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Synthesis of *dl*-Mesembrine and Its *trans* Isomer[1]

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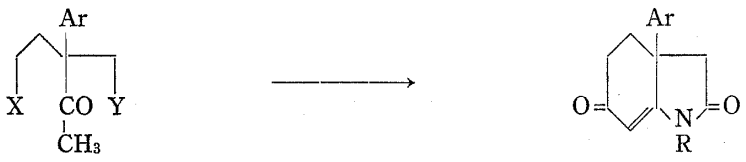
dl-Mesembrine (=3a-(3,4-dimethoxyphenyl)-1-methyloctahydroindol-6-one) (XIII) and its *trans* isomer (XIV) were prepared from 3a-(3,4-dimethoxyphenyl)-1-methyloctahydroindol-2,6-dione (IV) in 4 steps. Stereochemistry of 3a-(3,4-dimethoxyphenyl)-1-methyloctahydroindol-2,6-dione was discussed on the basis of nuclear magnetic resonance (NMR) informations.

In the preceding paper,[3] we have shown that the hydrolytic cyclization of 3-acetyl-3-(3,4-dimethoxyphenyl)adiponitrile (I), methyl 3-(2-cyanoethyl)-3-(3,4-dimethoxyphenyl)levulinate (II) and methyl 4-cyanomethyl-4-(3,4-dimethoxyphenyl)-5-oxocaproate (III) in 65% sulfuric acid furnished 3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6-hexahydroindol-2,6-dione (IV) in 60%, 72.9% and 73% yields respectively.



I : X=Y=CN
II : X=CN, Y=CO_2Me
III : X=CO_2Me, Y=CN

IV : R=H
V : R=Me

Ar=3,4-dimethoxyphenyl

Chart 1

In this report, we wish to describe the transformation of V to *dl*-mesembrine (XIII)[4] and its *trans* isomer (XIV) by the sequence of reactions shown in Chart 2.

Catalytic hydrogenation of V over Raney Ni (W-4) gave a mixture of two or more stereoisomers of 3a-(3,4-dimethoxyphenyl)-6-hydroxy-1-methyloctahydroindol-2-one (VI) as amorphous powder in 30—46% yield, together with 3a-(3,4-dimethoxyphenyl)-1-methyl-2,3,3a,4,5,6-hexahydroindol-2-one (VII) and the known perhydroindoline derivative (VIII).[3] The product composition was variable depending on the activity of the catalyst. To avoid hydrogenolysis of the carbon–oxygen linkage at C-6 during the hydrogenation, reduction with metal hydrides[5] as well as catalytic hydrogenation under various conditions[6] was attempted. However,

1) A brief communication of this work has appeared: T. Oh-ishi and H. Kugita, *Tetrahedron Letters*, **1968**, 5445.
2) Location: *No. 2–50, Kawagishi 2–Chome, Toda, Saitama.*
3) T. Oh-ishi and H. Kugita, *Chem. Pharm. Bull.* (Tokyo), **18**, 291 (1970).
4) A. Popelak and G. Lettenbauer, "The Alkaloids," Vol. IX, ed. by R.H.F. Manske, Academic Press, New York and London, 1967, Chapter 11. The first total synthesis of *dl*-mesembrine has been reported: M. Shamma and H.R. Rodriguez, *Tetrahedron Letters*, **1965**, 4847. Another synthesis of the alkaloid by the annelation reaction between 3-(3,4-dimethoxyphenyl)-1-methyl-2-pyrroline and methyl vinyl ketone has recently been reported: T.J. Curphey and H.L. Kim, *Tetrahedron Letters*, **1968**, 1441; R.V. Stevens and M.P. Wentland, *J. Am. Chem. Soc.*, **90**, 5580 (1968); S.L. Keely, Jr. and F.C. Tahlk, *ibid.*, **90**, 5584 (1968).
5) *a*) M. Viscontini and W. Kaiser, *Helv. Chim. Acta*, **48**, 1927 (1965); *b*) J.M. Osbond, *J. Chem. Soc.*, **1961**, 4711; *c*) Z. Horii, K. Morikawa and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1472 (1968).
6) M.C. Dart and H.B. Henbest, *J. Chem. Soc.*, **1960**, 3563.

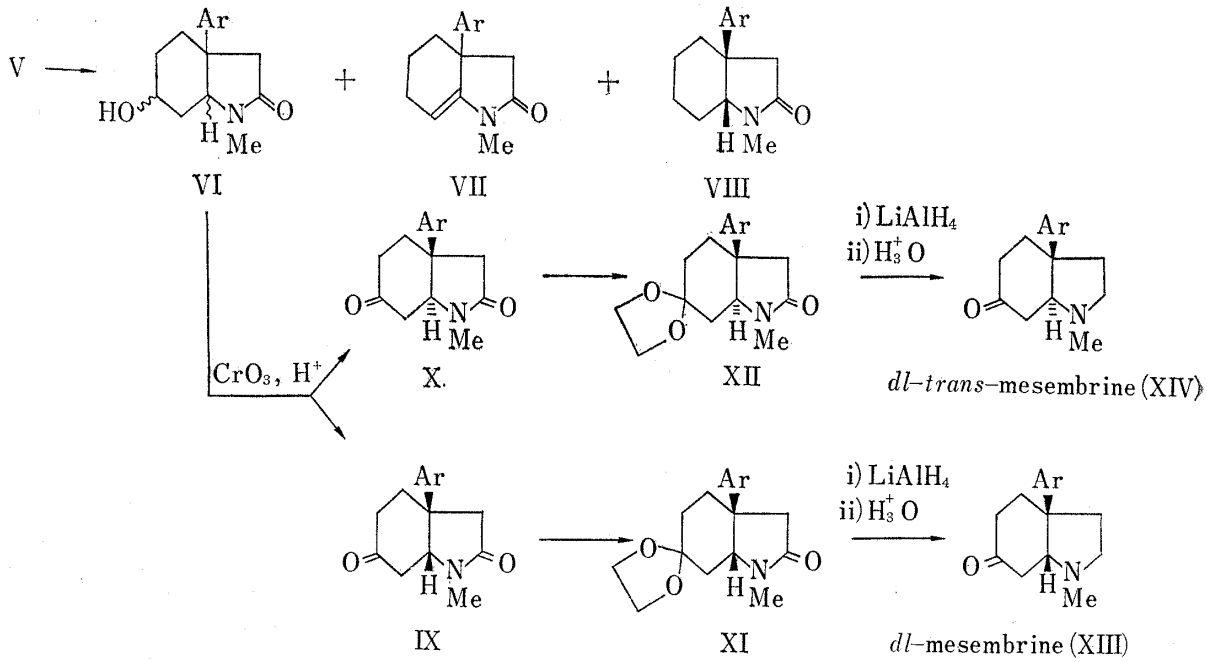


Chart 2

the desired product VI could not be obtained in any higher yield than by the original method.

The stereoisomeric mixture VI, without being resolved, was subjected to Jones' oxidation at −5° to give a nearly 1:1 mixture of *cis*-(IX) and *trans*-3a-(3,4-dimethoxyphenyl)-1-methyl-octahydroindol-2,6-dione (X), which were separated into the pure *cis* isomer (IX) in 19.1% yield and the *trans* one (X) in 25.5% yield by alumina chromatography.

Structural assignment to the isomers was made on the basis of NMR spectra (Fig. 1). C-7a methine proton of X appeared as a multiplet at 4.11—3.62 ppm. Although the methoxy group (3.87 ppm) obscured this signal partly, it revealed a large coupling constant with one of the C-7 protons (10 cps). With this only, however, the *trans* structure of this compound could not be established because this pattern of signal might also be ascribable to the C-7a methine proton of the *cis* form if it takes the conformation IX-B (Fig. 2). The *trans* structure became obvious when the other isomer IX was proved to possess the *cis* structure by the fact that its C-7a proton signal appears at 4.30 ppm as a triplet (J=4.5 cps), hardly conceivable for the axial-oriented C-7a proton of the *trans* structure X. The signal of the C-7a

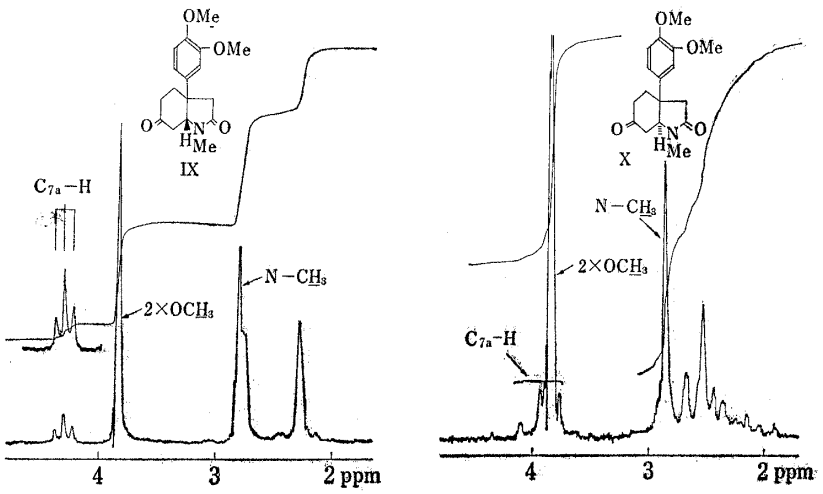


Fig. 1. NMR Spectra of IX and X in $CDCl_3$

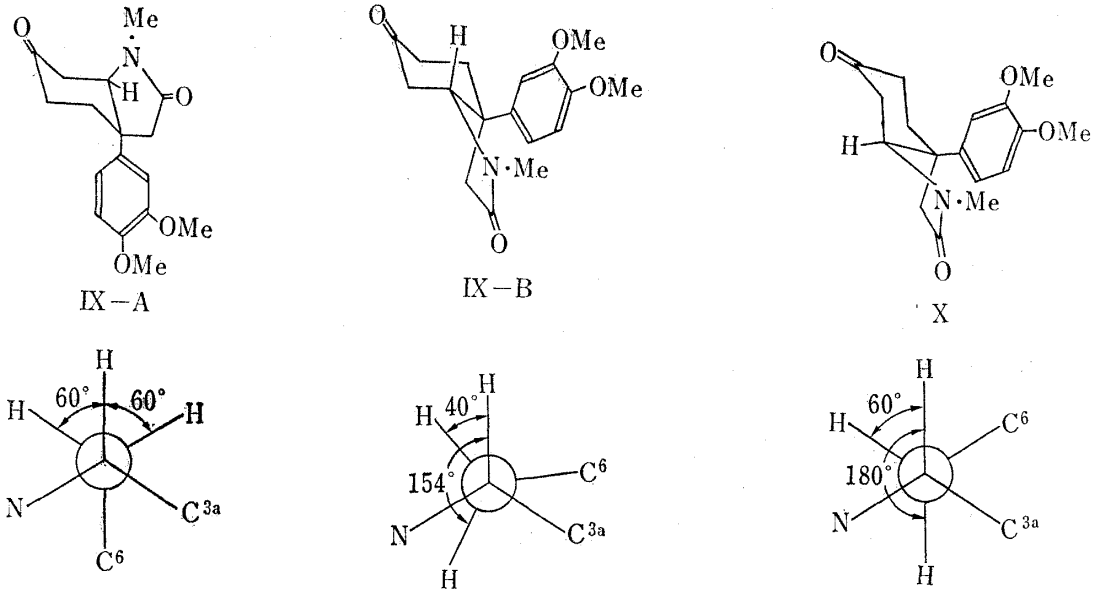


Fig. 2. Conformations of IX and X

proton of IX seems to provide information concerning the conformation of the *cis* structure. Dreiding models show that IX–A is more favourable than IX–B for this spectral evidence.

The *cis* isomer (IX) was ketalyzed with 2-ethyl-2-methyl-1,3-dioxolane and *p*-toluenesulfonic acid. Reduction of the crude oily ketal (XI) with lithium alminum hydride followed by treatment with 10% hydrochloric acid gave *dl*-mesembrine (XIII) as a colourless oil in 72.5% overall yield from IX. The compound XIII was identical with authentic *dl*-mesembrine[7] in infrared (IR, Fig. 3a) and NMR (Fig. 4a) spectra.

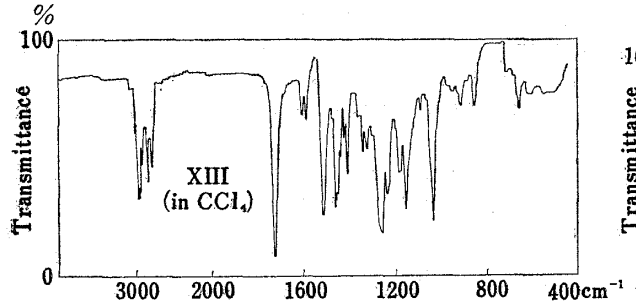


Fig. 3a. IR Spectrum of *dl*-Mesembrine measured on Hitachi EPI-G21 Spectrophotometer

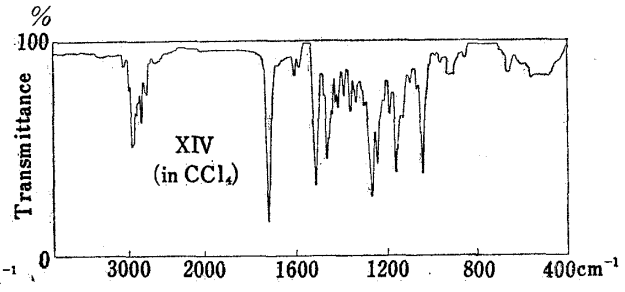


Fig. 3b. IR Spectrum of *dl-trans*-Mesembrine measured on Hitachi EPI-G21 Spectrophotometer

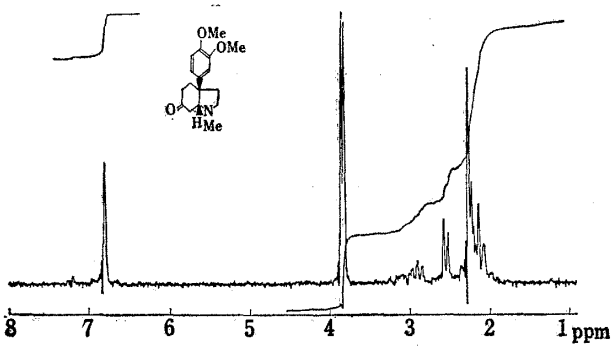


Fig. 4a. NMR Spectrum of *dl*-Mesembrine (XIII) in $CDCl_3$

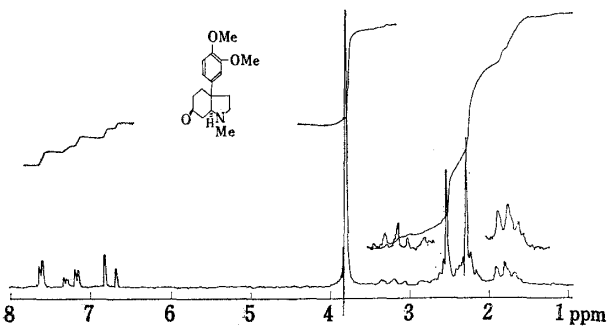


Fig. 4b. NMR Spectrum of *dl-trans*-Mesembrine (XIV) in $CDCl_3$

7) We are indebted to Dr. A. Popelak for providing us with the authentic sample of *dl*-mesembrine.

The *trans* isomer (X) gave the crystalline ketal (XII) in 77.5% yield. Reduction of the ketal (XII) with lithium alminum hydride and subsequent treatment with 10% hydrochloric acid likewise gave the *trans* isomer of *dl*-mesembrine (XIV) in 71% yield, whose IR and NMR spectra are shown in Fig. 3b and Fig. 4b.

Experimental[8]

Catalylic Hydrogenation of V——A mixture of V (7.0 g), Raney Ni (W-4, 7 ml)[9] and EtOH (250 ml) was hydrogenated at 110—120° and 120 atm for 5 hr. The filtrate was evaporated to dryness. The oily residue was chromatographed on alumina. Elution with benzene gave a viscous oil. Distillation gave pure VII (0.38 g, 5.7%), bp 183° (0.1 mmHg). *Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.88. Found: C, 70.95; H, 7.37; N, 4.82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1665. UV λ_{max}^{EtOH} $m\mu$ (ε): 231 (16030). NMR ($CDCl_3$) δ: 2.68 (2H, doublet, C-3 methylene protons), 2.97 (3H, singlet, $NC\underline{H}_3$), 5.13 (1H, triplet, J=3 cps, C-7a proton).

Elution with benzene–ether (10:1) gave VIII (3.22 g, 48%), mp 85—87°, as plates, which was identical with the sample prepared in the preceding paper.[3]

Further elution with ether–EtOH (20:1) gave VI (2.14 g, 30.2%) as an amorphous powder, which would be a stereoisomeric mixture. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3200 (OH), 1690 (C=O). The amorphous product was used in the next reaction without further purification.

Hydrogenation of V over Raney Ni (W-2)[10] at 70° and 120 atm gave VI (16.5 %), VII (23.9%), VIII (33.5%), and a mixture of VII and VIII (*ca.* 24%).

Jones' Oxidation of VI[11]——To a vigourously stirred solution of crude VI (7.7 g) in acetone (580 ml) was added a mixture of CrO_3 (3.0 g), water (9 ml), and conc. H_2SO_4 (2.54 ml) at −5°. Stirring was continued at the same temperature for 15 min. After the decomposition of excess CrO_3 by addition of iso-PrOH, the mixture was neutralized with solid $NaHCO_3$. Filtration and evaporation of the filtrate gave a greenish oil, which was taken up in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue (6.74 g) was chromatograhped on alumina (200 g) with benzene–acetone (95:5). Early part of the eluate gave X (1.95 g, 25.5%), mp 195—201.° Recrystallization from EtOH gave a pure sample, mp 205—208°. *Anal.* Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.02; H, 6.71; N, 4.46. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1680. NMR ($CDCl_3$) δ: 2.88 (3H, singlet, $N\text{–}C\underline{H}_3$), 3.67—4.11 (1H, C-7a proton; partly obscured by the signal at 3.87 ppm due to methoxy group).

Following part of the eluate gave IX (0.65 g, 8.5%), which contained a little amount of X.

Further elution with the same solvent gave pure IX (1.46 g, 19.1%), mp 130—131°. Recrystallization from EtOH gave a pure sample of IX, mp 129—131°. *Anal.* Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.26; H, 7.13; N, 4.73. IR ν_{max}^{Nujol} cm^{-1}: 1715, 1670. NMR ($CDCl_3$)δ: 2.81 (3H, singlet, $N\text{–}C\underline{H}_3$), 4.30 (1H, triplet, J=4.5 cps, C-7a proton).

***dl*-Mesembrine (XIII)**——A mixture of IX (1.0 g), *p*-toluenesulfonic acid (0.2 g), and 2-ethyl-2-methyl-1,3-dioxolane (20 ml) was heated to reflux for 2 hr. To the cooled reaction mixture was added saturated $NaHCO_3$ solution. It then was evaporated *in vacuo*. The residue was taken up in $CHCl_3$, washed with water, dried over Na_2SO_4 and evaporated to give the ketal (XI) (1.32 g) as a colourless oil. IR ν_{max}^{Liq} cm^{-1}: 1695 (lactam). The crude ketal, without further purification, was reduced with excess lithium aluminum hydride (1.0 g) in refluxing ether (30 ml) and tetrahydrofuran (60 ml) for 23 hr. After the decomposition of excess reagent by addition of water, the inorganic substance was removed by filtration. The filtrate was dried and evaporated to give an oily residue, which was dissolved in 10% HCl (30 ml) and kept standing at room temperature for two days. The acid solution was made alkaline with solid NaOH and extracted with ether. The extract was washed with water, dried over Na_2SO_4 and evaporated to give a colourless oil (0.85 g). Distillation gave pure *dl*-mesembrine (XIII) (0.69 g, 72.3%), bp 178° (0.07 mmHg), which is identical with authentic *dl*-mesembrine[7] in IR (CCl_4) and NMR ($CDCl_3$) spectra. Hydrochloride of XIII, mp 179—181°. *Anal.* Calcd. for $C_{17}H_{24}O_3NCl$: C, 62.66; H, 7.42; N, 4.30; Cl, 10.88. Found: C, 62.51; H, 7.10; N, 4.29; Cl, 10.77.

***trans* 6-Ethylenedioxy-3a-(3,4-dimethoxyphenyl)-1-methyloctahydroindole (XII)**——A mixture of X (1.47 g), *p*-toluenesulfonic acid (0.3 g), and 2-ethyl-2-methyl-1,3-dioxolane (30 ml) was heated to reflux

8) All melting and boiling points are uncorrected. IR spectra were measured on a Nippon Bunko Model IR-S or IR-E spectrophotometer. NMR spectra were determined on a Japan Electron Optics Co. JNM C-60 spectrometer with tetramethylsilane as an internal standard.

9) A.A. Palvic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

10) R. Mozingo, "Organic Syntheses," Vol. 21, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1941, p. 15.

11) A. Bowers, T.G. Halsall, E.R.H. Jones and A.J. Lemin, *J. Chem. Soc.*, 1953, 2548.

for 2 hr. To the cooled reaction mixture was added saturated $NaHCO_3$ solution. It then was evaporated *in vacuo*. The residue was taken up in $CHCl_3$, washed with water, dried over Na_2SO_4 and evaporated to give crystals. Recrystallization from EtOH gave XII (1.3 g, 77.5%), mp 165—169°. *Anal.* Calcd. for $C_{19}H_{25}O_5N$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.82; H, 6.95 ; N, 3.60. IR ν_{max}^{Nujol} cm^{-1}: 1685 (lactam).

***dl-trans*-Mesembrine (XIV)**——The *trans*-ketal (XII) (1.30 g) was reduced with lithium aluminum hydride (1.0 g) in refluxing ether (30 ml) and tetrahydrofuran (60 ml). Working up and treatment with 10% HCl (30 ml) as described for *cis*-isomer gave *dl-trans*-mesembrine (XIV) as crystals. Recrystallization from hexane–ether gave pure XIV (0.77 g, 71.0%), mp 95—97°. *Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.41; H, 7.77; N, 4.97. Hydrochloride of XIV, mp 223—225° (decomp.). *Anal.* Calcd. for $C_{17}H_{24}O_3NCl$; C, 62.66; H, 7.42; N, 4.30; Cl, 10.88. Found: C, 62.53; H, 7.19; N, 4.31; Cl, 11.37.

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