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Utilization of Protopine and Related Alkaloids. III.[1] Acid Catalyzed Cyclization of Anhydromethylberberine. The Revised Structures for Hydroxyisoanhydrodihydromethylberberine and Isoanhydromethylberberine

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When anhydromethylberberine derived from α-allocryptopine was treated with dilute hydrochloric acid, it gave three products, whose structures were identified to contain the spiro-type skelton instead of "Perkin's compound" by the nuclear magnetic resonance spectroscopy.

In 1918, Perkin[3] showed that berberinium salt (I), when heated on steam-bath with concentrated sodium hydroxide solution, underwent simultaneous reduction and oxidation with the formation of dihydroanhydroberberine (II) and oxyberberine (III). The methosulfate (IV) was decomposed with methylalcoholic potassium hydroxide to afford anhydromethylberberine (V). When V was heated with dilute hydrochloric acid, it was converted

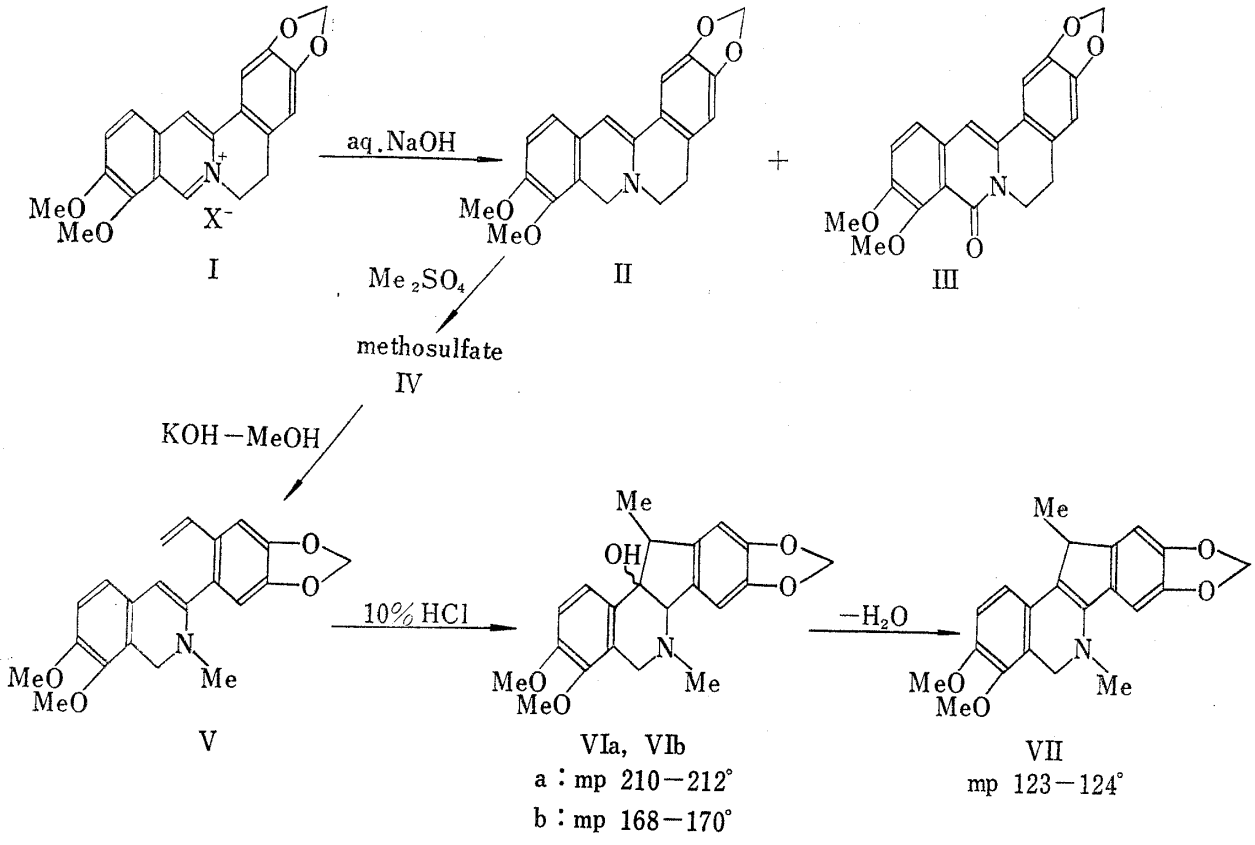

Chart 1

1) Part II: M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **17**, 404 (1969).
2) Location: *Minato-ku, Tokyo.*
3) W.H. Perkin, *J. Chem. Soc.*, **1918**, 722.

into the stereoisomeric hydroxyisoanhydrodihydromethylberberine-A (VIa) and -B (VIb), which were dehydrated to isoanhydromethylberberine (VII) with concentrated hydrochloric acid or phosphoryl chloride.

On the other hand, we reported[4] that anhydroprotopine (VIII) derived from protopine afforded three products with dilute hydrochloric acid, which were identified to be the stereoisomeric N-methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′,3′-hydroxy-5′,6′-methylenedioxyindanes (IXa and IXb) and N-methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′-5′,6′-methylenedioxyindene (X) by the nuclear magnetic resonance (NMR) spectra.

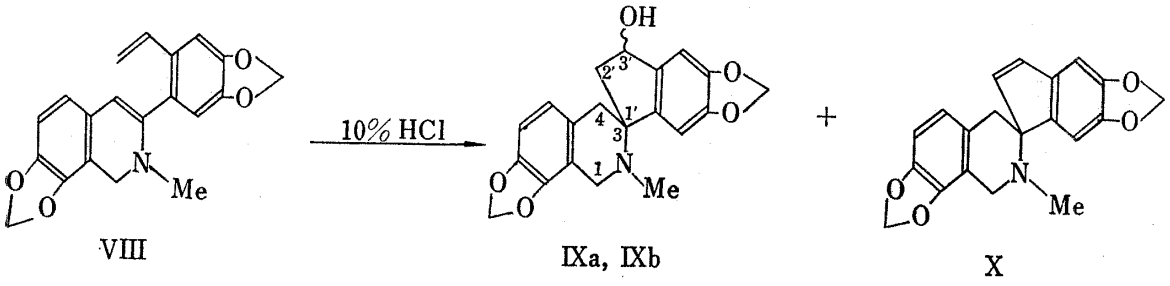

Chart 2

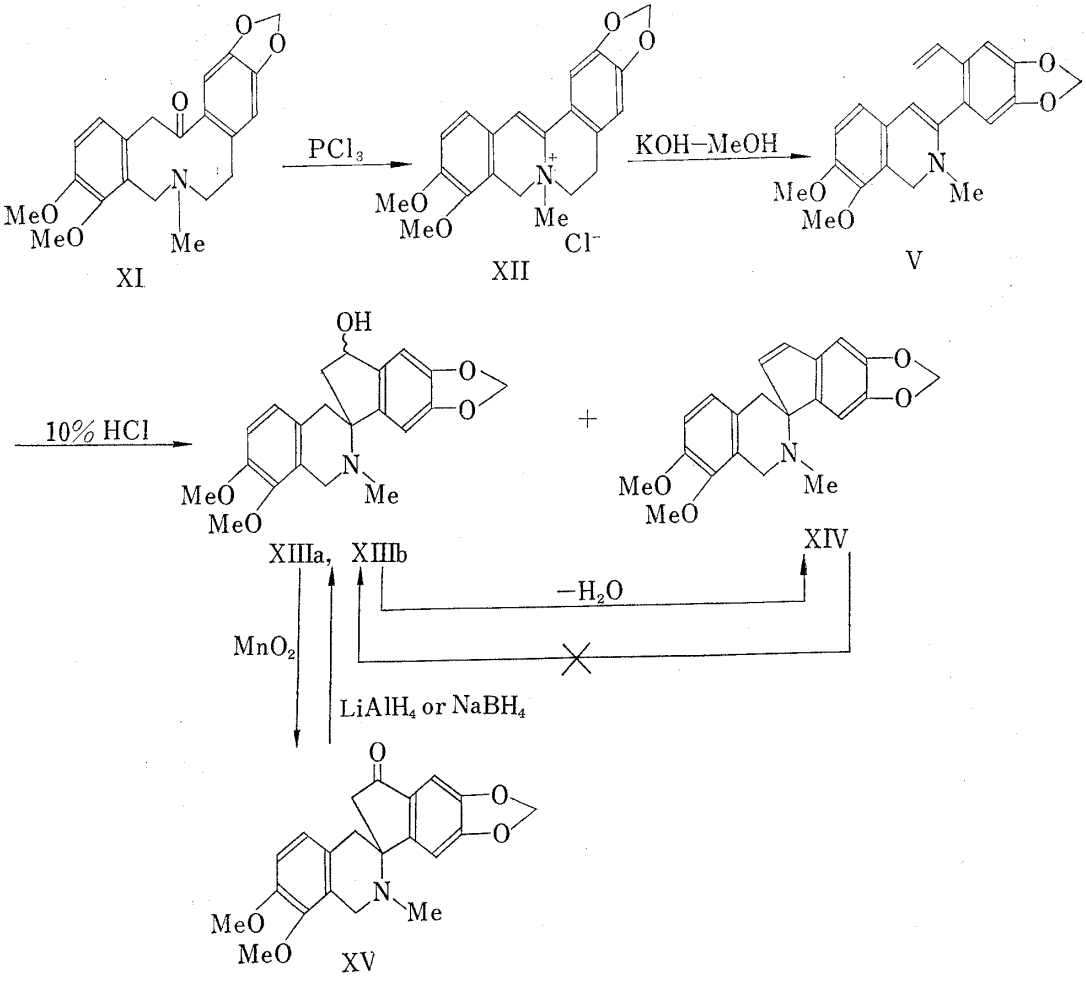

Chart 3

4) M. Onda, K. Abe, and K. Yonezawa, *Chem. Pharm. Bull.* (Tokyo), **16**, 2005 (1968).

Since V is closely related to VIII, the structures for VI and VII proposed by Perkin are expected to be incorrect. This paper is concerned with the revision of structures for VI and VII, which was carried out in our laboratory by utilizing α-allocryptopine, one of the major alkaloid of *Bocconia cordata*, as the starting material.

As shown in Chart 3, α-allocryptopine (XI) gave dihydroanhydroberberine methochloride (XII) with phosphorous chloride, which was converted to anhydromethylberberine (V) by Hofmann degradation.

When V was heated on a boiling water bath with dilute hydrochloric acid, three following bases were obtained: XIIIa, mp 220—222°, $C_{21}H_{23}O_5N$; XIIIb, mp 172.5—173.5°, $C_{21}H_{23}O_5N$; XIV, mp 124—124.5°, $C_{21}H_{21}O_4N$. It seems probably that XIIIa and XIIIb are the stereoisomers from their formula. The fact that these bases show no doublet methyl signals in the NMR spectra indicates that Perkin's structure for VIa and VIb should be surely excluded.

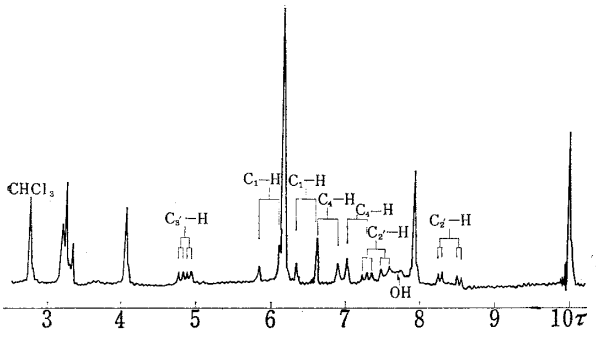

Fig. 1. NMR Spectrum of XIIIa (60 Mc)

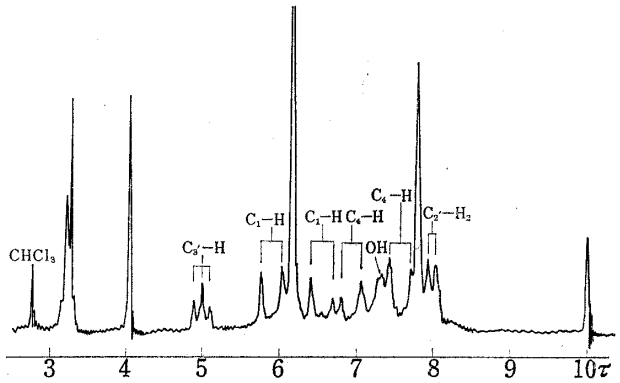

Fig. 2. NMR Spectrum of XIIIb (60 Mc)

Table I. Nuclear Magnetic Resonance Spectral Data of XIIIa, IXa, XIIIb, IXb, XIV and X

	Arom.-H C_5, C_6	Arom.-H C'_4, C'_7	C_1–H_2	C_4–H_2	$C_{2'}$–H_2	$C_{3'}$–H	N–CH_3	$CH_2<^{O-}_{O-}$	CH_3O–
XIIIa	3.29, 3.19,	3.24	6.09 (d) 6.72 (d) J=16	6.68 (d) 6.93 (d) J=17	7.40 (q) J_{gem}=15 J=8 8.39 (q) J_{gem}=15 J=4	4.83 (q) J=8,4	7.92	4.06 (s)	6.15 (s)
IXa	3.35 (d) 3.49 (d) J=8	3.19 (s) 3.32 (s)	6.08 (d) 6.51 (d) J=17	6.81 (d) 7.13 (d) J=16	7.41 (q) J_{gem}=14 J=7 8.37 (q) J_{gem}=14 J=3	4.85 (q) J=7,3	7.98	4.08 (s)	
XIIIb	3.27 (s)	3.21 (s)	5.89 (d) 6.51 (d) J=16	6.96 (d) 7.52 (d) J=16	7.98 (d) J=6	4.98 (t) J=6	7.79	4.05 (s)	6.13 (s)
IXb	3.36 (d) 3.52 (d) J=8	3.18 (s) 3.22 (s)	5.98 (d) 6.54 (d) J=17	6.93 (d) 7.52 (d) J=16	7.90 (d) J=6	4.96 (t) J=6	7.79	4.06 (s) 4.08 (d) 4.11 (d) J=1.0	
XIV	2.95, 3.02,	3.27	5.85 (d) 6.54 (d) J=17	6.73 (d) 7.39 (d) J=15.4	7.21 (d) 7.82 (d) J=19		7.90 (s)	3.95 (s)	6.16 (s)
X	3.24 (s)		5.85 (d) 6.19 (d) J=18	6.79 (d) 7.36 (d) J=17	3.73 (d) J=6	3.34 (d) J=6	7.91 (s)	4.06 (s)	6.12 (s) 6.14 (s)

As shown in Fig. 1, Fig. 2, and Table I, the NMR spectra of XIIIa and XIIIb exhibit the close similarities to those of the spiro compounds (IXa and IXb). This result shows that the ring skelton of XIIIa and XIIIb are same as that of IXa and IXb.

On comparison with the NMR spectra of XIIIa and XIIIb, N-methyl of XIIIa appears at upper field (7.92 τ) than that (7.79 τ) of XIIIb. Accordingly, from the same reason that were assigned to the configuration of IXa and IXb, C_3'–OH probably orientates *trans* to C'_1–N in XIIIa and *cis* in XIIIb. Furthermore, this is confirmed by the fact that the infrared (IR) spectrum of XIIIb (Fig. 3) exhibits the absorption band at 3617 cm^{-1}, which is invariable with the change of concentration (in CCl_4) to show the presence of intramolecular hydrogen bond.

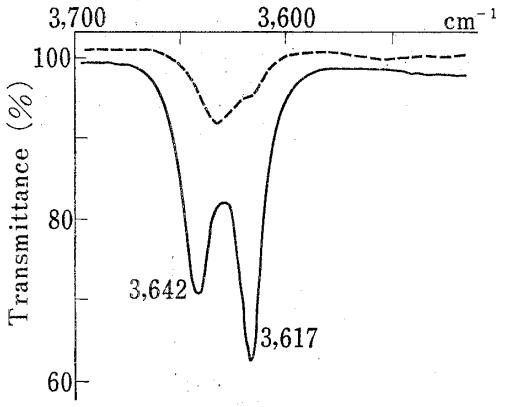

Fig. 3. IR Spectra of XIIIa and XIIIb

——: XIIIb 0.002M in CCl_4
------: XIIIa 0.0007M in CCl_4

XIIIa and XIIIb were dehydrated to yield XIV with concentrated hydrochloric acid, whose IR and NMR spectra show no longer –OH. The NMR spectra of XIV and X show that both compounds contain the same ring skelton.

Judging from the melting points of Perkin's products, XIIIa and XIIIb correspond to VIa and VIb, respectively. Therefore the structures of hydroxyisoanhydrodihydromethylberberine-A and -B should be *trans*- and *cis*-N-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′,3′-hydroxy-5′,6′-methylenedioxyindane, respectively, and also the structure

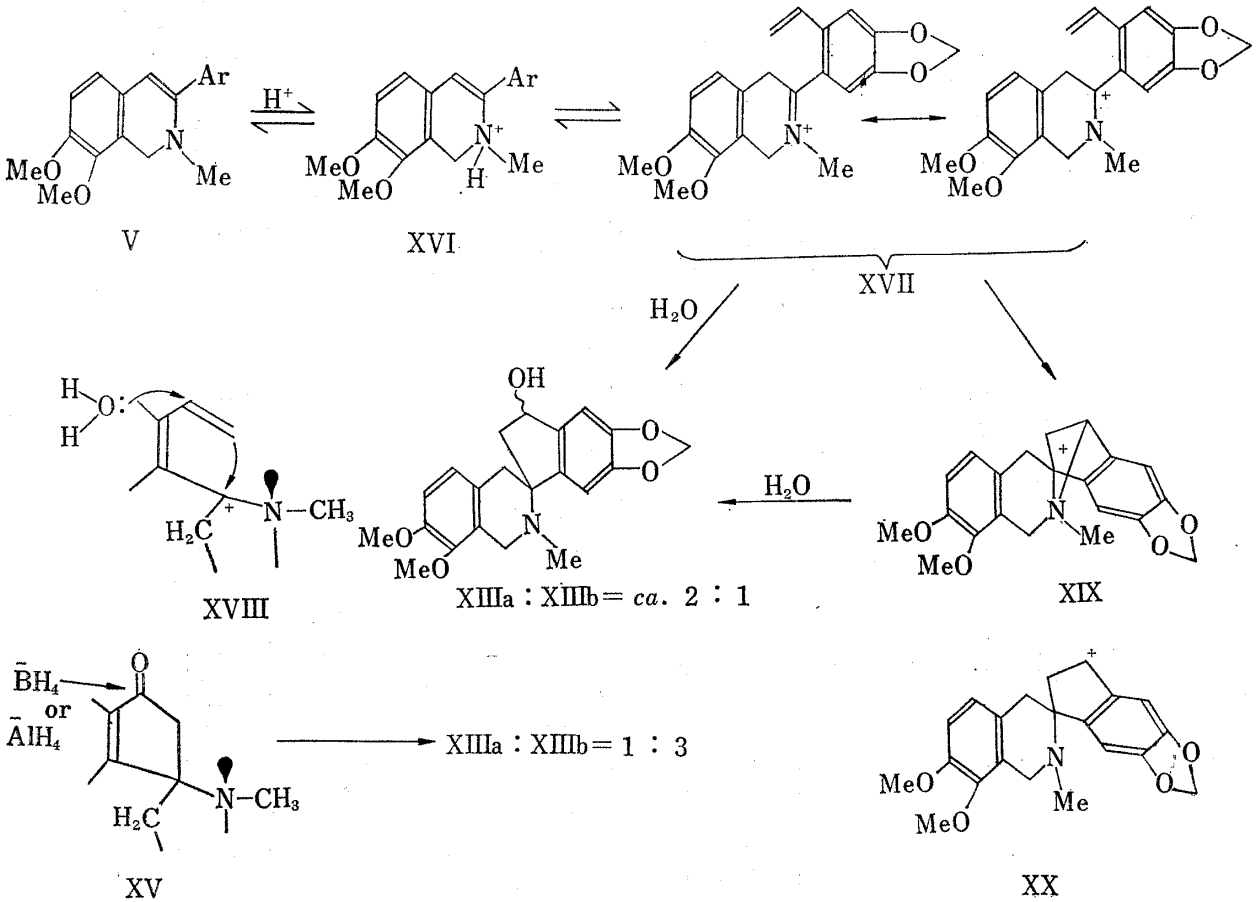

Chart 4

of isoanhydromethylberberine should be N-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′-5′,6′-methylenedioxyindene.

The product ratio, XIIIa/XIIIb, is shown to be around 2:1 on the basis of the intensities of N-methyl in the NMR spectra. As shown in Chart 4, it is quite reasonable for the enamine (V) to convert into XVII in the presence of acid.

There are two plausible pathways considered from XVII to a mixture of XIIIa and XIIIb:

i) One-step Process: The cyclization and hydroxylation with the participation of H_2O synchronously proceed, and H_2O may preferentially attack from the opposite side to the nitrogen in order to avoid the interaction with the bulkiness of N-methyl group, resulting in the predominance of the *trans*-isomer (XIIIa). In other words, it is the concerted *trans*-addition to the double bond controlled by steric factor in the transition state.

ii) Two-step Process: The fact that XIIIa is stereoselectively formed indicates that the intermediate ion (XX) is not important, from which it is expected to be that the product ratio, XIIIa/XIIIb, is about 1:1. If the nitrogen can act as the neighboring group, it is very attractive to consider the intermediate ion (XIX) despite the torsional strain contained in the formation of four membered ring. At the second stage, H_2O attacks at C_3' from the opposite side to the nitrogen to predominate XIIIa.

XIIIa and XIIIb are easily oxidized to the ketone (XV) with active manganese oxide. XV is quantitatively reduced to a mixture of XIIIa and XIIIb with sodium borohydride or lithium aluminum hydride. That the product ratio, XIIIa/XIIIb, is around 1:3 on the basis of the intensities of N-methyl in the NMR spectra is interesting and shows that the metal hydride ions preferentially attack at the carbon of carbonyl group from the opposite side to the nitrogen to avoid the interaction with the lone pair of electrons on the nitrogen and/or with the bulkiness of N-methyl group and result in the formation of the *cis*-isomer (XIIIb) predominantly. Briefly speaking, metal hydride ions approach through the preferred steric course as shown in Chart 4.

Experimental

Melting points were determined on a micro hot-stage and were uncorrected. Intramolecular hydrogen bond was measured with Japan Spectroscopic Co. Model DS-403G spectrophotometer. Nuclear magnetic resonance spectra were measured in $CDCl_3$ with a Hitachi Perkin-Elmer (H-60) at 60 Mc. Chemical shifts were given in τ values, using tetramethylsilane as internal reference.

Dihydroanhydroberberine Methochloride (XII)——A suspension of α-allocryptopine (3 g) in PCl_3 (15 ml) was refluxed for 3 hr with stirring. After cooling, the reaction mixture was diluted with benzene (50 ml) and then filtered, followed by washing with benzene. The crude solid was digested with 20% NH_4OH and filtered. After drying, the solid was heated with benzene (30 ml) to dissolve unreacted α-allocryptopine and filtered, followed by washing with benzene. The solid was recrystallized from H_2O to give pale yellow granules (2.85 g), mp 170—173°. *Anal.* Calcd. for $C_{21}H_{22}O_4NCl \cdot 1\frac{3}{4}H_2O$: C, 60.01; H, 6.01; N, 3.34. Found: C, 59.99; H, 5.90; N, 3.49.

Anhydromethylberberine (V)——A suspension of XII (2.65 g) in 25% KOH-MeOH (25 ml) was refluxed for 40 min. After cooling, the precipitate was filtered, and washed with H_2O and then MeOH. There was obtained pale yellow granules (1.72 g), mp 80—85°. This compound was easily oxidized with air, especially in solution, and showed only one spot on thin-layer chromatography (TLC),[5] so it was used for the next reaction without purification.

Hydroxyisoanhydrodihydromethylberberine-A (XIIIa) and -B (XIIIb)——A mixture of V (2 g) and 10% HCl (10 ml) was heated for 20 min on a boiling water bath. After cooling, the reaction mixture was made alkaline with ammonia to extract AcOEt. The solid residue was washed with ether to afford the mixture of XIIIa and XIIIb (0.76 g) which were sparingly soluble in ether. It was recrystallized from MeOH to give colorless prisms (XIIIa, 108 mg), mp 220—222°. *Anal.* Calcd. for $C_{21}H_{23}O_5N$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.04; H, 6.43; N, 3.60. The ether-filtrate, contained XIIIb as the major component and XIV as the minor, was evaporated to dryness to give semi-solid (*ca.* 1.0 g). The residue was dissolved in benzene and passed through Al_2O_3 column (70 g). The first fraction eluted with benzene-AcOEt (9:1) contained XIV as the major component. The second fraction eluted with benzene-AcOEt (8:2)afforded XIIIb

5) Alumina plate, 0.25 mm; solvent, *n*-hexane-benzene=2:1 (v/v).

(189 mg) which was recrystallized from ether to give colorless prisms, mp 172.5—173.5°. *Anal.* Calcd. for $C_{21}H_{23}O_5N$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.61; H, 6.41; N, 3.67. The third fraction eluted with benzene–AcOEt (7:3) afforded a mixture of XIIIa and XIIIb (161 mg).

N-Methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′-5′,6′-methylenedioxyindene (XIV)——a) The above mentioned first fraction gave a solid residue (*ca.* 120 mg). By the chromatographical separation over Al_2O_3 (20 g) using benzene as eluent was obtained XIV (85 mg) which was recrystallized from *n*-hexane–acetone to yield colorless rosettes, mp 124—124.5°. *Anal.* Calcd. for $C_{21}H_{21}O_4N$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.87; H, 6.34; N, 3.74.

b) A mixture of XIIIa and XIIIb (125 mg) was added to a solution of conc. HCl (1 ml) and DMSO (4 ml), and the solution was heated for 1 hr on a boiling water bath. After cooling, the reaction mixture was made alkaline with ammonia to extract with AcOEt. The residue was chromatographed on silica gel (10 g) using benzene–AcOEt (85:15) as eluent to afford colorless rosettes (65 mg), mp124—124.5°, which was identified with XIV through the melting point on admixture.

N-Methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′-5′,6′-methylenedioxyindan-3-one (XV)——To the solution of a mixture of XIIIa and XIIIb (308 mg) in benzene (50 ml) was added MnO_2 (800 mg) and the solution was stirred at 70—80° for 30 min. After cooling, the reaction mixture was filtered and evaporated *in vacuo*. The residue was recrystallized from acetone–$CHCl_3$ to afford colorless prisms (208 mg), mp 207—209°. *Anal.* Calcd. for $C_{21}H_{21}O_5N$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.63; H, 5.76; N, 3.71.

Reduction of XV——a) To a solution of XV (100 mg) in MeOH (40 ml) was added $NaBH_4$ (30 mg) at room temperature with stirring. After refluxed for 10 min, the reaction mixture was evaporated *in vacuo* and then H_2O was added, followed by extraction with AcOEt. The AcOEt–extract gave a solid residue (100 mg), whose TLC showed the presence of XIIIa and XIIIb and the NMR spectrum showed that the product ratio, XIIIa/XIIIb, is approximately 3:1 from the intensities of N-methyl.

b) To a solution of XV (89 mg) in THF (3 ml) was added a solution of $LiAlH_4$ (10 mg) in dry ether (2 ml) and the reaction mixture was stirred for 10 min. After working up, there was obtained the same product (88 mg) in similar proportion as above.

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