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Utilization of Protopine and Related Alkaloids. I. Ring Closure of Anhydroprotopine

Masayuki Onda, Kaoru Abe, and Kyoko Yonezawa

School of Pharmacy, Kitasato University[1]

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When anhydroprotopine was treated with dilute hydrochloric acid, it gave the different compounds from the "Perkin's compound". Their structures were identified to contain the spiro-type skeleton by the nuclear magnetic resonance spectroscopy, and two of them (VI and VII) were assigned to be the stereoisomers by the successive reactions and also physico-chemical investigation.

We have recently described[2] the isolation of three nematocidal alkaloids, sanguinarine, chelerythrine, and bocconine, from *Bocconia cordata*, whose structures contain benzo[*c*]-phenanthridine skeleton. These alkaloids are the minor constituents and the major ones are protopine and α-allocryptopine which are biologically inactive and contain ten membered ring system.

In the interests of utilization of these biologically inactive alkaloids, attempts to convert protopine to sanguinarine have been carried out in our laboratory.

In 1916, Perkin[3] presented the enormous papers concerning the chemistry of cryptopine, a close relative of protopine. According to his paper, anhydrocryptopine (I) derived from cryptopine yielded two isomeric hydroxyisoanhydrodihydrocryptopine (II) by treatment with dilute hydrochloric acid and the formation mechanism of II was roughly proposed without the evidences for the structure of the products as shown in Chart 1.

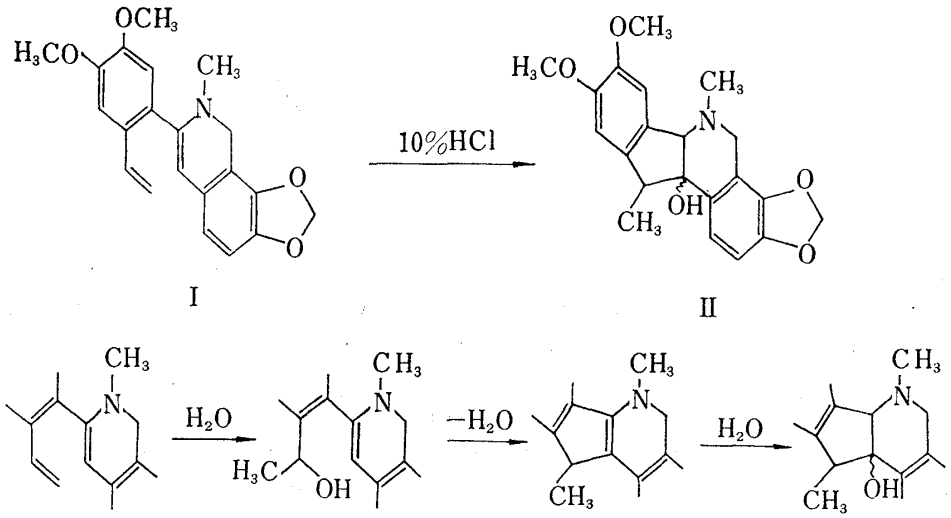

Chart 1

On the other hand, it seems rather likely to us that the route-(a) and/or route-(b)[4] (Chart 2) will be involved in the formation of II to yield the different ring systems from the

1) Location: *Shiba-shirokane, Minato-ku, Tokyo.*
2) M. Onda, K. Takiguchi, M. Hirakura, H. Fukushima, M. Akagawa, and F. Naoi, *Nippon Nogei-kagaku Kaishi*, **39**, 168 (1965).
3) W.H. Perkin, *J. Chem. Soc.*, **1916**, 815.
4) D.W. Brown and S.F. Dyke, *Tetrahedron Letters*, **1966**, 3975.

"Perkin's compound". If the route-(a) is involved, a magnificent intermediate for the benzo[*c*]phenanthridine derivative would be expected. Accordingly, we reinvestigated the products obtaining from protopine *via* Perkin's procedure.

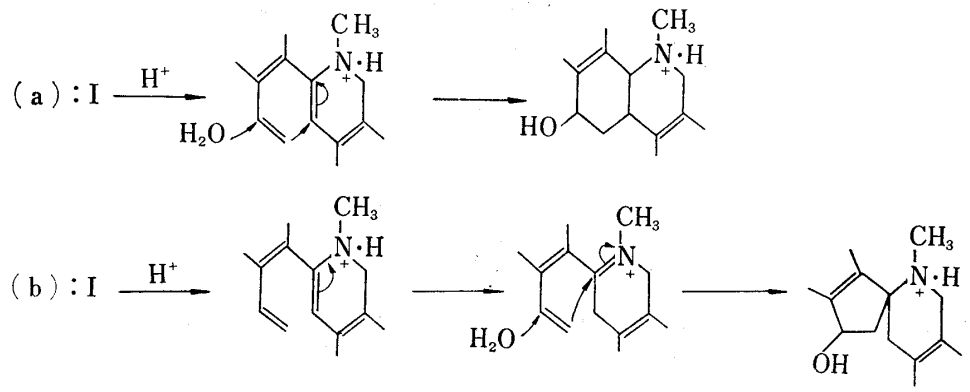

Chart 2

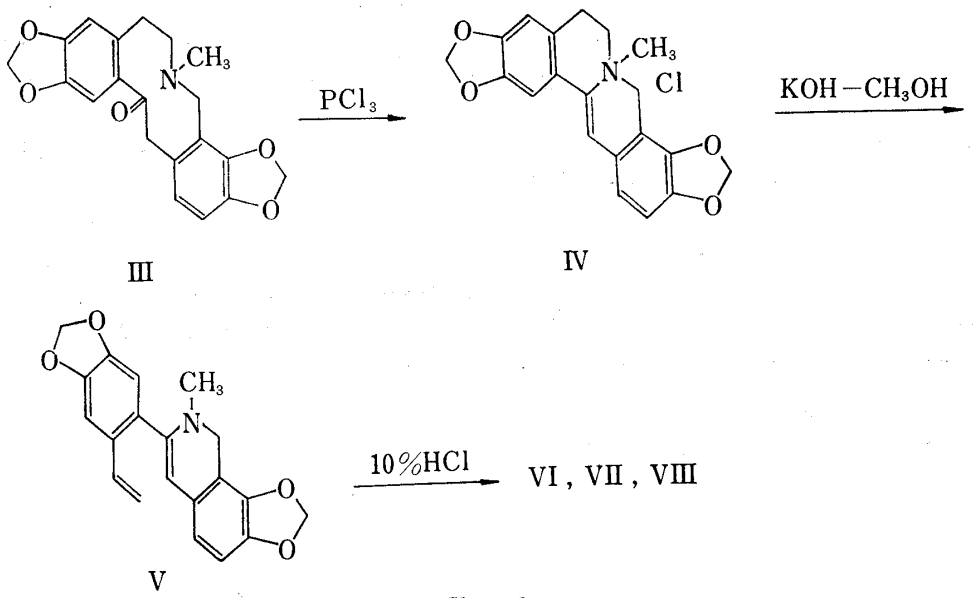

Chart 3

As shown in Chart 3, protopine (III) gives isoprotopine chloride (IV) with phosphorous chloride, which is converted to anhydroprotopine (V) by Hofmann degradation.

When V was treated with dilute hydrochloric acid, three following bases were obtained: VI, mp 209—209.5°, $C_{20}H_{19}O_5N$; VII, mp 216—217°, $C_{20}H_{19}O_5N$; VIII, mp 147—148°, $C_{20}H_{17}O_4N$. Both VI and VII show no doublet methyl signals in the nuclear magnetic resonance (NMR) spectra. This result indicates that Perkin's proposal should be surely excluded in the formation of VI and VII. The infrared (IR) spectra of VI and VII (in Nujol) show the absorption band at around 3340 cm^{-1} corresponding to –OH and the NMR spectra also show the presence of –OH at 7.60 and 7.95 τ, respectively, which disappear by the addition of deuterium oxide. As shown in Fig. 1 and 2, and Table I, VI and VII show the signals at 4.96 (t) (1H), and 4.85 (q) τ (1H), respectively, corresponding to $-CH_2-\underset{OH}{CH}-OH$ which shift *ca.* 1.1 ppm for lower field on acetylation.

Further, the fact that VI and VII are easily oxidized to the same ketone (IX) with active manganese oxide shows the presence of $Ar-\underset{OH}{CH}-CH_2-$ in its molecule. Also VI exhibits two AB-type quartets at 5.98 (d), 6.54 (d) (J=17), and 6.93 (d), 7.52 (d) τ (J=16 cps), and an

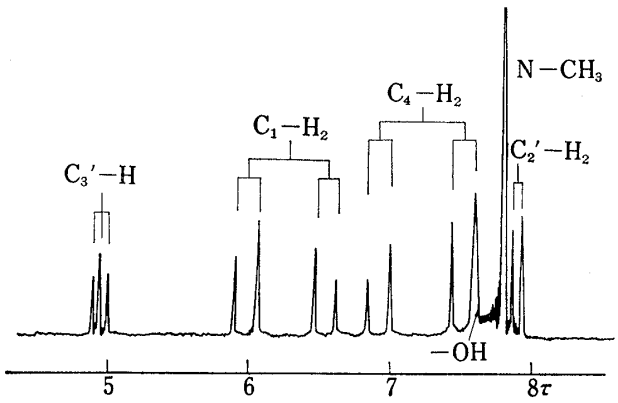

Fig. 1. NMR Spectrum of VI (100 Mc)

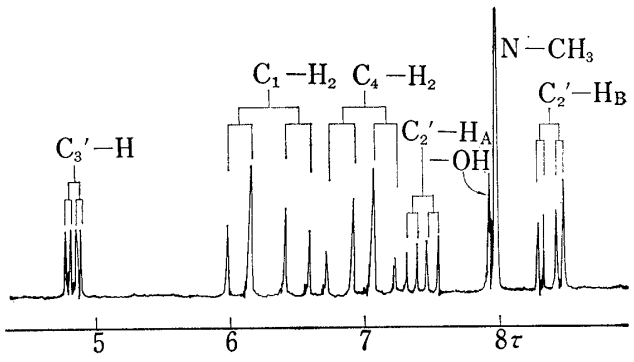

Fig. 2. NMR Spectrum of VII (100 Mc)

Table I. Nuclear Magnetic Resonance Spectral Data of VI, VII, VIII and IX

	Arom –Hs		C_1–H_2	C_4–H_2	$C_{2'}$–H_2	$C_{3'}$–H	N–CH_3	CH_2 O– O–
	C_5, C_6	$C_{4'}$, $C_{7'}$						
VI	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
VII	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 J=3	7.98	4.08 (s)
VIII	3.33 (d) 3.52 (d) J=8.5	3.25 (s)	5.90 (d) 6.32 (d) J=17	6.79 (d) 7.37 (d) J=15.6	3.74 (d) J=6	3.34 (d) J=6	7.94	4.04 (s) 4.06 (s)
IX	3.33 (d) 3.53 (d) J=8.5	2.91 (s) 2.98 (s)	5.87 (d) 6.57 (d) J=16	6.67 (d) 7.39 (d) J=16	7.16 (d) 7.82 (d) J=18.5		7.90	3.91 (s) 4.06 (s)

A_2X-type at 7.90 (d) and 4.96 (t) τ (J=6 cps), while VII exhibits two AB-type quartets at 6.08 (d), 6.51 (d) (J=17), and 6.81 (d), 7.13 (d) τ (J=16 cps), and an ABX-type at 7.41 (q) (J=14 and 7), 8.37 (q) (J=14 and 3) and 4.85 (q) τ (J=7 and 3 cps). From the NMR data mentioned above, the route-(a) is excluded in the ring formation. Both VI and VII have the same ring system *via* the route-(b) and are presumably the isomers of C–OH configuration of five membered ring.

As shown in Chart 4, VI and VII are dehydrated to yield VIII with concentrated hydrochloric acid, whose IR and NMR spectra show no longer –OH. The NMR spectrum of VIII exhibits two AB-type quartets at 5.90 (d), 6.32 (d) (J=17) and 6.79 (d), 7.37 (d) τ (J=15.6 cps), and two olefinic protons at 3.34 (d) and 3.74 τ (J=6 cps). The compound (VIII) catalytically absorbs one mole equivalent of hydrogen to yield X, in whose NMR spectrum two olefinic protons disappear. Consequently, VIII has the same ring system with VI and VII. The methiodide of VIII offers an orange base (XI) by Hofmann degradation, whose ultraviolet absorption (UV) spectrum shows an absorption band at λ_{max}^{EtOH} 361 mμ (log ε=4.6) corresponding to 1-benzylideneindenes.[5] This result exclusively provides the evidence for the structure of VIII. Judging from the facts that VI and VII are the major products and

5) E.D. Bergmann and Y. Hirshberg, *Bull. Soc. Chim. France*, **17**, 1091 (1950); *ibid.*, **18**, 669 (1951).

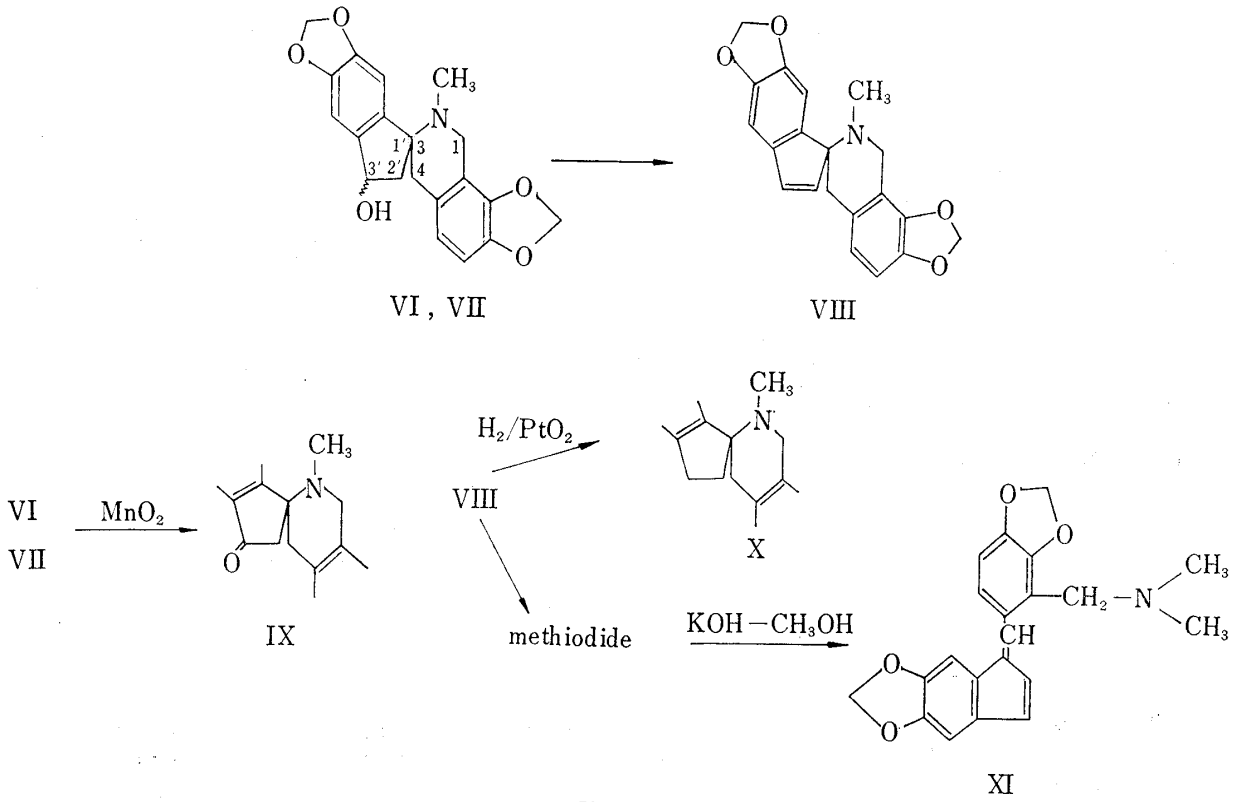

Chart 4

VIII is the minor (see experimental), and that VIII is not hydrated with dilute hydrochloric acid to yield VI and VII, VIII is presumably formed through VI and VII during the reaction.

Configuration of C_3'–OH of VI and VII: On comparison with the NMR spectra of VI and VII, N–methyl of VI appears at lower field than that of VII, and C_4–H_2 and C_3'–H of VI appear at upper field than those of VII. From the dipole contribution and the magnetic anisotropy of C–OH and C–N<, C_3'–OH probably orientates *cis* to C_1'–N in VI and *trans* in VII. The fact that the IR spectrum of VI exhibits the absorption band at 3600 cm^{-1}, which is invariable with the change of concentration (in CCl_4) to show the presence of intramolecular hydrogen bond (Fig. 3), also supports the above deduction.

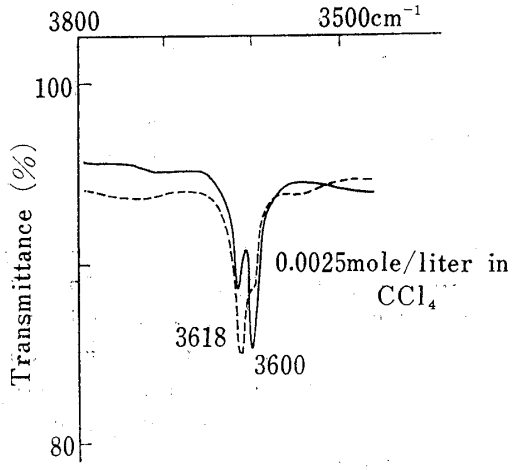

Fig. 3 IR Spectra of VI and VII
——— (VI) - - - - - - (VII)

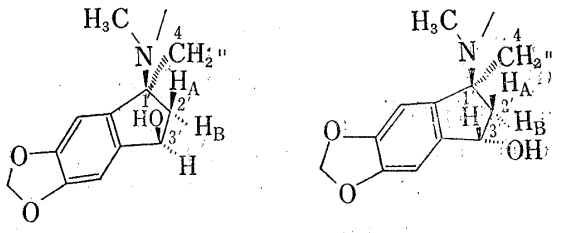

Chart 5

The assignment of C_2'–H_2 is slightly complicated. Rosen, *et al.*[6] successfully identified the configuration of substituted indanes by means of the measurement of the vicinal coupling constants. That is, the application of the principle of the Karplus equation for the dihedral

6) W.E. Rosen, L. Dorfman, and M.P. Linfield, *J. Org. Chem.*, **29**, 1723 (1964).

angles involved generally provides $J_{cis}>J_{trans}$ in the ethane fragment of cyclopentene. Due to this generalization, one proton of VII appearing at 8.37 ($J_{vicinal}=3$) corresponds to HB and another at 7.41 τ ($J_{vicinal}=7$ cps) corresponds to HA (Chart 5).

This assignment reveals that C_3'–OH shields C_2'–HB (*cis* to OH) and conversely, C_1'–N deshields C_2'–HA (*cis* to N). On the other hand, two protons of VI overlap at 7.90 τ. It is reasonably deduced that in VI the contradiction of the paramagnetic anisotropy of C_1'–N for HA by the diamagnetic anisotropy of C_3'–OH, and the release of the diamagnetic anisotropy of C_3'–OH from HB result in making HA and HB magnetically nearly equivalent. This deduction is actually supported by the triplet of C_3'–H in VI.

Unfortunately, we could not find out the compound which was formed *via* the six membered ring formation. However, it seems to be still remained the adequate choice of the condensation reagents for us to study further.

Experimental

Melting points were determined on a micro hot-stage and were uncorrected. Ultraviolet spectra were measured with a Hitachi EPS-2U and infrared spectra with a JASCO Model IR-S. Intramolecular hydrogen bond was measured with a Perkin-Elmer 221 spectrophotometer. Nuclear magnetic resonance spectra were measured in $CDCl_3$ with a Hitachi Perkin-Elmer (H-60) at 60 Mc, and a Varian Associates (HA-100) recording spectrometer at 100 Mc. Chemical shifts are given in τ values, using tetramethylsilane as internal reference.

N-Methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′-3′-hydroxy-5′,6′-methylenedioxyindane (VI) and (VII)——A mixture of anhydroprotopine (V)[7] (8.0 g) and 10% HCl (80 ml) was heated for 20 min on a boiling water bath. The crystals began to separate from the clear solution 5 min later. After cooling, the solid was collected and made alkaline with ammonia to extract with AcOEt. The solid residue was washed with ether to afford the mixture of VI and VII (5.6 g)[8] which were sparingly soluble in ether and the ether solution contained VIII as the major product. A mixture of VI and VII (1.0 g) was dissolved in AcOEt (30 ml) and passed through silica gel column (100 g), followed by elution with benzene–AcOEt (1:1). The first fraction afforded VI (111 mg) which was recrystallized from AcOEt–ether to give colorless prisms, mp 209—209.5°. TLC[9]: *Rf* 0.53. *Anal.* Calcd. for $C_{20}H_{19}O_5N$: C, 67.97; H, 5.42; N, 3.96. Found: C, 68.03; H, 5.36; N, 4.16.

The second afforded a mixture of VI and VII (593 mg). The third afforded VII (304 mg) which was recrystallized from AcOEt–ether to give colorless prisms, mp 216—217°. TLC: *Rf* 0.36. *Anal.* Calcd. for $C_{20}H_{19}O_5N$: C, 67.97; H, 5.42; N, 3.96. Found: C, 67.60; H, 5.48; N, 4.20.

N-Methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′-5′,6′-methylenedioxyindene (VIII)——a) The above mentioned ether solution gave a solid residue (*ca.* 1.5 g). By the chromatographical separation over Al_2O_3 (80 g) using benzene as eluent VIII was obtained from the first fraction, which was recrystallized from *n*-hexane–benzene to yield colorless rosettes, mp 147—148°. TLC: *Rf* 0.95. *Anal.* Calcd. for $C_{20}H_{17}O_4N$: C, 71.62; H, 5.11; N, 4.17. Found: C, 71.65; H, 5.11; N, 4.20. Methiodide: Yellow granules, mp 230°. *Anal.* Calcd. for $C_{21}H_{20}O_4NI$: C, 52.83; H, 4.22; N, 2.93. Found: C, 52.66; H, 4.55; N, 2.73. HCl-salt: Colorless granules, mp 260—262°. *Anal.* Calcd. for $C_{20}H_{18}O_4NCl\cdot\frac{1}{4}H_2O$: C, 63.83; H, 4.95; N, 3.72. Found: C, 63.99; H, 4.79; N, 3.61.

b) A mixture of the equivalent amounts of VI and VII (109 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 benzene. The solid residue was chromatographed on Al_2O_3 (12 g) using benzene as eluent to afford colorless rosettes (51 mg), mp 145—147°, from the first fraction, which was identified with VIII through the melting point on admixture. The second fraction, which was successively eluted with AcOEt, gave the unreacted starting material (52 mg), and the TLC of this fraction showed the presence of almost same amounts of VI and VII.

N-Methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′-5′,6′-methylenedioxyindan-3-one (IX)——To the solution of a mixture of the equivalent amounts of VI and VII (100 mg) in benzene (30 ml) was added MnO_2 (350 mg) and the solution was stirred at 70—80° for several hours until the starting materials completely disappeared on TLC. After cooling, the reaction mixture was filtered and evaporated under reduced pressure. The residue was passed through silica gel column (10 g) and the benzene–$CHCl_3$ (2:1)

7) mp 113—115° (lit.[3], mp 114—115°), picrate: yellow plates, mp 195—196° (MeOH). *Anal.* Calcd. for $C_{26}H_{20}O_{11}N_4$: C, 55.32; H, 3.55; N, 9.92. Found: C, 55.38; H, 3.17; N, 9.62.

8) Product ratio (VI/VII) is approximately 1:3 from the intensities of N-methyl in the NMR spectrum.

9) TLC (thin-layer chromatography): silica gel, 0.25 mm; solvent, benzene–AcOEt (1:3 v/v).

fraction gave colorless prisms (70 mg), mp 253—255°, after recrystallization from *n*-hexane–AcOEt. IR ν_{max}^{Nujol} cm^{-1}, 1694 (>C=O). *Anal.* Calcd. for $C_{20}H_{17}O_5N$: C, 68.37; H, 4.84; N, 3.98. Found: C, 68.48; H, 4.80; N, 3.76.

N-Methyl-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-spiro-1′-5′,6′-methylenedioxyindane (X)——The hydrochloride of VIII (196 mg) was hydrogenated over previously reduced PtO_2 (100 mg) in MeOH (30 ml) to absorb one mole equivalent of hydrogen within 20 min. The filtered solution was evaporated *in vacuo*, and the residue was made alkaline with ammonia to extract with AcOEt. The residue, in which no starting material was contained on TLC, was passed through silica gel column (18 g) and eluted with benzene to yield colorless prisms (63 mg), mp 138—139°, after recrystallization from *n*-hexane–ether. *Anal.* Calcd. for $C_{20}H_{19}O_4N$: C, 71.21; H, 5.63; N, 4.17. Found: C, 71.41; H, 5.44; N, 4.20.

1-(2′-Dimethylaminomethyl-3′,4′-methylenedioxybenzylidene)-5,6-methylenedioxyindene (XI)——A mixture of the methiodide of VIII (400 mg) and 25% KOH–MeOH (4 ml) was refluxed for 1 hr on water bath. The reaction mixture was evaporated *in vacuo* and then water was added. The precipitate was extracted with ether. The residue (225 mg) was recrystallized from *n*-hexane to afford orange prisms (XI) (160 mg), mp 130°. UV λ_{max}^{EtOH} mμ (log ε): 259 (4.4), 268 (4.5), 308 (4.5), 361 (4.6). *Anal.* Calcd. for $C_{21}H_{19}O_4N$: C, 72.20; H, 5.48; N, 4.00. Found: C, 72.33; H, 5.32; N, 3.75.

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