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Chemical Transformation of Protoberberines. VII.[1] Efficient Conversion of Protoberberines into Benzindenoazepines *via* 8,14-Cycloberbines[2]

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A simple and convenient transformation of berberine (**1**) into *trans*-, *cis*-, and unsaturated benzindenoazepines through regioselective C_{14}–N bond cleavage of 8,14-cycloberbines is described. Acidic treatment of the 8,14-cycloberbine (**2**) effected regioselective ring opening to afford the *trans*- and *cis*-benzindenoazepines (**7a** and **7b**) as the kinetically and thermodynamically controlled products, respectively. Dehydration of their *N*-methyl derivatives (**11a** and **11b**) gave the unsaturated benzindenoazepine (**20**), which was obtained more efficiently from the 8,14-cycloberbine (**2**) by treatment with *p*-toluenesulfonic acid in benzene followed by *N*-methylation. Similarly, the ring D-inverted 8,14-cycloberbine (**23**) was converted to the corresponding *trans*-, *cis*-, and unsaturated benzindenoazepines (**24a**, **24b**, and **27**, respectively).

Keywords——berberine; 8,14-cycloberbine; regioselective ring cleavage; acid-catalyzed ring cleavage; benzindenoazepine; unsaturated benzindenoazepine; rhoeadine alkaloid; *p*-toluenesulfonic acid–benzene

The benzindenoazepine skeleton has been utilized as the key intermediate for the synthesis of rhoeadine,[3] protopine,[4] phthalideisoquinoline,[5] and spirobenzylisoquinoline[6] alkaloids and their analogues (Chart 1). The biogenetic precursors of these alkaloids have been shown to be protoberberine alkaloids.[7] Several new alkaloids possessing a benzindenoazepine skeleton have recently been found[8] (Chart 2), and they are presumably biosynthesized from protoberberine alkaloids. Consequently, it would be of great value to develop a simple and general synthesis of a benzindenoazepine from a protoberberine, even though some interesting transformations have already been reported.[9,10]

In the previous paper,[11] we reported the synthesis of the unique 8,14-cycloberbine (**2**) from berberine (**1**) and its ready conversion to the spirobenzylisoquinoline (**3**) *via* regioselective C_8–N bond cleavage. This method has been successfully applied to the total synthesis of (±)-fumaricine (**4**)[12] and (±)-ochrobirine (**5**)[13] from the corresponding protoberberines. The potential utility of 8,14-cycloberbines was further demonstrated by conversion of **2** into the benzindenoazepine (**6**) using methyl iodide in methanol, probably through an S_N1-type reaction.[11] Therefore, we next investigated regioselective C_{14}–N bond cleavage of 8,14-cycloberbines under solvolytic conditions catalyzed by various acids with the aim of developing a new and efficient synthesis of benzindenoazepines from protoberberines. Independently, Shamma *et al.*[14] reported similar transformation of the 8,14-cycloberbine (**2**)[11] to benzindenoazepines and an elegant synthesis of a rhoeadine skeleton. This paper describes our own results on the regioselective cleavage of cycloberbines into

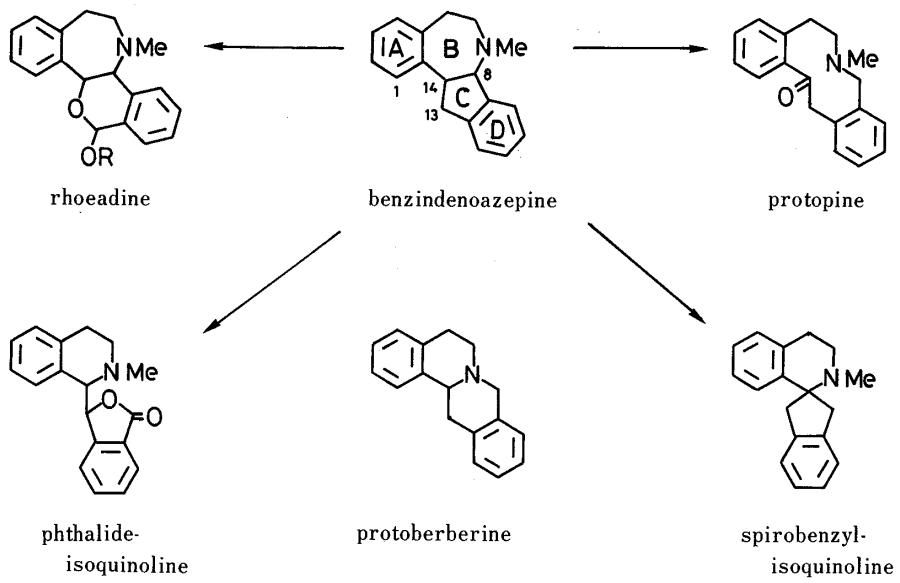

Chart 1

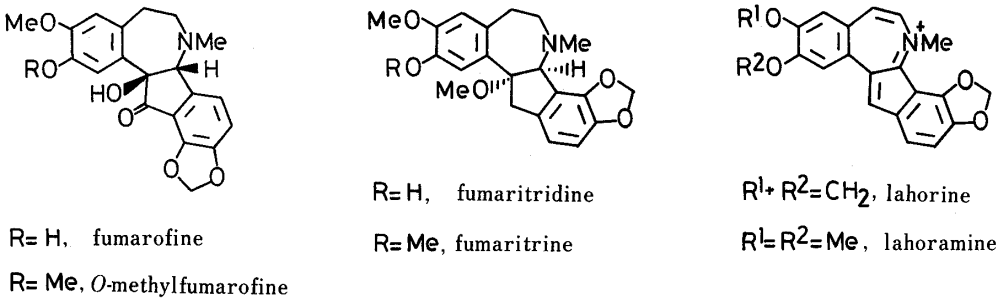

Chart 2

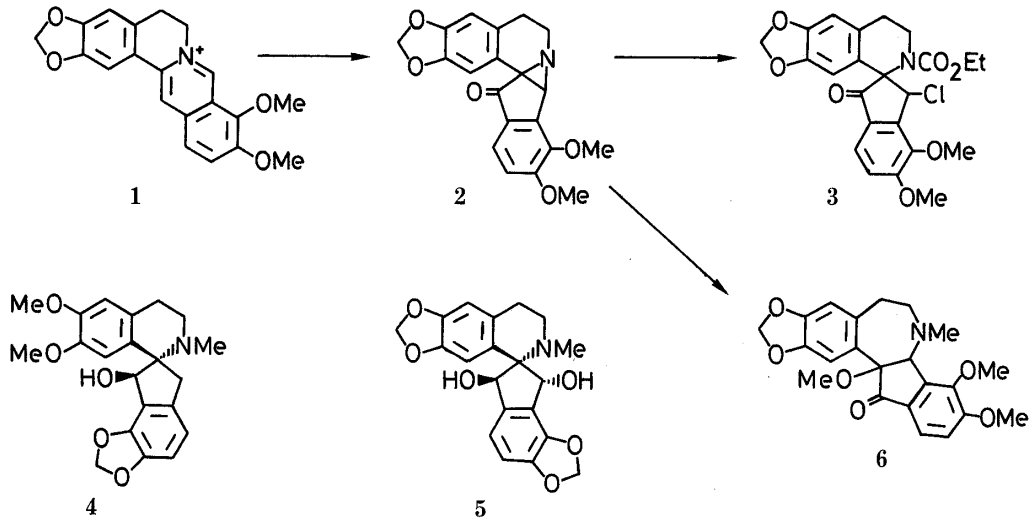

Chart 3

benzindenoazepines.

On treatment with 10% hydrochloric acid at room temperature, the cycloberbine (**2**) smoothly underwent ring opening to afford two diastereoisomeric benzindenoazepines (**7a**

and **7b**) in 82% yield in 1 : 1 ratio. The B/C ring junctures of **7a** and **7b** were assigned as *trans* and *cis*, respectively, from a comparison of their H-8 signals (**7a**, 4.18 ppm; **7b**, 4.37 ppm) in the proton nuclear magnetic resonance (^{1}H-NMR) spectra on the basis of the stereochemical assignment reported for simple benzindenoazepines.[15] These assignments were supported by the fact that the H-1 signal of **7a** appeared at lower field (7.24 ppm) than that of **7b** (6.95 ppm), because the H-1 is in nearly the same plane as the carbonyl group in the *trans*-fused system from an inspection of the Dreiding model. The stereochemistry of **7a** and **7b** was further confirmed by isomerization of the *trans* isomer (**7a**) into the more stable *cis* isomer (**7b**), namely, treatment of **7a** with 10% hydrochloric acid at 70 °C gave **7a** (17%) and **7b** (65%). The regioselective C_{14}–N bond cleavage of the cycloberbine (**2**) and the isomerization of the benzindenoazepines (**7a** and **7b**) were also investigated under various acidic conditions and the results are summarized in Table I. The longer or higher the reaction time or temperature, the greater was the predominance of the *cis* isomer (**7b**) in the product.

The above results suggest that the benzindenoazepines (**7a** and **7b**) are the kinetically controlled product and the thermodynamically controlled product, respectively, and there exists an equilibrium between them. The formation and equilibration reactions should proceed *via* the carbocation intermediate (**8**), which is attacked preferentially by water from the side opposite to H-8 to avoid the steric hindrance caused by H-1 under kinetically controlled conditions, leading to the *trans* isomer.[16]

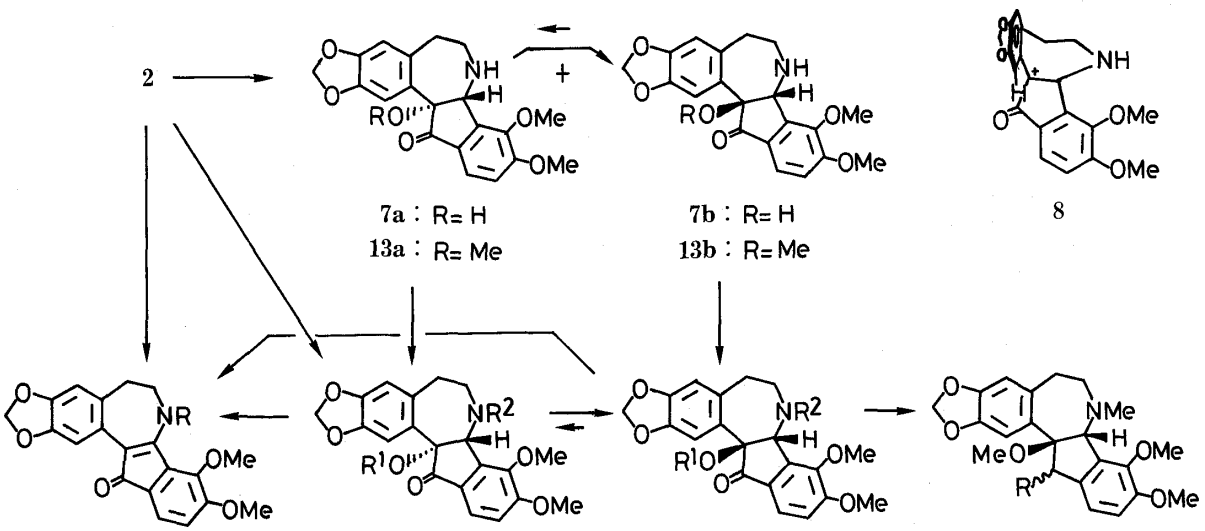

Chart 4

On treatment with acetic anhydride in pyridine, the *trans* isomer (**7a**) furnished the *N*-acetyl derivative (**9**) in 78% yield, whereas the *cis* isomer (**7b**) afforded the *N*,*O*-diacetyl derivative (**10**) in 66% yield. Methylation of **7a** and **7b** with methyl iodide in tetrahydrofuran (THF) yielded the *N*-methyl derivatives (**11a** and **11b**) in 97 and 90% yields, respectively. The former (**11a**) was identical with the authentic *trans* benzindenoazepine[17] derived from the cycloberbine (**2**) and isomerized into the *cis* isomer (**11b**) on treatment with an acid. Acetylation of the *N*-methyl derivatives (**11a** and **11b**) with acetic anhydride in pyridine gave the corresponding *O*-acetyl derivatives (**12a** and **12b**) in 69 and 70% yields, respectively.

Treatment of the cycloberbine (**2**) with trifluoroacetic acid in methanol–benzene afforded

TABLE I. Regioselective C_{14}–N Bond Cleavage of the Cycloberbine (**2**) and Equilibrium of the Benzindenoazepines (**7a** and **7b**) in Acidic Media

Starting compound	Reaction conditions			Product	
	Acid	Temp. (°C)	Time (h)	Yield (%)	Ratio (**7a** : **7b**)[b]
2	10% HCl	RT[a]	1/2	82	1 : 1
2	10% HCl	70	1	79	1 : 3.4
2	10% HCl	70	3	78	1 : 5.5
2	35% HCl	RT	1/12	81	1 : 2.9
2	10% H_2SO_4	RT	1/2	74	1 : 0.7
2	10% H_2SO_4	70	3	90	1 : 3.7
2	20% $HClO_4$/THF	Reflux	44	81	1 : 1.7
7a	10% HCl	RT	14	85	1 : 1.3
7a	10% HCl	70	3	82	1 : 3.8
7b	10% HCl	RT	14	81	1 : 32[c]
7b	10% HCl	70	3	79	1 : 10[c]
7b	20% $HClO_4$/THF	Reflux	48	88	1 : 5[c]

a) RT: room temperature. *b*) The ratio was calculated from the isolated products. *c*) The ratio was estimated from the integration values of H-8 signals in the ^{1}H-NMR spectrum of the product mixture.

the *cis* benzindenoazepine (**13b**) in 94% yield. This was also obtained in 81 or 92% yield by similar treatment with 35% hydrochloric acid or conc. sulfuric acid, respectively, as an acidic catalyst. The reaction of **2** with hydrogen chloride in methanol provided the *trans* and *cis* benzindenoazepines (**13a** and **13b**) in 23 and 70% yields, respectively. The former (**13a**) isomerized easily to the *cis* isomer (**13b**) upon treatment with an acid in methanol. The H-1 signal of the *trans* isomer (**13a**) appeared again at lower field (7.40 ppm) than that of the *cis* isomer (7.26 ppm) in the ^{1}H-NMR spectra.[18] *N*-Methylation of **13b** afforded in 94% yield the *N*-methyl derivative (**14**), which was shown to be identical with the benzindenoazepine (**6**)[9] obtained directly from the cycloberbine (**2**). The stereochemistry of **6** previously obtained was thus established. Sodium borohydride reduction of the *N*-methyl derivative (**14**) gave two diastereoisomeric alcohols (**15** and **16**) in 60 and 36% yields, respectively. The predominant alcohol (**15**) should be the product obtained by hydride attack from the convex side of the starting molecule. Their stereochemistry was supported by the appearance of the H-13 signal of **15** at higher field (4.85 ppm) than that of **16** (5.41 ppm) due to the deshielding effect of the aromatic ring A on H-13 of **16**.

The rhoeadine alkaloids, (±)-*cis*-alpinine (**17**) and (±)-*cis*-alpinigenine (**18**), have been elegantly synthesized from the benzindenoazepine (**19**) as an important key intermediate.[3b] In order to synthesize such unsaturated benzindenoazepines, dehydration of the saturated benzindenoazepines (**11a** and **11b**) was attempted by treatment with Lewis acids such as boron trifluoride and titanium tetrachloride. Dehydration of **11a** and **11b** with boron trifluoride etherate afforded the expected unsaturated benzindenoazepine (**20**)[19] in 32 and 25% yields, respectively, and that with titanium tetrachloride gave **20** in 30 and 42% yields. The same product was also obtained in 41% yield from the methoxyl derivative (**14**) by treatment with boron trifluoride etherate.

On the other hand, the cycloberbine (**2**) afforded the *N*-acetyl derivative (**9**) or the unsaturated benzindenoazepine (**21**) in 89 or 56% yield on exposure to acetic acid at room temperature or under reflux, respectively. The former was converted to the latter in 41% yield under reflux in acetic acid. The direct formation of **21** from the cycloberbine (**2**) suggests that under acidic condition without a nucleophile the carbocation (**8**) derived from **2** would afford

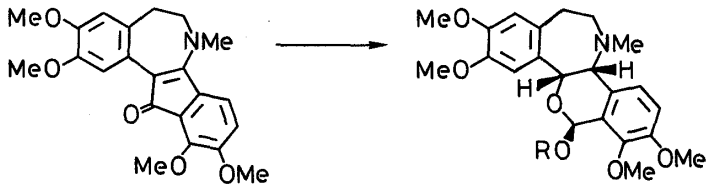

Chart 5

the elimination product (**21**). Thus, treatment of **2** in trifluoroacetic acid or with *p*-toluenesulfonic acid (*p*-TsOH) in benzene provided the unsaturated benzindenoazepine (**21**) in 44 or 96% yield, respectively. The product was methylated with dimethyl sulfate in hexamethylphosphoramide (HMPA) in the presence of sodium hydride to yield the *N*-methyl derivative (**20**) in 92% yield.

The product (**20**) has the same structure as the key intermediate (**19**) except for the substituents on rings A and D. In order to convert protoberberine alkaloids into natural rhoeadine alkaloids according to the above method, it is necessary to change the substitution pattern on ring D in protoberberines from 9,10- to 11,12-substitution. In a previous paper,[1,20] we developed efficient methods for conversion of naturally occuring 9,10-oxygenated protoberberines into non-natural 11,12-oxygenated protoberberines *via* ring D inversion, and berberine (**1**) was transformed into the 11,12-oxygenated betaine (**22**).

Irradiation of the betaine (**22**) in methanol afforded the 8,14-cycloberbine (**23**) in 82% yield. This was treated with 10% hydrochloric acid at 70 °C to give a mixture of two diastereoisomeric benzindenoazepines (**24a** and **24b**; 1 : 11 ratio),[21] which was difficult to separate completely. The mixture was methylated with dimethyl sulfate in THF in the presence of 10% sodium hydroxide to give the *N*-methyl *cis* derivative (**25b**) and the recovered *trans* isomer (**24a**) in 46 and 7% overall yields from **23**. The *trans* isomer resisted methylation under the above conditions. The *trans* isomer was easily isomerized to the *cis* isomer (**24b**) with 10% hydrochloric acid. The *cis* *N*-methyl derivative (**25b**) was subjected to dehydration by exposure to boron trifluoride etherate to produce the unsaturated benzindenoazepine (**26**)[19] in 25% yield. The product has the same substitution pattern on ring D as the key

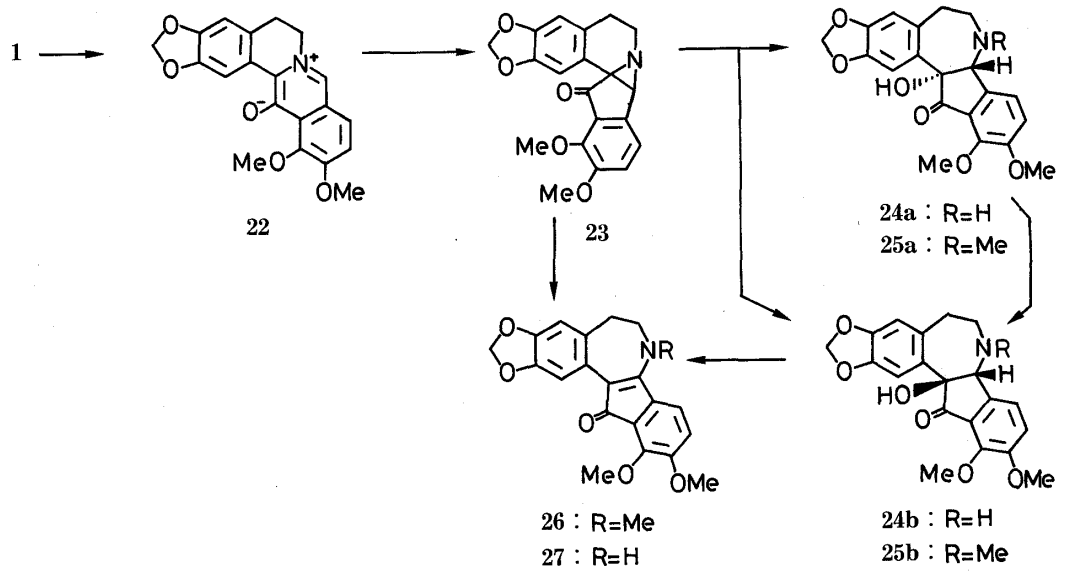

Chart 6

intermediate (**19**) for rhoeadine alkaloids, and was synthesized more conveniently by an alternative route. Treatment of the cycloberbine (**23**) with *p*-TsOH in benzene afforded the unsaturated benzindenoazepine (**27**) in 67% yield, and this was methylated with dimethyl sulfate to provide the *N*-methyl derivative (**26**) in 76% yield.

Thus, we developed a novel and convenient synthesis of *trans*-, *cis*-, and unsaturated benzindenoazepines from berberine *via* regioselective C_{14}–N bond cleavage of the 8,14-cycloberbines. The present simple conversion provides a new and efficient route for the synthesis of the benzindenoazepine alkaloids and related alkaloids shown in Chart 1 from protoberberine alkaloids.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Organic extract were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography was carried out with alumina (Aluminiumoxid 90, Aktivitätsstufe II—III, 70—230 mesh, Merck) and silica gel (Kieselgel 60, 70—230 mesh, Merck). Preparative thin-layer chromatography (p-TLC) was performed on alumina (Aluminiumoxid GF_{254} Type 60/E, Merck) and silica gel (Kieselgel GF_{254} Type 60, Merck). Infrared (IR) spectra were measured with a JASCO A-102 spectrometer, mass spectra (MS) with a Hitachi M-80 spectrometer, and ^{1}H-NMR spectra with a JEOL FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard unless otherwise stated.

***rel*-(8*R*,14*R*)- and *rel*-(8*R*,14*S*)-5,6,7,8,13,14-Hexahydro-14-hydroxy-9,10-dimethoxy-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (7a and 7b)**[22]——A solution of the cycloberbine (**2**, 106.2 mg) in 10% HCl (10 ml) was stirred at room temperature for 30 min, then made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was chromatographed on p-TLC (Al_2O_3) with $CHCl_3$ to afford two fractions. The less polar fraction gave the *trans*-azepine (**7a**, 45.4 mg, 41%) as pale yellow prisms, mp 199.5—200.5 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200 (OH, NH), 1700 (CO). MS *m/e*: 369 (M^+). ^{1}H-NMR δ: 7.46, 6.87 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 7.24 (1H, s, C_1-H), 6.47 (1H, s, C_4-H), 5.76 (2H, s, OCH_2O), 4.18 (1H, s, C_8-H), 3.86, 3.80 (each 3H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.12; N, 3.79. Found: C, 64.88; H, 5.10; N, 3.56. The more polar fraction gave the *cis*-azepine (**7b**, 45.5 mg, 41%) as colorless prisms, mp 112—114 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200 (OH, NH), 1710 (CO). MS *m/e*: 369 (M^+). ^{1}H-NMR δ: 7.53, 6.98 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 6.95 (1H, s, C_1-H), 6.56 (1H, s, C_4-H), 5.86, 5.80 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.37 (1H, s, C_8-H), 3.93 (6H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{20}H_{19}NO_6 \cdot$MeOH: C, 62.84; H, 5.78; N, 3.49. Found: C, 63.04; H, 5.72; N, 3.40. Similar reactions were carried out under other conditions and the results are summarized in Table I.

Isomerization of the *trans*-Azepine (7a) and the *cis*-Azepine (7b) to Each Other——General Procedure: A solution of the *trans*- or *cis*-azepine (**7a** or **7b**) in an acid was stirred. Work-up as described above afforded **7a** and **7b**. The conditions and results are summarized in Table I.

***rel*-(8*R*,14*R*)-7-Acetyl-5,6,7,8,13,14-hexahydro-14-hydroxy-9,10-dimethoxy-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (9)**——1) A solution of **7a** (120 mg) in pyridine (5 ml) and acetic anhydride (5 ml) was heated at 75 °C for 4 h, then the organic solvents were evaporated off. The residue was taken up in $CHCl_3$ and the $CHCl_3$ layer was washed with sat. $NaHCO_3$ and water, dried, and concentrated to give the residue, which was chromatographed on Al_2O_3 with $CHCl_3$ to afford the *N*-acetyl derivative (**9**, 104.7 mg, 78%) as colorless prisms, mp 209—211 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1710 (CO), 1630 (NCO). MS *m/e*: 411 (M^+). ^{1}H-NMR δ: 7.69, 7.02 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 7.38 (1H, s, C_1-H), 6.69 (1H, s, C_4-H), 5.92 (2H, s, OCH_2O), 4.81 (1H, s, C_8-H), 3.93, 3.79 (each 3H, s, $OCH_3 \times 2$), 2.29 (3H, s, $COCH_3$). *Anal.* Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.14; N, 3.40. Found: C, 63.96; H, 5.09; N, 3.40.

2) A solution of **2** (127.2 mg) in acetic acid (10 ml) was stirred at room temperature for 3 h. The solution was made alkaline with aqueous K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was chromatographed on p-TLC (Al_2O_3, $CHCl_3$) to afford **9** (131.8 mg, 89%).

***rel*-(8*R*,14*S*)-14-Acetoxy-7-acetyl-5,6,7,8,13,14-hexahydro-9,10-dimethoxy-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (10)**——A solution of **7b** (187 mg) in pyridine (5 ml) and acetic anhydride (5 ml) was heated at 75 °C for 4 h, then the solvents were evaporated off. The residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with sat. $NaHCO_3$ and water, dried, and concentrated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to afford the *N*,*O*-diacetyl derivative (**10**, 152 mg, 66%) as colorless plates, mp 216—218 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (OCO), 1720 (CO), 1640 (NCO). MS *m/e*: 453 (M^+). ^{1}H-NMR δ: 7.60, 7.07 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 7.39 (1H, s, C_1-H), 7.10, 6.35 (each 1H, s, C_4- and C_8-H), 5.97, 5.92 (2H, AB-q, J=1.5 Hz, OCH_2O), 3.99, 3.82 (each 3H, s, $OCH_3 \times 2$), 2.24, 2.09 (each 3H, s, $COCH_3 \times 2$). *Anal.* Calcd for $C_{24}H_{23}NO_8$: C, 63.57; H, 5.11; N, 3.09. Found: C, 63.27; H, 5.05; N, 3.02.

***rel*-(8*R*,14*R*)-5,6,7,8,13,14-Hexahydro-14-hydroxy-9,10-dimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (11a)**——A solution of **7a** (200 mg) in THF (5 ml) and MeI (5 ml) was heated under reflux for 1.5 h with stirring and the solvents were evaporated off. The residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with 10% aqueous NaOH and water, dried, and concentrated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to afford the *N*-methyl derivative (**11a**, 201.1 mg, 97%) as pale yellow prisms, mp 157—158.5 °C (MeOH) (lit.[14a] mp 182—183 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1710 (CO). MS *m/e*: 383 (M^+). ^{1}H-NMR δ: 7.52, 6.93 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 7.00 (1H, s, C_1-H), 6.49 (1H, s, C_4-H), 5.73 (2H, s, OCH_2O), 4.33 (1H, s, C_8-H), 3.88, 3.77 (each 3H, s, $OCH_3 \times 2$), 2.74 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.82; H, 5.44; N, 3.39. This compound was identical with an authentic specimen synthesized according to the method of Shamma *et al.*[14a]

***rel*-(8*R*,14*S*)-5,6,7,8,13,14-Hexahydro-14-hydroxy-9,10-dimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (11b)**——A solution of **7b** (202.3 mg) in THF (10 ml) and MeI (5 ml) was heated under reflux for 1 h with stirring. Work-up as usual gave the *N*-methyl derivative (**11b**, 189.5 mg, 90%) as colorless prisms, mp 187—189 °C (MeOH) (lit.[14a] mp 192—193 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1700 (CO). MS *m/e*: 383 (M^+). ^{1}H-NMR δ: 7.58, 6.96 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 7.21 (1H, s, C_1-H), 6.48 (1H, s, C_4-H), 5.87 (2H, s, OCH_2O), 4.48 (1H, s, C_8-H), 3.96, 3.90 (each 3H, s, $OCH_3 \times 2$), 2.56 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.81; H, 5.55; N, 3.48.

Isomerization of the *trans*-Azepine (11a) and the *cis*-Azepine (11b) to Each Other——1) A solution of **11a** (34 mg) in 10% HCl (7 ml) was heated at 70 °C for 3 h with stirring. Work-up as usual gave the residue (28 mg, 82%) which was shown to be a 1 : 1 mixture of **11a** and **11b** as estimated from the ^{1}H-NMR integration of H-8 signals.

2) A solution of **11b** (30 mg) in 10% HCl (7 ml) was heated at 70 °C for 3 h with stirring. Work-up as usual gave the residue (25.2 mg, 84%), which was shown to be a mixture of **11a** and **11b** (1 : 20, estimated as above).

3) A solution of **11b** (40 mg) in THF (5 ml) and 20% aqueous $HClO_4$ (3 ml) was heated under reflux for 37 h with stirring. Work-up as usual gave the residue (35.1 mg, 88%), which was shown to be a mixture of **11a** and **11b** (1 : 35, estimated as above).

***rel*-(8*R*,14*R*)-14-Acetoxy-5,6,7,8,13,14-hexahydro-9,10-dimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (12a)**——A solution of **11a** (40 mg) in pyridine (3 ml) and acetic anhydride (3 ml) was heated at 70 °C for 22 h, then the solvents were evaporated off. Work-up as usual gave the *O*-acetyl derivative (**12a**, 30.6 mg, 69%) as colorless needles, mp 192—194 °C (MeOH) (lit.[14a] mp 186—187 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (OCO), 1700 (CO). MS *m/e*: 425 (M^+). ^{1}H-NMR δ: 7.67, 7.05 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 7.59 (1H, s, C_1-H), 6.64 (1H, s, C_4-H), 5.92, 5.91 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.91 (1H, s, C_8-H), 3.96, 3.84 (each 3H, s, $OCH_3 \times 2$), 2.83 (3H, s, NCH_3), 2.00 (3H, s, $COCH_3$). *Anal.* Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.63; H, 5.46; N, 3.22.

***rel*-(8*R*,14*S*)-14-Acetoxy-5,6,7,8,13,14-hexahydro-9,10-dimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (12b)**——A solution of **11b** (50 mg) in pyridine (3 ml) and acetic anhydride (3 ml) was heated at 70 °C for 24 h, then the solvents were evaporated off. Work-up as usual gave the residue, which was chromatographed on Al_2O_3 with $CHCl_3$ to afford the *O*-acetyl derivative (**12b**, 38.8 mg, 70%) as colorless prisms, mp 172—174 °C (MeOH) (lit.[14a] mp 178—181 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (OCO), 1710 (CO). MS *m/e*: 425 (M^+). ^{1}H-NMR δ: 7.60, 7.04 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 7.32 (1H, s, C_1-H), 6.48 (1H, s, C_4-H), 5.94, 5.90 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.98 (1H, s, C_8-H), 3.99, 3.94 (each 3H, s, $OCH_3 \times 2$), 2.77 (3H, s, NCH_3), 2.21 (3H, s, $COCH_3$). *Anal.* Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 65.09; H, 5.58; N, 3.21.

***rel*-(8*R*,14*R*)- and *rel*-(8*R*,14*S*)-5,6,7,8,13,14-Hexahydro-9,10,14-trimethoxy-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (13a and 13b)**——1) Trifluoroacetic acid (1 drop) was added to a solution of **2** (97.1 mg) in C_6H_6 (10 ml) and MeOH (3 ml) and the reaction solution was kept standing overnight at room temperature. The reaction solution was made alkaline with 10% aqueous NaOH, and the organic solvents were evaporated off. The residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to afford the *cis* methoxyl derivative (**13b**, 99.7 mg, 94%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (NH), 1695 (CO). MS *m/e*: 383 (M^+). High-resolution MS: Calcd for $C_{21}H_{21}NO_6$: 383.1370. Found: 383.1369. ^{1}H-NMR δ: 7.61, 7.06 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 7.26 (1H, s, C_1-H), 6.70 (1H, s, C_4-H), 5.96, 5.90 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.41 (1H, s, C_8-H), 3.96, 3.95, 3.30 (each 3H, s, $OCH_3 \times 3$).

2) Conc. sulfuric acid (2 drops) was added to a solution of **2** (103.1 mg) in MeOH (4 ml) and C_6H_6 (10 ml) and the reaction solution was kept standing overnight at room temperature. Work-up as usual gave **13b** (103.5 mg, 92%).

3) Conc. hydrochloric acid (2 drops) was added to a solution of **2** (105.8 mg) in MeOH (4 ml) and C_6H_6 (10 ml) and the reaction solution was kept standing overnight at room temperature. Work-up as usual gave **13b** (93.7 mg, 81%).

4) A solution of **2** (30 mg) in MeOH (6 ml) saturated with dry HCl gas was stirred at 0 °C for 1.5 h and room temperature for 1 h. Work-up as usual gave the residue, which was chromatographed on p-TLC (SiO_2, Et_2O) to afford two fractions. The less polar fraction gave **13b** (22.8 mg, 70%). The more polar fraction gave the *trans* methoxy derivative (**13a**, 7.4 mg, 23%) as colorless plates, mp 175—177 °C (MeOH) (lit.[14b] mp 179—180 °C). IR $\nu_{max}^{CHCl_3}$

cm^{-1}: 3350 (NH), 1700 (CO). MS *m/e*: 383 (M^+). ^{1}H-NMR δ: 7.62, 6.99 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 7.40 (1H, s, C_1-H), 6.66 (1H, s, C_4-H), 5.95 (2H, s, OCH_2O), 4.61 (1H, s, C_8-H), 3.94, 3.91, 3.21 (each 3H, s, $OCH_3 \times 3$). *Anal.* Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.75; H, 5.44; N, 3.63.

Isomerization of the *trans*-Azepine (13a) to the *cis*-Azepine (13b)——A solution of **13a** (10 mg) in MeOH (3 ml) saturated with dry HCl gas was kept standing overnight. Work-up as usual gave **13b** (8.7 mg, 87%).

***rel*-(8*R*,14*S*)-5,6,7,8,13,14-Hexahydro-9,10,14-trimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (14)**——Methyl iodide (2 ml) was added to a stirred solution of **13b** (245 mg) in THF (10 ml) and 20% aqueous K_2CO_3 (5 ml) and stirring was continued for 4 h at room temperature. THF was evaporated off and the residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried, and concentrated. The residue was chromatographed on Al_2O_3 with C_6H_6–AcOEt (4:1) to afford the *N*-methyl derivative (**14**, 230 mg, 94%) as colorless prisms, mp 193—194 °C (MeOH). This product was identical with an authentic specimen synthesized previously.[11]

***rel*-(8*R*,13*S*,14*S*)- and *rel*-(8*R*,13*R*,14*S*)-5,6,7,8,13,14-Hexahydro-9,10-14-trimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-ol (15 and 16)**——$NaBH_4$ (0.1 g) was added to a solution of **14** (96.8 mg) in MeOH (10 ml) and $CHCl_3$ (3 ml) and the reaction solution was stirred at room temperature for 12 h. Water (5 ml) was added to the reaction solution and the organic solvents were evaporated off. The residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried, and concentrated. The residue was chromatographed on p-TLC [SiO_2, C_6H_6–AcOEt (4:1)] to afford two fractions. The less polar fraction gave the alcohol (**16**, 34.9 mg, 36%) as colorless plates, mp 185—186 °C (MeOH). IR ν_{max}^{KBr} cm^{-1}: 3500 (OH). MS *m/e*: 399 (M^+). ^{1}H-NMR δ: 7.91 (1H, s, C_1-H), 7.16, 6.97 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 6.63 (1H, s, C_4-H), 5.95, 5.93 (2H, AB-q, J=1.5 Hz, OCH_2O), 5.41 (1H, d, J=11.5 Hz, C_{13}-H), 4.76 (1H, s, C_8-H), 3.93, 3.88, 3.14 (each 3H, s, $OCH_3 \times 3$), 2.02 (3H, s, NCH_3). *Anal.* Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.99; H, 6.25; N, 3.80. The more polar fraction gave the isomeric alcohol (**15**, 57.9 mg, 60%) as colorless cubes, mp 190—192 °C (MeOH). IR ν_{max}^{KBr} cm^{-1}: 3375 (OH). MS *m/e*: 399 (M^+). ^{1}H-NMR δ: 7.24, 6.94 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 7.11 (1H, s, C_1-H), 6.63 (1H, s, C_4-H), 5.97, 5.95 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.90 (1H, s, C_8-H), 4.85 (1H, d, J=9 Hz, C_{13}-H), 3.94, 3.88, 3.01 (each 3H, s, $OCH_3 \times 3$), 2.10 (3H, s, NCH_3). *Anal.* Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.24; H, 6.17; N, 3.47.

5,6,7,13-Tetrahydro-9,10-dimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (20)——1) Boron trifluoride etherate or titanium tetrachloride was added to a solution of the benzindenoazepine (**11a**, **11b**, or **14**) in anhyd. C_6H_6 or CH_2Cl_2 and the resulting mixture was heated under reflux with stirring. Aqueous K_2CO_3 was added to the reaction mixture and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried, and concentrated. The residue was chromatographed on p-TLC (Al_2O_3, $CHCl_3$) to afford the unsaturated benzindenoazepine (**20**) as purple-red needles, mp 185—186 °C (MeOH) (lit.[19] mp 185—187 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (CO). MS *m/e*: 365 (M^+). ^{1}H-NMR δ: 7.64 (1H, s, C_1-H), 7.16, 6.69 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 6.47 (1H, s, C_4-H), 5.83 (2H, s, OCH_2O), 3.85, 3.76 (each 3H, s, $OCH_3 \times 2$), 3.13 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.93; H, 5.12; N, 3.61. The results were as follows: the starting azepine; the Lewis acid; the solvent; the reaction time; and the yield of **20**.

i) **11a** (168.8 mg); $BF_3 \cdot OEt_2$ (300 mg); C_6H_6 (7 ml); 5 h; 51.7 mg (32%).
ii) **11b** (146.5 mg); $BF_3 \cdot OEt_2$ (300 mg); C_6H_6 (6 ml); 5 h; 34.9 mg (25%).
iii) **11a** (30 mg); $TiCl_4$ (3 drops); CH_2Cl_2 (5 ml); 70 min; 8.6 mg (30%).
iv) **11b** (20 mg); $TiCl_4$ (1 drop); CH_2Cl_2 (5 ml); 6 h; 8 mg (42%).
v) **14** (50.9 mg); $BF_3 \cdot OEt_2$ (250 mg); CH_2Cl_2 (10 ml); 4 h; 19.1 mg (41%).

2) Dimethyl sulfate (5 drops) was added to a solution of **21** (97.5 mg) and NaH (30 mg, 50% dispersion in mineral oil) in HMPA (0.5 ml) and the resulting solution was kept standing at room temperature for 1.5 h. Aqueous ammonia (28%, 1 ml) was added to the reaction solution and stirring was continued for 1 h at room temperature, then the whole was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried, and concentrated. The residue was chromatographed on p-TLC (Al_2O_3, $CHCl_3$) to afford **20** (93.4 mg, 92%).

5,6,7,13-Tetrahydro-9,10-dimethoxy-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (21)——1) A solution of **2** (147.9 mg) in AcOH (10 ml) was heated under reflux for 2 h. Acetic acid was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with aqueous K_2CO_3 and water, dried, and concentrated. The residue was chromatographed on SiO_2 with C_6H_6–AcOEt (2:1) to afford the unsaturated benzindenoazepine (**21**, 82.9 mg, 56%) as red needles, mp 238—240 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3375 (NH), 1660 (CO). MS *m/e*: 351 (M^+). ^{1}H-NMR δ: 7.87 (1H, s, C_1-H), 7.21, 6.74 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 6.69 (1H, s, C_4-H), 5.90 (2H, s, OCH_2O), 3.97, 3.89 (each 3H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.50; H, 4.76; N, 3.73.

2) A solution of **9** (97.4 mg) in AcOH (10 ml) was heated under reflux for 2 h. Work-up as usual gave **21** (30.9 mg, 41%).

3) A solution of **2** (85 mg) in trifluoroacetic acid (5 ml) was kept standing at room temperature for 1 h and trifluoroacetic acid was evaporated off. Work-up as usual gave **21** (37.5 mg, 44%).

4) *p*-Toluenesulfonic acid (120 mg) was added to a solution of **2** (144.5 mg) in anhyd. C_6H_6 (30 ml) and the

reaction mixture was heated under reflux for 1.5 h with stirring. Benzene was evaporated off and the residue was taken up in $CHCl_3$. Work-up as usual gave **21** (139.4 mg, 96%).

11,12-Dimethoxy-2,3-methylenedioxy-8,14-cycloberbin-13-one (23)——A solution of **22** (200 mg) in MeOH (300 ml) was irradiated through a Pyrex filter (100 W high-pressure mercury lamp, Riko Kagaku Co.) at room temperature for 40 min in a stream of nitrogen. The solvent was evaporated off. The residue was chromatographed on SiO_2 with C_6H_6–AcOEt (4 : 1) to afford **23** (164 mg, 82%) as pale yellow needles, mp 187.5—188.5 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO). MS *m/e*: 351 (M^+). ^{1}H-NMR δ: 7.23 (1H, s, C_1-H), 7.00 (2H, s, C_9- and C_{10}-H), 6.55 (1H, s, C_4-H), 5.86 (2H, s, OCH_2O), 4.00, 3.82 (each 3H, s, $OCH_3 \times 2$), 3.70 (1H, s, C_8-H). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.18; H, 4.69; N, 3.97.

***rel*-(8*R*,14*R*)- and *rel*-(8*R*,14*S*)-5,6,7,8,13,14-Hexahydro-14-hydroxy-11,12-dimethoxy-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (24a and 24b)**——1) A solution of **23** (54.8 mg) in 10% HCl (5 ml) was stirred at 70 °C for 3 h. The reaction mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated to leave the residue (56.9 mg, 99%), which was a 1 : 11 mixture of **24a** and **24b** as estimated from the H-8 integrations. The crude material was separated only partially into **24a** and **24b** by SiO_2 (230—400 mesh, Merck) column chromatography using $CHCl_3$ and MeOH (49 : 1).

The Pure **24a**: A semi-solid: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH, NH), 1705 (CO). MS *m/e*: 369 (M^+). High-resolution MS: Cald for $C_{20}H_{19}NO_6$: 369.1199. Found: 369.1205. ^{1}H-NMR δ: 7.42 (1H, s, C_1-H), 7.23 (2H, s, C_9- and C_{10}-H), 6.64 (1H, s, C_4-H), 5.92 (2H, s, OCH_2O), 4.29 (1H, s, C_8-H), 4.07, 3.90 (each 3H, s, $OCH_3 \times 2$).

The Pure **24b**: Colorless plates, mp 205—207 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH, NH), 1705 (CO). MS *m/e*: 369 (M^+). ^{1}H-NMR δ: 7.38, 7.27 (2H, AB-q, J=8.5 Hz, C_9- and C_{10}-H), 6.70, 6.68 (each 1H, s, C_1- and C_4-H), 5.90, 5.87 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.20 (1H, s, C_8-H), 4.11, 3.89 (each 3H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.12; N, 3.79. Found: C, 64.97; H, 5.00; N, 3.85.

2) A solution of **23** (50 mg) in 10% HCl (7 ml) was stirred at room temperature for 30 min. Work-up as usual gave the residue (47.6 mg, 91%), which was a 1 : 3 mixture of **24a** and **24b** as estimated from the H-8 integrations.

3) A solution of **23** (1.31 g) in THF (70 ml) and 20% aqueous $HClO_4$ (30 ml) was heated under reflux for 37 h with stirring. Work-up as usual gave the residue (1.13 g, 82%), which was a 1 : 5 mixture of **24a** and **24b** as estimated from the H-8 integrations.

Isomerization of 24a and 24b——A solution of the azepines [**24a** and **24b** (1 : 3 ratio), 63 mg] in 10% HCl (7 ml) was stirred at 70 °C for 3 h. Work-up as usual gave a mixture of the azepines [**24a** and **24b** (1 : 11 ratio), 56 mg (89%)].

***rel*-(8*R*,14*S*)-5,6,7,8,13,14-Hexahydro-14-hydroxy-11,12-dimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (25b)**——Dimethyl sulfate (0.1 ml) was added to an ice-cooled solution of the azepines (**24a** and **24b**, 1 : 11 ratio, 56.9 mg) in THF (2 ml) and 10% NaOH (1 ml), and the reaction mixture was stirred at 0 °C for 3.5 h. Aqueous ammonia (28%, 1 ml) was added to the reaction mixture and stirring was continued for 1 h at room temperature. THF was evaporated off and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was chromatographed on p-TLC (Al_2O_3, $CHCl_3$) to afford two fractions. The less polar fraction gave the *trans* azepine (**24a**, 4 mg, 7% from **23**). The more polar fraction gave the *N*-methyl *cis* azepine (**25b**, 27.5 mg, 46% from **23**) as pale yellow prisms, mp 191—192 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1705 (CO). MS *m/e*: 383 (M^+). ^{1}H-NMR δ: 7.33—7.24 (3H, C_1-, C_9- and C_{10}-H), 6.57 (1H, s, C_4-H), 5.95, 5.93 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.40 (1H, s, C_8-H), 4.01, 3.93 (each 3H, s, $OCH_3 \times 2$), 2.54 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.70; H, 5.34; N, 3.60.

5,6,7,13-Tetrahydro-11,12-dimethoxy-7-methyl-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (26)——1) Boron trifluoride etherate (5 drops) was added to a solution of **25b** (30 mg) in anhyd. CH_2Cl_2 (2 ml) and the resulting mixture was heated under reflux for 1 h with stirring. Aqueous K_2CO_3 was added to the reaction solution and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried, and concentrated. The residue was chromatographed on p-TLC (Al_2O_3, $CHCl_3$) to afford the unsaturated benzindenoazepine (**26**, 7.1 mg, 25%) as red needles, mp 189—190 °C (MeOH) (lit.[19] mp 188—189 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (CO). MS *m/e*: 365 (M^+). ^{1}H-NMR δ: 7.60 (1H, s, C_1-H), 7.06, 6.66 (2H, AB-q, J=8 Hz, C_9- and C_{10}-H), 6.53 (1H, s, C_4-H), 5.90 (2H, s, OCH_2O), 4.03, 3.88 (each 3H, s, $OCH_3 \times 2$), 3.40 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.00; H, 5.13; N, 3.54.

2) Sodium hydride (30 mg, 50% dispersion in mineral oil) was added to a solution of **27** (34.3 mg) in HMPA (0.5 ml) and anhyd. C_6H_6 (2 ml) and the resulting solution was stirred at room temperature for 15 min. Dimethyl sulfate (3 drops) was added to the reaction solution and stirring was continued for 2 h at room temperature. Work-up as usual gave the residue, which was chromatographed on p-TLC [SiO_2, C_6H_6–AcOEt (4 : 1)] to afford **26** (27.2 mg, 76%).

5,6,7,13-Tetrahydro-11,12-dimethoxy-2,3-methylenedioxybenz[*d*]indeno[1,2-*b*]azepin-13-one (27)——A solution of **23** (108.7 mg) and *p*-TsOH (130 mg) in anhyd. C_6H_6 (10 ml) was heated under reflux for 2 h with stirring. Work-up as usual gave the residue, which was chromatographed on SiO_2 with C_6H_6–AcOEt (4 : 1) to afford the unsaturated benzindenoazepine (**27**, 72.3 mg, 67%) as red needles, mp 237—239 °C (MeOH). IR ν_{max}^{KBr} cm^{-1}: 3725 (NH), 1650 (CO). MS *m/e*: 351 (M^+). ^{1}H-NMR δ (DMSO-d_6): 8.60 (1H, br s, NH), 7.74 (1H, s, C_1-H), 7.28, 6.95 (2H, AB-q, J=

8 Hz, C_9- and C_{10}-H), 6.68 (1H, s, C_4-H), 5.93 (2H, s, OCH_2O), 3.85, 3.80 (each 3H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.43; H, 4.81; N, 3.99.

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16) Shamma *et al.*[14b] explained the formation of **7a** in terms of the attack of a nucleophile on the carbocation intermediate having a conformation like that of the cycloberbine (**2**), before attainment of the completely plannar conformation.
17) Treatment of the cycloberbine (**2**) with formaldehyde followed by reduction with sodium cyanoborohydride afforded the *trans* benzindenoazepine (**11a**).[14a]
18) The H-8 signal of the *trans* isomer (**13a**) appeared at lower field (4.61 ppm) than that (4.41 ppm) of the *cis* isomer (**13b**). This is contrary to the cases of **7a** and **7b** and the literature.[15] The H-8 signals, therefore, are not suitable for the stereochemical determination of the benzindenoazepines described in this paper. The comparison of H-1 signals is useful for stereochemical assignment in our case.
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21) The reaction of **23** with 10% hydrochloric acid at room temperature or with 20% perchloric acid in THF under reflux gave **24a** and **24b** in 1 : 3 or 1 : 5 ratio in 91 or 82% yield, respectively.
22) The numbering of the benzindenoazepines described in this paper is in accord with that for protoberberines.