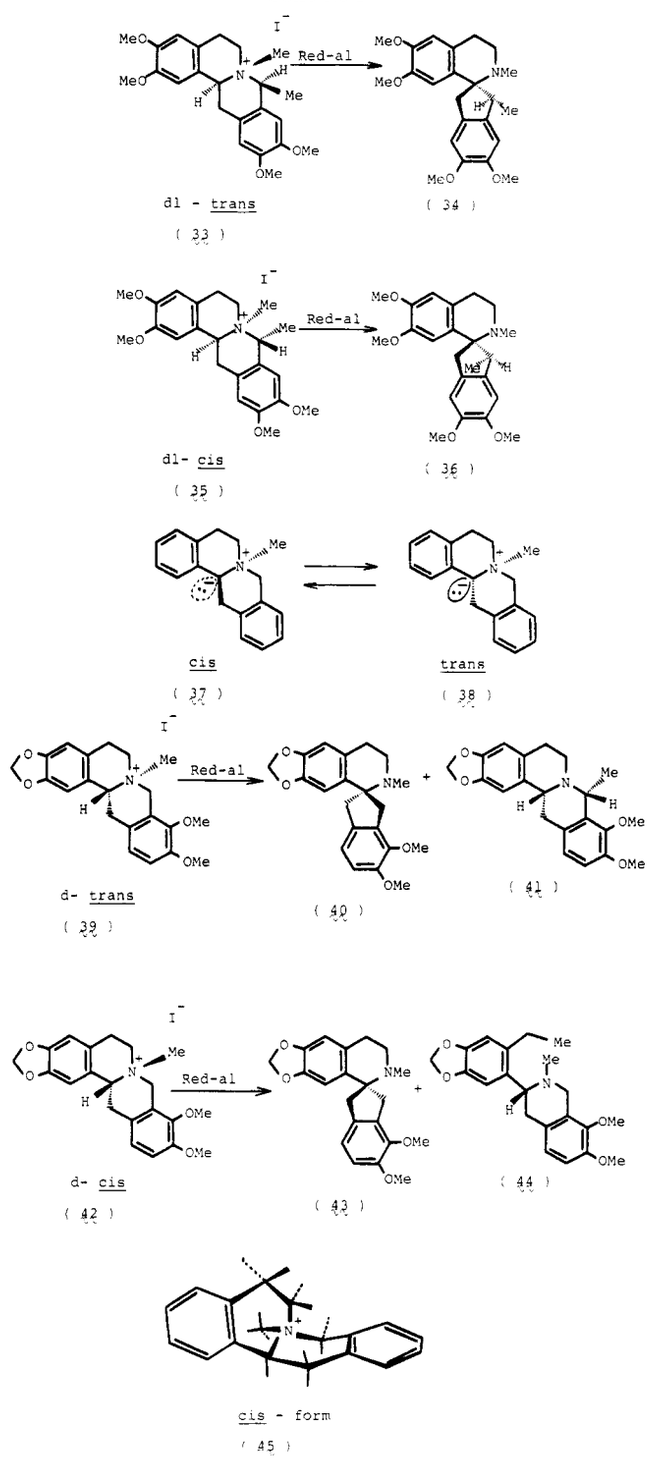
In the previous paper,[3] we deduced the retention of the configuration at the migrating atom in the Stevens rearrangement because the trans methiodides **33** and **35** afforded mainly the spirobenzylisoquinolines **34** and **36**, respectively. It was thus interesting that the stereoisomer **21** was obtained as one of the main products from the cis methiodide **19**. Furthermore, a 1:1 mixture of the trans and cis methiodides (**10a** and **11**) gave the stereoisomer (**15**) of **12a**, which was not obtained by the reaction using the pure trans methiodide (**10a**) as described above. We could account for this phenomenon as follows. The anion (**37**) formed at the C_{14} position of the cis methiodides would cause the inversion and the resulting *trans*-quinolizidinium ion (**38**) gave rise to the rearrangement to the spirobenzylisoquinolines.[16] Since the energy barrier for inversion of the anion is expected to be less than 6 kcal/mol,[17] the interchange of the betaines (**37** and **38**) would occur very easily as the case of the free bases of dibenzo[*a*,*g*]quinolizidines.[18]

Therefore the optically active (*R*)-(+)-canadine[19] was transformed into a mixture of the methiodides, fractional recrystallization of which furnished the trans isomer (**39**) in 51% yield and the cis one (**42**) in 20.7% yield. The former (**39**), which showed its quaternary N-methyl group at δ 2.83 in the NMR spectrum (Me_2SO-d_6),[3] gave the (−)-spirobenzyliso-

Scheme III



Scheme IV



quinoline (**40**)[5] and the (+)-8β-methylberbine (**41**) on refluxing with the complex hydride in dioxane. On the other hand, the latter (**42**), which exhibited the methyl group at δ 3.22 in the NMR spectrum (Me_2SO-d_6),[3] yielded the (+)-spirobenzylisoquinoline (**43**)[5] and (+)-3-(2-ethyl-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-methylisoquinoline (**44**). The CD spectrum (methanol) of **40** showed two Davydov splittings centered at 276 and 205 nm, corresponding to the A → Lb and A → B bands, respectively, with negative first Cotton effects, whereas **43** showed a symmetrical curve of **40** as shown in Figure 1, indicating the absolute configurations of **40** and **43** to be 14*S* and 14*R*, respectively.[5,20]

On the consideration of the above findings, the conformation of the *cis*-quinolizidinium methiodides would exist in a more distorted form than a typical cis form (**45**)[21] having two half-chair conformations. It was thus estimated that the orientation of the anion at the C_{14} position of the cis methiodide is not favorable for the rearrangement.

Furthermore, we may again emphasize that the chemical shift of the quaternary *N*-methyl group in the NMR spectrum which is measured in Me_2SO-d_6 or $CDCl_3$ provides a good criterion to distinguish the *trans*- and *cis*-quinolizidinium iodides.

We can summarize the above Stevens rearrangement of berbine methiodides as follows. Quasi-axially oriented hydrogens at the C_8 and C_{14} positions of berbine methiodides were predominantly abstracted by sodium bis(2-methoxyethoxy)aluminum hydride in hot dioxane. In the case of the *trans*-quinolizidinium ions, the stereochemistry at the C_8 and C_{14} positions was retained during the conversion into the spirobenzylisoquinolines, and the 8-methylberbines were formed with the inversion of the configuration at the C_8 position. On the other hand, the *cis*-quinolizidinium ions gave

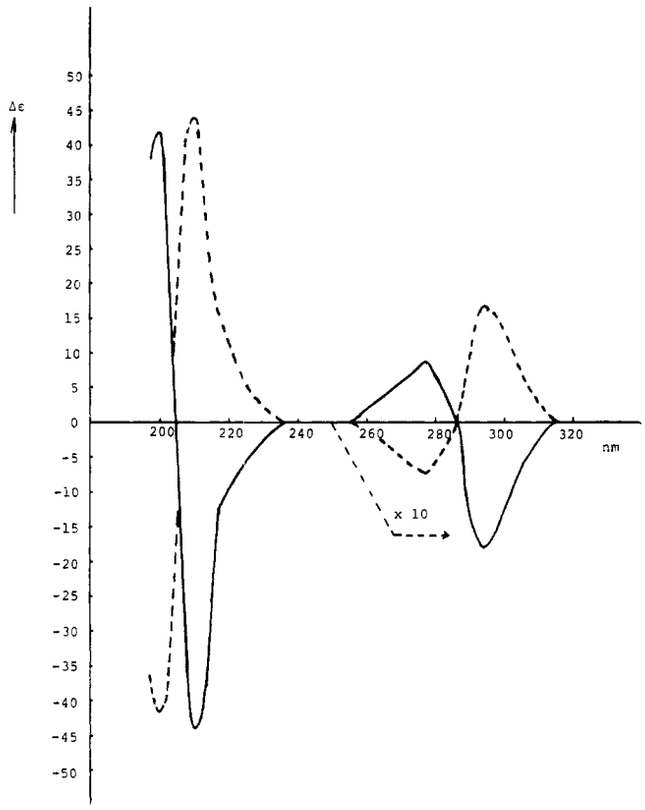


Figure 1. CD curves of the (−)-spirobenzylisoquinoline **40** (—) and (+)-**43** (- - - -) in methanol.

the spirobenzylisoquinolines with the retention of the stereochemistry at the C_8 position and the inversion at the C_{14} position, and the 8-methylberbines with the retention at the C_8 position.

Experimental Section

All melting points are uncorrected. UV spectra were taken with a Hitachi 124 spectrophotometer, IR spectra with a Hitachi 215 spectrophotometer, NMR spectra with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference), and mass spectra with a Hitachi RMU-7 spectrometer. Optical rotations were measured with a JASCO-PIP-SL automatic polarimeter. CD curves were taken with a JASCO J-20 spectropolarimeter. A 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (Wako Chemicals) was used for the following reactions.

(±)-Xylopinine *trans*- and *cis*-Methiodides (1a and 4). A mixture (2.45 g) of (±)-xylopinine *trans*- and *cis*-methiodides prepared according to the known method[22] was washed with chloroform. The resulting mass, which was insoluble in chloroform, was recrystallized from methanol to give (±)-xylopinine *trans*-methiodide (**1a**, 1.25 g) as hygroscopic, colorless crystals: mp 250–252 °C; NMR (Me_2SO-d_6) δ 2.85 (3 H, s, NCH_3), 3.80 (12 H, s, 4 OCH_3), 6.83 (1 H, s, ArH), 6.87 (1 H, s, ArH), 6.95 (2 H, s, 2 ArH).

Anal. Calcd for $C_{22}H_{28}NO_4I \cdot 0.2H_2O$: C, 52.74; H, 5.71; N, 2.80. Found: C, 52.46; H, 5.45; N, 2.79. The chloroform-soluble portion was recrystallized repeatedly from methanol to give (±)-xylopinine *cis*-methiodide (**4**, 200 mg) as hygroscopic, pale yellowish crystals: mp 233–234 °C; NMR (Me_2SO-d_6) δ 3.20 (3 H, s, NCH_3), 3.73 (12 H, s, 4 OCH_3), 6.73 (1 H, s, ArH), 6.76 (1 H, s, ArH), 6.85 (2 H, s, 2 ArH).

Anal. Calcd for $C_{22}H_{28}NO_4I \cdot 0.2H_2O$: C, 52.74; H, 5.71; N, 2.80. Found: C, 52.45; H, 5.62; N, 2.73.

(±)-[13,13,14-$^2H_3$]Xylopinine *trans*-Methiodide (1b). (±)-[13,13,14-$^2H_3$]Xylopinine, which was prepared by the known method,[10] was converted to its methiodide salts, from which the trans isomer, mp 250–252 °C, was separated in the same manner as above.

(±)-5,6,13,14α-Tetrahydro-9,10-dimethoxy-8β-methyl-2,3-methylenedioxyberbine (9). To a solution of 8-methyldihydroberberine (**8**,[11] 2 g, 5.7 mmol) in methanol (100 mL), sodium borohydride (0.5 g, 13.6 mmol) was added in small portions at 10 °C with stirring. After stirring for 2 h at room temperature, the solvent was evaporated in vacuo. The resulting residue was partitioned between benzene and water. The benzene layer was dried over anhydrous sodium sulfate and evaporated to give a solid, which was recrystallized from ethanol to afford **9** (1.7 g, 84.6%), mp 152–153 °C (lit.[3] mp 152–153 °C), whose spectral data were identical with those of the authentic sample.[3]

(±)-5,6,13,14α-Tetrahydro-9,10-dimethoxy-8β-methyl-2,3-methylenedioxyberbinium *trans*-Methiodide (10a). To a solution of (±)-8β-methylcanadine (**9**, 3.5 g, 9.9 mmol) in acetonitrile (80 mL) was added methyl iodide (10 mL), and the resulting mixture was allowed to stand overnight. After evaporation of the solvent, the resulting residue, which was estimated as a 5:4 mixture of the *trans*- and *cis*-methiodides by the NMR spectrum (Me_2SO-d_6), was washed with chloroform. The resulting mass, which was insoluble in chloroform, was repeatedly recrystallized from methanol to give **10a** (380 mg) as pale yellowish prisms: mp 240–242 °C; NMR (Me_2SO-d_6) δ 1.93 (3 H, d, J = 8 Hz, 8-CH_3), 2.76 (3 H, s, NCH_3), 3.79 (6 H, s, 2 OCH_3), 6.02 (2 H, s, OCH_2O), 6.85 (1 H, s, ArH), 7.09 (3 H, br s, 3 ArH).

Anal. Calcd for $C_{22}H_{26}NO_4I$: C, 53.34; H, 5.29; N, 2.83. Found: C, 53.11; H, 5.26; N, 2.78.

(±)-8β-Ethyl-2,3,10,11-tetramethoxy-14α*H*-berbine (17). To a solution of the sulfate **16**[12] (2 g) in methanol (500 mL) was added in portions sodium borohydride (2.5 g) below 10 °C with stirring and the mixture was stirred for 4 h at room temperature. After evaporation of the solvent, the residue was partitioned between water and benzene. The benzene layer was washed with water, dried over potassium carbonate, and evaporated to give a powder, recrystallization of which from methanol afforded **17** (960 mg, 66.8%) as colorless needles: mp 150–151 °C; IR ($CHCl_3$) 2820–2750 cm^{-1} (Bohlmann bands); NMR ($CDCl_3$) δ 0.70 (3 H, t, J = 7 Hz, CH_2CH_3), 1.50–2.20 (2 H, m, CH_2CH_3), 3.83 (12 H, s, 4 OCH_3), 6.55 (1 H, s, ArH), 6.58 (2 H, s, 2 ArH), 6.70 (1 H, s, ArH).

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.65. Found: C, 71.94; H, 7.55; N, 3.69.

(*Z*)-1-(3-Benzyloxy-4-methoxybenzylidene)-1,2,3,4-tetrahydro-2-propionyl-6,7-dimethoxyisoquinoline (25). A mixture of the 3,4-dihydroisoquinoline (**24**)[23] hydrochloride (1 g) and propionic anhydride (2.5 mL) in pyridine (2.5 mL) was heated for 3 h on a steam bath. After evaporation of the reagents under reduced pressure, the residue was recrystallized from methanol to afford **25** (830 mg, 79.6%) as yellowish needles: mp 158–159 °C; UV (MeOH) λ_{max} (log ε) 330 (4.14), 293 nm (3.97); IR ($CHCl_3$) 1625 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.80 (3 H, t, J = 7 Hz, CH_2CH_3), 3.83 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 5.12 (2 H, s, OCH_2Ph), 6.52–7.38 (11 H, m, 10 ArH and >=CH–).

Anal. Calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.60; N, 2.96. Found: C, 73.41; H, 6.80; N, 2.95.

11-Benzyloxy-8-ethyl-5,6-dihydro-2,3,10-trimethoxydibenzo[*a*,*g*]quinolizinylium Iodide (26). A mixture of the above enamide **25** (733 mg), anhydrous methanol (290 mL), dioxane (250 mL), and 57% hydriodic acid (0.2 mL) was irradiated for 15 min with a 450-W high-pressure mercury lamp enclosed in a quartz well under cooling with ice. The resulting yellow crystals were recrystallized from methanol to give **26** (234 mg, 25.8%) as pale yellow crystals: mp 248–249 °C; UV (MeOH) λ_{max} (log ε) 339 sh (3.86), 308 (4.08), 288 sh (4.22), 266 sh nm (3.86).

Anal. Calcd for $C_{29}H_{30}NO_4I \cdot 0.5H_2O$: C, 58.63; H, 5.26; N, 2.36. Found: C, 58.46; H, 5.27; N, 2.27.

(±)-11-Benzyloxy-8β-ethyl-2,3,10-trimethoxy-14α*H*-berbine (27). To a solution of the above iodide **26** (181 mg) in methanol (54 mL) was added in small portions sodium borohydride (181 mg) below 10 °C with stirring and, after addition, the mixture was stirred for 5 h at room temperature and then refluxed for 30 min. After evaporation of the solvent, the residue was partitioned between water and chloroform. The chloroform layer was washed with water, dried over potassium carbonate, and evaporated to leave a powder, which was recrystallized from methanol to give **27** (77.3 mg, 54.2%) as colorless needles: mp 157–158 °C; IR ($CHCl_3$) 2850–2750 cm^{-1} (Bohlmann bands); NMR ($CDCl_3$) δ 0.72 (3 H, t, J = 7 Hz, CH_2CH_3), 3.85 (9 H, s, 3 OCH_3), 5.10 (2 H, s, OCH_2Ph).

Anal. Calcd for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N, 3.05. Found: C, 75.19; H, 7.27; N, 2.93.

(±)-8β-Ethyl-2,3,10-trimethoxy-14α*H*-berbin-11-ol (28). A mixture of the above base **27** (58 mg) and concentrated hydrochloric acid (9 mL) in ethanol (9 mL) was refluxed for 4 h. After evaporation of the solvent and reagent, the residue was partitioned between 10% ammonia and chloroform. The chloroform layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to leave

a powder, recrystallization of which from methanol afforded **28** (12 mg, 26%) as colorless plates: mp 169–170 °C; IR ($CHCl_3$) 3570 (OH), 2830–2750 cm^{-1} (Bohlmann bands); NMR ($CDCl_3$) δ 0.72 (3 H, t, J = 6.6 Hz, CH_2CH_3), 1.50–2.20 (2 H, m, CH_2CH_3), 3.85 (9 H, s, 3 OCH_3), 6.55 (3 H, s, 3 ArH), 6.70 (1 H, s, ArH).

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.50; H, 7.60; N, 3.60.

Mannich Reaction of 1,2,3,4-Tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline (29). A mixture of the phenolic isoquinoline (**29**)[23] hydrochloride (1.0 g) and propionaldehyde (2 mL) in glacial acetic acid (100 mL) was refluxed for 2.5 h. After evaporation of the reagents under reduced pressure, the residue was partitioned between 10% ammonia and chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to leave a gum, which was purified by silica gel column chromatography with benzene–methanol (98:2 v/v). Evaporation of the eluate gave a gum, recrystallization of which from ethanol yielded (±)-8α-ethyl-2,3,10-trimethoxy-14αH-berbin-9-ol (**30**, 483 mg, 47.8%) as colorless prisms: mp 204.5–205.5 °C; IR ($CHCl_3$) 3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.03 (3 H, t, J = 6 Hz, CH_2CH_3), 1.22–1.90 (2 H, m, CH_2CH_3), 3.80 (9 H, s, 3 OCH_3), 4.20 (1 H, t, J = 8.2 Hz, 14-H), 6.54 (4 H, s, 4 ArH); NMR (Me_2SO-d_6) δ 1.00 (3 H, t, J = 6 Hz, CH_2CH_3), 3.73 (6 H, s, 2 OCH_3), 3.75 (3 H, s, OCH_3), 6.48 (1 H, d, J = 10 Hz, ArH), 6.66 (1 H, s, ArH), 6.77 (1 H, d, J = 10 Hz, ArH), 6.78 (1, H, s, ArH), which gave a positive Gibbs indophenol test.[11]

Anal. Calcd for $C_{22}H_{27}NO_4 \cdot 0.5H_2O$: C, 69.89; H, 7.47; N, 3.71. Found: C, 70.26; H, 7.26; N, 3.68.

The mother liquor during the above recrystallization was evaporated to leave a gum, which was further chromatographed on silica gel in benzene. The resulting mass was recrystallized from ethanol to give (±)-8α-ethyl-2,3,10-trimethoxy-14αH-berbin-11-ol (**31**, 229 mg, 22.7%) as colorless scales: mp 137–138 °C; IR ($CHCl_3$) 3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.08 (3 H, t, J = 6.2 Hz, CH_2CH_3), 1.50–1.90 (2 H, m, CH_2CH_3), 3.87 (9 H, s, 3 OCH_3), 4.22 (1 H, t, J = 8.4 Hz, 14-H), 6.55 (3 H, s, 3 ArH), 6.60 (1 H, s, 3 ArH); NMR (Me_2SO-d_6) δ 1.00 (3 H, t, J = 7 Hz, CH_2CH_3), 3.72 (9 H, s, 3 OCH_3), 6.43 (1 H, s, ArH), 6.60 (2 H, s, 2 ArH), 6.72 (1 H, s, ArH), which showed a negative Gibbs indophenol test.[11]

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.70; H, 7.50; N, 3.50.

(±)-8α-Ethyl-2,3,10,11-tetramethoxy-14αH-berbine (32). To a solution of the above base **31** (256 mg) in methanol (10 mL) was added an excess of diazomethane in ether, which was prepared from N-nitrosomethylurea, and the mixture was allowed to stand overnight at room temperature. After evaporation of the solvents, the residue was dissolved in dilute hydrochloric acid, which was washed with ether. The acidic solution was then basified with 10% aqueous sodium hydroxide solution. Extraction with chloroform, followed by washing the extract with water, drying over anhydrous sodium sulfate, and evaporation of the chloroform extract, gave a powder, which was recrystallized from methanol to yield **32** (120 mg, 45%) as colorless crystals: mp 121–122.5 °C; NMR ($CDCl_3$) δ 1.06 (3 H, t, J = 7 Hz, CH_2CH_3), 1.40–1.90 (2 H, m, CH_2CH_3), 3.81 (3 H, s, OCH_3), 3.86 (9 H, s, 3 OCH_3), 4.25 (1 H, t, J = 8 Hz, 14-H), 6.52 (1 H, s, ArH), 6.58 (3 H, s, 3 ArH).

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.00; H, 7.90; N, 3.30.

(±)-8β-Ethyl-2,3,10,11-tetramethoxy-14αH-berbinium *trans*- (18) and *cis*- (19) Methiodides. To a solution of the 8β-ethylberbine **17** (2.37 g) in acetonitrile (120 mL) was added methyl iodide (6 mL) and the mixture was allowed to stand for 3 days at room temperature in a dark place. After evaporation of the reagents, the residue was recrystallized from methanol to give the *trans*-methiodide (**18**, 1.35 g, 41.6%) as orange prisms: mp 244.5–246 °C; NMR ($CDCl_3$) δ 1.33 (3 H, t, J = 7 Hz, CH_2CH_3), 2.77 (3 H, s, NCH_3), 3.87 (6 H, s, 2 OCH_3), 3.89 (6, H, s, 2 OCH_3), 6.33, 6.70, 6.83, and 7.00 (each 1 H, each s, 4 ArH).

Anal. Calcd for $C_{24}H_{32}NO_4I \cdot 0.2H_2O$: C, 54.59; H, 5.99; N, 2.65. Found: C, 54.28; H, 6.25; N, 2.82.

The resulting mass from the mother liquor during the above recrystallization was recrystallized from methanol to give the *cis*-methiodide (**19**, 1.64 g, 50.5%) as colorless needles: mp 194–196 °C; NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 6.2 Hz, CH_2CH_3), 3.57 (3 H, s, NCH_3), 3.85 (6 H, s, 2 OCH_3), 3.88 (6 H, s, 2 OCH_3), 6.53, 6.68, 6.80, and 6.88 (each 1 H, each s, 4 ArH).

Anal. Calcd for $C_{24}H_{32}NO_4I \cdot 0.2H_2O$: C, 54.59; H, 5.99; N, 2.65. Found: C, 54.30; H, 6.20; N, 2.40.

(*R*)-(+)-Canadine *trans*-(39) and *cis*- (42) Methiodides. To a solution of (+)-canadine[19] (580 mg, 1.71 mmol) in methanol (50 mL) was added methyl iodide (3 mL), and the mixture was allowed to stand overnight. After evaporation of the solvent, the resulting residue was washed with chloroform. The mass which was insoluble in chloroform was recrystallized from methanol to give (+)-canadine *trans*-methiodide (**39**, 420 mg, 51%): mp 252–254 °C (lit.[24] 252–254 °C); $[\alpha]^{18}_D$ +115.2° (c 0.13, MeOH) (lit.[24] $[\alpha]^{21}_D$ +124.5°); CD (MeOH) nm ($\Delta\epsilon$) 288 (−0.15), 267 (+0.07), 254 (−0.29), 236 (+6.79), 223 (+5.85), 215 (13.69). The above chloroform solution was evaporated and the resulting residue was recrystallized from methanol to give (+)-canadine *cis*-methiodide (**42**, 170 mg, 20.7%): mp 220 °C (lit.[25] 220 °C); $[\alpha]^{18}_D$ +100° (c 0.04, MeOH); CD (MeOH) nm ($\Delta\epsilon$) 287 (+0.61), 269 (+0.30), 266 (+0.37), 236 (+12.89), 266 (+6.56), 213 (+28.69).

Reaction of (±)-Xylopinine *trans*-Methiodide (1a) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **1a** (1 g, 2.012 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (5.8 g, 0.02 mol) in dry dioxane (100 mL) was refluxed for 24 h under a current of nitrogen. After evaporation of the solvent, the excess reagent was decomposed with 10% aqueous sodium hydroxide solution on cooling. The separated benzene layer was washed with water, dried over sodium sulfate, and evaporated to leave a brownish caramel, which was purified by silica gel column chromatography. The elution with benzene–methanol (99.5:0.5 v/v) afforded a solid, recrystallization of which from ethanol yielded (±)-β-coralydine (**3a**, 42 mg, 6%): mp 95–96 °C (lit.[3] 95–96 °C); mass spectrum m/e 369, 354, 192, 190, 178, 163. Further elution with benzene–methanol (99:1 v/v) gave a solid, recrystallization of which from ethanol afforded (±)-2,3,10,11-tetramethoxyochotensane (**2a**, 572 mg, 77%): mp 138–139 °C; NMR ($CDCl_3$) δ 2.26 (3 H, s, NCH_3), 2.77–2.95 (4 H, m, CH_2CH_2), 3.22 (2 H, br s, 8-H and 14-H), 3.33 (2 H, br s, 8-H and 14-H), 3.59 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.83 (6 H, s, 2 OCH_3), 6.43 (1 H, s, ArH), 6.47 (1 H, s, ArH), 6.69 (2 H, s, 2 ArH); mass spectrum m/e 369, 354, 204, 164.

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.75; H, 7.28; N, 3.75.

Reaction of (±)-Xylopinine *cis*-Methiodide (4) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **4** (100 mg, 0.2012 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (580 mg, 2.012 mmol) in dry dioxane (10 mL) was refluxed for 24 h under the same conditions as above. The same workup as above gave a caramel, which was developed by preparative TLC on silica gel with methanol–chloroform (1:9 v/v) and then methanol–ethyl acetate–benzene (1:4:5 v/v). The part with R_f 0.75 was extracted with chloroform–methanol (9:1 v/v) to afford *O*-methylcorytenchirine (**5**, 15 mg, 20%), mp 86–88 °C (lit.[9] mp 86–88 °C), whose spectral data were identical with those of the authentic sample.[9] The part with R_f 0.5 was extracted with chloroform–methanol (9:1 v/v) to leave **2a** (38 mg, 51%), which was identical with the authentic sample prepared as above.

Reaction of (±)-[13,13,14-$^2H_3$]Xylopinine *trans*-Methiodide (1b) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **1b** (330 mg, 0.66 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (1.9 g, 6.6 mmol) in dry dioxane (30 mL) was refluxed for 24 h under the same conditions as above. The same workup as above gave a brownish caramel, which was purified by silica gel column chromatography. The elution with benzene–methanol (99.5:0.5 v/v) afforded a solid, recrystallization of which from ethanol gave (±)-[13,13,14-$^2H_3$]coralydine (**3b**, 55 mg, 22.5%): NMR ($CDCl_3$) δ 1.53 (3 H, d, J = 7 Hz, 8-CH_3), 3.83 (12 H, s, 4 OCH_3), 6.57 (1 H, s, ArH), 6.61 (1 H, s, ArH), 6.65 (1 H, s, ArH), 6.72 (1 H, s, ArH); mass spectrum m/e 372, 357, 193, 191, 180, 165. Further elution with benzene–methanol (99:1 v/v) gave a solid, which was recrystallized from ethanol to afford **2b** (115 mg, 47%): NMR ($CDCl_3$) δ 2.26 (3 H, s, NCH_3), 2.77–2.95 (4 H, m, CH_2CH_2), 3.22 (1 H, br s, 8-H), 3.33 (1 H, br s, 8-H), 3.81 (3 H, s, OCH_3), 3.83 (6 H, s, 2 OCH_3), 6.43 (1 H, s, ArH), 6.47 (1 H, s, ArH), 6.69 (2 H, s, 2 ArH); mass spectrum m/e 371, 356, 206, 204, 166.

Reaction of (±)-5,6,13,14-Tetrahydro-9,10-dimethoxy-8β-methyl-2,3-methylenedioxyberbinium *trans*-Methiodide (10a) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A solution of **10a** (360 mg, 0.727 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (2.1 g, 7.27 mmol) in dry dioxane (40 mL) was refluxed for 24 h under the same conditions as above, followed by the workup as above, to afford a brownish caramel, which was purified by silica gel column chromatography with benzene–methanol (99.5:0.5 v/v) as eluent. The first fraction afforded a solid, recrystallization of which from ethanol gave (±)-5,6,13,14-tetrahydro-9,10-dimethoxy-8,8-dimethyl-2,3-methylenedioxyberbine (**13a**, 60 mg, 22.5%) as pale yellowish crystals: mp 114–115 °C; NMR ($CDCl_3$) δ 1.52 (3 H, s, 8-CH_3), 1.72 (3 H, s, 8-CH_3), 3.83 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 5.83 (2, H, s, OCH_2O), 6.52 (1 H, s, ArH), 6.60 (1 H,

s, ArH), 7.17 (2 H, s, 2 ArH); IR ($CHCl_3$) 935 cm^{-1}; mass spectrum *m/e* 367, 352, 192, 176, 174.

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.51; H, 6.77; N, 3.59.

The second fraction afforded the spirobenzylisoquinoline (**12a**, 25 mg, 9.4%) as a caramel: NMR ($CDCl_3$) δ 1.30 (3 H, d, J = 7 Hz, 8-CH_3), 2.33 (3 H, s, NCH_3), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.75 (2 H, s, OCH_2O), 6.25 (1 H, s, ArH), 6.48 (1 H, s, ArH), 6.70 (1 H, d, J = 10 Hz, ArH), 6.88 (1 H, d, J = 10 Hz, ArH); IR ($CHCl_3$) 935 cm^{-1}; mass spectrum *m/e* 367, 352, 190, 188, 178, 163, which was converted into the hydrochloride. Recrystallization from methanol–ether afforded colorless crystals, mp 210–213 °C dec.

Anal. Calcd for $C_{22}H_{25}NO_4$·HCl: C, 65.42; H, 6.49; N, 3.47. Found: C, 65.59; H, 6.48; N, 3.38.

The third fraction gave 1-(2-ethyl-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (**14a**, 40 mg, 15%) as a caramel: NMR ($CDCl_3$) δ 1.07 (3 H, t, J = 7 Hz, CH_2CH_3), 2.45 (3 H, s, NCH_3), 3.80 (6 H, s, 2 OCH_3), 5.76 (2 H, s, OCH_2O), 5.90 (1 H, s, ArH), 6.50 (1 H, s, ArH), 6.70 (1 H, s, ArH), 6.73 (1 H, s, ArH); IR ($CHCl_3$) 935 cm^{-1}, which was converted into the hydrochloride. Recrystallization from methanol–ether gave colorless crystals, mp 124–125 °C.

Anal. Calcd for $C_{22}H_{27}NO_4$·HCl·H_2O: C, 62.33; H, 6.90; N, 3.30. Found: C, 62.32; H, 7.17; N, 3.29.

Reaction of the Mixture of (±)-5,6,13,14α-Tetrahydro-9,10-dimethoxy-8α-methyl-2,3-methylenedioxyberbinium *trans*- and *cis*-Methiodides (10a and 11) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A solution of a mixture of **10a** and **11** (2.1 g, 4.24 mmol), which was obtained from the above mother liquor during the preparation of the *trans*-methiodide (**10a**), and 70% sodium bis(2-methoxyethoxy)aluminum hydride (12.2 g, 0.0424 mol) in dry dioxane (200 mL) was refluxed for 24 h under the same conditions as above and the workup of the reaction mixture left a brownish caramel, which was purified by silica gel column chromatography with benzene–methanol (99.5:0.5 v/v) as eluent. The first fraction afforded **13a** (187 mg, mp 114–115 °C), which was identical with the authentic sample prepared as above. The second fraction afforded **12a** (88 mg), which was identical with the authentic sample prepared as above. The third fraction gave **14a** (127 mg), which was also identical with the above authentic sample. Further elution with benzene–methanol (99:1 v/v) afforded **15** (315 mg) as a caramel: NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 7 Hz, 8-CH_3), 2.33 (3 H, s, NCH_3), 3.70 (3, H, s, OCH_3), 3.73 (3 H, s, OCH_3) 6.46 (1 H, s, ArH), 6.49 (1 H, s, ArH), 6.73 (1 H, d, J = 10 Hz, ArH), 6.86 (1 H, d, J = 10 Hz, ArH); IR ($CHCl_3$) 935 cm^{-1}; mass spectrum *m/e* 367, 352, 190, 188, 178, 163, which was converted into the hydrochloride. Recrystallization from methanol–ether yielded colorless crystals, mp 223–225 °C dec.

Anal. Calcd for $C_{22}H_{25}NO_4$·HCl: C, 65.42; H, 6.49; N, 3.47. Found: C, 65.15; H, 6.56; N, 3.18.

Reaction of (±)-[*N*-C^2H_3]-5,6,13,14α-Tetrahydro-9,10-dimethoxy-8β-methyl-2,3-methylenedioxyberbinium *trans*-Methiodide (10b) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **10b** (50 mg, 0.1 mmol) prepared according to the method in case of the methiodide (**10a**) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (290 mg, 1.0 mmol) in dry dioxane (5 mL) was heated for 24 h under the same conditions as above. The same workup as above afforded a caramel, which was developed by preparative TLC on silica gel with methanol–chloroform (0.5:9.5 v/v) and then methanol-ethyl acetate-benzene (0.5:4:5.5 v/v). The part with R_f 0.8 gave **13b** (8.3 mg): NMR ($CDCl_3$) δ 1.52 (3 H, s, 8-CH_3), 3.83 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 5.83 (2 H, s, OCH_2O), 6.52 (1 H, s, ArH), 6.60 (1 H, s, ArH), 7.17 (2 H, s, 2 ArH). The part with R_f 0.65 yielded **14b** (3.2 mg): NMR ($CDCl_3$) δ 1.07 (3 H, t, J = 7 Hz, CH_2CH_3), 3.80 (6 H, s, 2 OCH_3), 5.76 (2 H, s, OCH_2O), 5.90 (1 H, s, ArH), 6.50 (1 H, s, ArH), 6.70 (1 H, s, ArH), 6.73 (1 H, s, ArH). The part with R_f 0.6 afforded **12b** (5.2 mg): NMR ($CDCl_3$) δ 1.30 (3 H, d, J = 7 Hz, 8-CH_3), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.75 (2 H, s, OCH_2O), 6.25 (1 H, s, ArH), 6.48 (1 H, s, ArH), 6.70 (1 H, d, J = 10 Hz, ArH), 6.88 (1 H, d, J = 10 Hz, ArH).

Reaction of (±)-8β-Ethyl-2,3,10,11-tetramethoxy-14α*H*-berbinium *trans*-Methiodide (18) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of the methiodide **18** (100 mg, 0.19 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (3 mL, 0.01 mol) in dry dioxane (15 mL) was refluxed for 24 h under the same conditions as above and worked up to give a gum (60.2 mg), which was chromatographed on silica gel by using benzene as an eluent, followed by benzene–methanol (99.8:0.2 v/v) and benzene–methanol (99.7:0.3 v/v). The eluate of the benzene–methanol (99.7:0.3 v/v) fraction was further purified by preparative TLC on silica gel developing with benzene–ethyl acetate–methanol (5:4:1 v/v).

A part with R_f 0.9 gave **17** (8.8 mg, 12%), 150–151 °C, whose spectral data were identical with those of the authentic sample. A part with R_f 0.55 gave the 8α-ethyl-8β-methylberbine (**22**, 11.5 mg, 15.2%), which was recrystallized from methanol to give yellowish needles: mp 165–167 °C; NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7 Hz, 8-CH_2CH_3), 1.52 (3 H, s, 8-CH_3), 3.85 (12 H, s, 4 OCH_3), 6.57, 6.63, 6.65, and 6.75 (each 1 H, each s, 4 ArH); mass spectrum *m/e* 397 (M^+), 382, 368, 206, 191.

Anal. Calcd for $C_{24}H_{31}NO_4$: N, 3.52. Found: N, 3.57.

A part with R_f 0.45 gave the spirobenzylisoquinoline **20** (23.5 mg, 31.0%) which was recrystallized from methanol to give colorless prisms: mp 121–122 °C; NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7 Hz, 8-CH_2CH_3), 1.50–1.99 (2 H, m, 8-CH_2CH_3), 2.22 (3 H, s, NCH_3), 3.50 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.87 (6 H, s, 2 OCH_3), 6.35, 6.45, 6.67, and 6.72 (each 1 H, each s, 4 ArH); mass spectrum *m/e* 397 (M^+), 382, 204, 192.

Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.51; H, 7.81; N, 3.52. Found: C, 72.42; H, 7.75; N, 3.46.

A part with R_f 0.18 gave the spiro isomer **21** (2 mg, 2.7%) as a syrup: NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6.2 Hz, 8-CH_2CH_3), 1.17–1.50 (2 H, m, 8-CH_2CH_3), 2.37 (3 H, s, NCH_3), 3.50 (3 H, s, OCH_3), 3.83 (9 H, s, 3 OCH_3), 6.37, 6.43, 6.70, and 6.75 (each 1 H, each s, 4 ArH).

Anal. Calcd for $C_{24}H_{31}NO_4$: 397.2253 (M^+). Found: 397.2234 (M^+).

Reaction of (±)-8β-Ethyl-2,3,10,11-tetramethoxy-14α*H*-berbinium *cis*-Methiodide (19). A mixture of the *cis*-methiodide **19** (785 mg, 1.5 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (5 mL, 0.017 mol) in dry dioxane (35 mL) was refluxed for 24 h and worked up as above to give a gum, which was chromatographed on silica gel. Elution with benzene–methanol (99.7:0.3 v/v) afforded a gum, which was purified by a preparative TLC on silica gel with benzene–ethyl acetate–methanol (5:4:1 v/v) to give the 8β-ethyl-8α-methylberbine (**23**, 102.6 mg, 17.2%) as yellow prisms: mp 158–159 °C (from methanol); NMR ($CDCl_3$) δ 0.60 (3 H, t, J = 7 Hz, 8-CH_2CH_3), 1.37 (3 H, s, 8-CH_3), 3.87 (12 H, s, 4 OCH_3), 6.57, 6.61, 6.70, and 6.75 (each 1 H, each s, 4 ArH), mass spectrum *m/e* 397 (M^+), 382, 368, 206, 191.

Anal. Calcd for $C_{24}H_{31}NO_4$·0.25H_2O: C, 71.70; H, 7.89; N, 3.48. Found: C, 71.70; H, 7.80; N, 3.70.

Further elution with benzene–methanol (99.5:0.5 v/v) gave the 8α-ethyl-8β-methylberbine (**22**, 30.4 mg, 5.1%) as yellowish needles, mp 165–167 °C (from methanol), whose spectral data were identical with those of the authentic sample.

Further elution with benzene–methanol (99.4:0.6 v/v) gave a gum, which was further purified by a preparative TLC on silica gel with benzene–ethyl acetate–methanol (5:4:1 v/v). A part with R_f 0.45 gave the spirobenzylisoquinoline **20** (36.9 mg, 6.2%) as colorless prisms, mp 121–122 °C (from methanol), which was identical with the authentic sample.

A part with R_f 0.18 furnished the isomer **21** (120.9 mg, 20.3%) as a syrup, IR and NMR spectra of which were identical with those of the authentic sample.

Reaction of (*R*)-(+)-Canadine *trans*-Methiodide (39) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of (+)-canadine *trans*-methiodide (**39**, 400 mg, 0.83 mmol) and 70% sodium bis(2-methoxyethoxy)aluminum hydride (2.4 g, 8.3 mmol) in dry dioxane (40 mL) was refluxed for 24 h under a current of nitrogen and worked up as above to give a brownish caramel, which was purified by silica gel column chromatography. Elution with benzene–methanol (99.5:0.5 v/v) afforded a solid, recrystallization of which from ethanol yielded (+)-5,6,13,14β-tetrahydro-9,10-dimethoxy-8α-methyl-2,3-methylenedioxyberbine (**41**, 132 mg) as pale yellow crystals, mp 190–192 °C, $[\alpha]^{20}_D$ +208° (*c* 0.125, MeOH), whose spectral data were identical with those of the racemate (**9**).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.23; H, 6.51; N, 3.71.

Further elution with benzene–methanol (99:1 v/v) gave a solid, recrystallization of which from ethanol yielded (−)-9,10-dimethoxy-2,3-methylenedioxyochotensane (**40**, 98 mg) as colorless crystals: mp 104–105 °C (lit.[5] 104–105 °C); $[\alpha]^{18}_D$ −56° (lit.[5] $[\alpha]^{16}_D$ −60°); CD (MeOH) nm ($\Delta\epsilon$) 294 (−1.80), 277 (+0.91), 210 (−44.27), 200 (+42.16).

Reaction of (*R*)-(+)-Canadine *cis*-Methiodide (42) with Sodium Bis(2-methoxyethoxy)aluminum Hydride. A mixture of **42** (160 mg, 0.33 mmol) and 70% sodium bis(2-methoxyethoxy)-aluminum hydride (952 mg, 3.3 mmol) in dry dioxane (5 mL) was heated for 24 h under the same conditions as above. The same workup as above gave a caramel, which was purified by silica gel column chromatography. Elution with benzene–methanol (99.5:0.5 v/v) afforded (+)-3-(2-ethyl-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahy-

dro-7,8-dimethoxy-2-methylisoquinoline (**44**, 53 mg) as a caramel, whose spectral data were identical with those of the racemate. Further elution with benzene–methanol (99:1 v/v) gave a solid, which was recrystallized from ethanol to afford (+)-9,10-dimethoxy-2,3-methylenedioxyochotensane (**43**, 33 mg) as colorless crystals: mp 104–105 °C (lit.[5] 104–105 °C); $[\alpha]^{18}_D$ +54° (lit.[5] $[\alpha]^{16}_D$ +60°); CD (MeOH) nm ($\Delta\epsilon$) 294 (+1.70), 277 (−0.75), 210 (+44.12), 200 (−41.91).

Acknowledgment. We are indebted to Professor H. Hatano, Tohoku University, for CD measurements. We also thank Mrs. R. Kobayashi, Miss R. Suenaga, Miss E. Nagaoka, Miss M. Tanno, and Mr. K. Kawamura, Pharmaceutical Institute, Tohoku University, for spectral measurements. We also thank Mitsubishi Foundation for its financial help.

Registry No.—**1a**, 62360-05-3; **1b**, 62815-47-8; **2a**, 62815-48-9; **2b**, 62815-13-2; **3a**, 58116-07-7; **3b**, 62815-49-0; **4**, 62860-06-4; **8**, 62815-50-3; **9**, 60354-88-3; **10a**, 62815-51-4; **10b**, 62815-52-5; **11**, 62860-07-5; **12a**, 62815-53-6; **12a** HCl, 62815-54-7; **12b**, 62815-55-8; **13a**, 62815-56-9; **13b**, 62815-57-0; **14a**, 62815-58-1; **14a** HCl, 62815-59-2; **14b**, 62815-60-5; **15**, 62815-61-6; **15** HCl, 62815-62-7; **16**, 62815-64-9; **17**, 62815-65-0; **18**, 62860-08-6; **19**, 62815-33-2; **20**, 62815-34-3; **21**, 62815-35-4; **22**, 62815-36-5; **23**, 62815-37-6; **24**, 18028-11-0; **25**, 62815-38-7; **26**, 62815-39-8; **27**, 62815-40-1; **28**, 62815-41-2; **29** HCl, 60356-10-7; **30**, 62815-42-3; **31**, 62815-43-4; **32**, 62815-44-5; **39**, 62860-02-0; **40**, 56974-42-6; **41**, 62815-45-6; **42**, 62860-03-1; **43**, 56974-43-7; **44**, 62815-46-7; (±)-[13,13,14-$^2H_3$]xylopinine, 62860-04-2; propionic anhydride, 123-62-6; propionaldehyde, 123-38-6; (*R*)-(+)-canadine, 2086-96-6; sodium bis(2-methoxyethoxy)aluminum hydride, 21608-56-0.

References and Notes

(1) Part 714: T. Kametani, Y. Kigawa, K. Takahashi, H. Nemoto, and K. Fukumoto, *Heterocycles*, **6**, 887 (1976).
(2) T. Kametani, S.-P. Huang, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, **41**, 2545 (1976).
(3) T. Kametani, A. Ujiie, S.-P. Huang, M. Ihara, and K. Fukumoto, *Heterocycles*, **4**, 1223 (1976); *J. Chem. Soc., Perkin Trans. 1*, 394 (1977).
(4) S. Kano, T. Yokomatsu, E. Komiyama, Y. Takagi, and S. Shibuya, *Chem. Pharm. Bull.*, **23**, 1171 (1975).
(5) J. Imai, Y. Kondo, and T. Takemoto, *Heterocycles*, **3**, 467 (1975); *Tetrahedron*, **32**, 1973 (1976).
(6) A. R. Lepley, *J. Am. Chem. Soc.*, **91**, 1237 (1969).
(7) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., Germany, 1970, p 131, and references cited therein.
(8) W. Awe, J. Thum, and H. Wichmann, *Arch. Pharm. (Weinheim, Ger.)*, **293**, 907 (1960).
(9) S.-T. Lu, T.-L. Su, T. Kametani, A. Ujiie, M. Ihara, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 63 (1976).
(10) T. Kametani and M. Ihara, *J. Chem. Soc. C*, 1305 (1968).
(11) M. Freund and H. Beck, *Ber.*, **37**, 2673 (1904).
(12) K. Y. Zee-Chen, K. D. Paull, and C. C. Cheng, *J. Med. Chem.*, **17**, 347 (1974).
(13) G. R. Lenz and N. C. Yang, *Chem. Commun.*, 1136 (1967).
(14) T. Kametani, A. Ujiie, M. Ihara, K. Fukumoto, and S.-T. Lu, *J. Chem. Soc., Perkin Trans. 1*, 1218 (1976).
(15) F. E. King, T. J. King, and L. C. Manning, *J. Chem. Soc.*, 563 (1957).
(16) Refluxing the *trans*- or *cis*-methiodides in dioxane without the complex hydride gave no change. Conversion of the *cis*-methiodide (**42**) to the trans one (**39**) was observed by heating at 245 °C, the fact of which was followed by NMR spectroscopy in Me_2SO-d_6.
(17) E. Buncel, "Carbanions: Mechanistic and Isotopic Aspects", Elsevier, Amsterdam, 1975, pp 35–66.
(18) T. Kametani, K. Fukumoto, M. Ihara, A. Ujiie, and H. Koizumi, *J. Org. Chem.*, **40**, 3280 (1975).
(19) A. Voss and J. Gadamer, *Arch. Pharm. (Weinheim, Ger.)*, **248**, 43 (1910).
(20) M. Shamma, J. L. Moniot, R. H. F. Manske, W. K. Chan, and K. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 310 (1972).
(21) K. Yoshikawa, I. Morishima, J. Kunitomo, M. Ju-ichi, and Y. Yoshida, *Chem. Lett.*, 961 (1975).
(22) L. E. Craig and D. S. Tarbell, *J. Am. Chem. Soc.*, **70**, 2783 (1948).
(23) T. Kametani, K. Nyu, S. Ikeda, T. Tominaga, and R. Iwashiro, *J. Pharm. Soc. Jpn.*, **93**, 1120 (1973).
(24) M. Tomita and M. Sugamoto, *J. Pharm. Soc. Jpn.*, **82**, 1141 (1962).
(25) H. A. D. Jowett and F. L. Pyman, *J. Chem. Soc.*, **103**, 290 (1913).

Heterogeneous Catalysis by Solid Superacids. 2.[1] Reduction of 2-Chloropropane and Its Reaction with Alkanes over Niobium Pentafluoride on Graphite

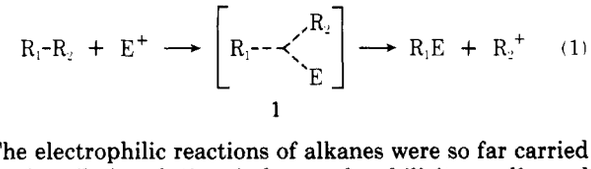
George A. Olah* and Joseph Kaspi[2]

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received January 28, 1977

Niobium pentafluoride on graphite was found to be an effective catalyst for the reduction of 2-chloropropane and its reaction with alkanes. In the absence of alkanes, 2-chloropropane is reduced to propane. Reaction of 2-chloropropane with C_3–C_5 alkanes having secondary or tertiary carbon atoms occurs readily accompanied by reduction. The major reaction is Bartlett–Nenitzescu type hydrogen transfer between the generated isopropyl cation and the corresponding alkane. Alkylation products are also formed, but in lower yield. Pentane and 2-methylbutane give in addition substantial amounts of 2-methylpropane. Methane, ethane, and 2,2-dimethylpropane were found to be unreactive under the reaction conditions.

Electrophilic reactions at carbon–carbon and carbon–hydrogen single bonds by strong electrophiles have been well established in recent years.[3] Alkanes, being weak σ bases, are not easily attacked and relatively strong electrophiles are needed. Protolytic reactions of alkanes by superacids,[4–7] nitration by nitronium salts,[8] halogenation by "positive" halogens[9–11] (such as formed by the reaction of elementary halogen with silver salts), as well as alkylation by carbenium ions[12–14] were reported. The mechanism of these reactions involves front side attack of the electrophile on the corresponding σ bonds to form a two-electron three-center bonded carbonium ion (**1**), which then cleaves to give the substitution product and an ionic product, i.e., proton or carbenium ion (eq 1).



(1)

1

The electrophilic reactions of alkanes were so far carried out primarily in solution, in low nucleophilicity media, and were catalyzed by superacid catalysts (usually based on SbF_5 or TaF_5). Prolonged reaction time and continuous contact with the catalyst can, however, cause extensive secondary reactions of the products. In contrast to electrophilic aromatic substitutions where products are generally stable (for example, nitrobenzenes, halobenzenes, or alkyl benzenes), this is not the case in electrophilic aliphatic substitution. For example, it is possible for R_1E (eq 1) to react further under the

*Address correspondence to Department of Chemistry, University of Southern California, Los Angeles, Calif. 90007.