C, 69.95; H, 6.71; N, 23.53. UV $\lambda_{\text{max}}^{\text{MeOH}}$ (ε): shoulder 240 (9.5×10^3), shoulder 267 (8.5×10^3), shoulder 278 (5.5×10^3), 341 (1.5×10^4). Mass M$^+$: Calcd. 240.1361. Found: 240.1358. NMR: 1.83, 2.14 (s, 9H, Me×3), 2.73 (s, 2H, CH_2), 7.65—7.85, 8.80—9.10 (m, 5H, aromatic H).

b) A solution of 1-hydrazinophthalazine hydrochloride (3.93 g) and mesityl oxide (1.96 g) in MeOH (60 ml) was refluxed for 3 hr and neutralized with $NaHCO_3$ (1.85 g). The solvent was removed *in vacuo* (50 ml) and the crystalline residue was separated from the solution by filtration, which after recrystallization from isopropyl ether gave **4a** (2.92 g), mp 132—133°.

1-[1-Methyl-2-(1-methyl-ethylidene)hydrazino]phthalazine (VII)——A solution of 1-methyl-1-(1-phthalazinyl)hydrazine⁽⁶⁾ hydrochloride (211 mg) and acetone (1 ml) in MeOH was refluxed for 3 hr under N_2, cooled and neutralized with $NaHCO_3$ (84 mg). The solvent was removed *in vacuo* and the residue was chromatographed on alumina. Elution with benzene gave 149 mg of VII, oil. *Anal.* Calcd. for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.01; H, 6.50; N, 25.96. NMR: 1.51 (s, 6H, Me×2), 2.83 (s, 3H, N-Me), 7.30—7.95 (m, 5H, aromatic H).

1-[2-(1,2-Dimethyl-butylidene)hydrazino]phthalazine (IX)——A solution of 3-methylpentane-2 one (2.6 g) and **1** (3.9 g) in MeOH was refluxed for 4 hr, cooled and concentrated. The residue was chromatographed on alumina. Elution with benzene $CHCl_3$ (1:1) gave 2.9 g of IX, oil. *Anal.* Calcd. for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.50; H, 7.41; N, 23.32. NMR: 0.90 (t, 3H, CH_2CH_3), 1.14 (d, 3H, $CHCH_3$), 1.30—1.85 (m, 2H, CH_2), 2.10 (s, 3H, Me), 2.39 (m, 1H, CH), 7.30—7.65, 7.68, 8.20—8.40 (m, 5H, aromatic H).

Acknowledgement The authors wish to express their gratitude to Dr. N. Koga, Director of this institute for his kind support and interest throughout the course of this work.

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[6] K.T. Potts and C. Lovelette, *J. Org. Chem.*, 34, 3221 (1969).

[Chem. Pharm. Bull. 24(5)1072—1075(1976)]

UDC 547.94.057 : 547.594.3.04 : 547.559.4.04

Synthesis of N-Methyl-2-[8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro-[4,5]decan-8-yl]ethylamine

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For the studies on modification of mesembrine (II), N-methyl-2-[8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decan-8-yl]ethylamine (I) was synthesized from 1,4-dioxaspiro[4,5]decan-8-one (III): the Cope reaction of III with ethyl cyanoacetate gave 1,4-dioxaspiro[4,5]decan-8-ylidene cyanoacetate (IV), whose Grignard reaction with 4-halogeno-1,2-dimethoxybenzene afforded ethyl 8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro-[4,5]decane-8-cyanoacetate (V). Hydrolysis of V followed by decarboxylation gave 8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decane-8-acetonitrile (VIII), which was reduced with $LiAlH_4$ to obtain 2-[8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decan-8-yl]-ethylamine (IX). Treatment of IX with ethyl chloroformate followed by reduction with $LiAlH_4$ furnished I.

It is said that *Sceletium expansum* L. BOL. and *Sceletium tortuosum* N.E. BROWN, which are used as a stimulant by the natives of South Africa, exert a strong narcotic action,⁽²⁾ and these species consist of a mixture of alkaloids closely related to the major alkaloid mesembrine⁽³⁾ (II).

The title compound (I), whose structure is the modification of mesembrine (II), was synthesized in an object of its pharmacological investigation.

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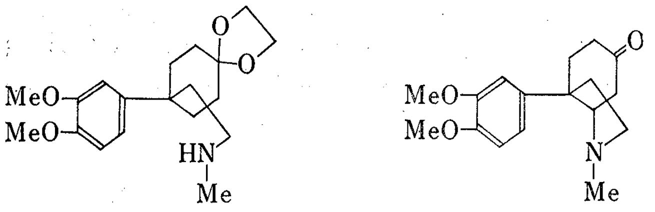
[1] Location: *Tanabe-dori, Mizuho-ku, Nagoya.*

[2] R.R. Arndt and P.E.J. Kruger, *Tetrahedron Letters*, 37, 3237 (1970).

[3] K. Bodendorf and W. Krieger, *Arch. Pharm.*, 290, 441 (1957).



I II

Chart 1

While various syntheses of mesembrine skeleton have been reported,4) the authors prepared I starting from 1,4-dioxaspiro[4, 5] decan-8-one5) (III) as shown in Chart 2.

The Cope reaction of III with ethyl cyanoacetate in the presence of ammonium acetate and acetic acid gave ethyl 1,4-dioxaspiro[4, 5] decan-8-ylidene cyanoacetate (IV), whose structural assignment was supported by the infrared (IR) and the nuclear magnetic resonance (NMR) spectra. The Grignard reaction of IV with 4-bromo-1,2-dimethoxybenzene in tetrahydrofuran gave a mixture of mp 40—42° (V) and 3,3′,4,4′-tetramethoxybiphenyl6) (VI) in a ratio of 9 : 1. IR spectrum of V showed absorptions at 1595, 1519, 1460, 890, and 812 cm^{-1}, which suggested 1,2,4-trisubstituted phenyl derivative. Absorptions of an ester carbonyl at 1752 cm^{-1} and a nitrile at 2250 cm^{-1} remained. In the NMR spectrum of V, aromatic protons at δ 6.82 ppm, two methoxy signals at δ 3.90 and δ 3.95 ppm, a methin signal at δ 3.58 ppm, an ethyl ester signals at δ 1.36 and δ 4.33 ppm, a ketal signal at δ 4.05 ppm, and cyclohexane protons at δ 1.19—3.40 ppm were observed. Thus the compound of mp 40—42° (V) was assigned the structure, ethyl 8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decane-8-cyanoacetate. This experimental results suggested that the Grignard reaction to the α,β-unsaturated ester (IV) proceeded predominantly *via* 1,4-addition.

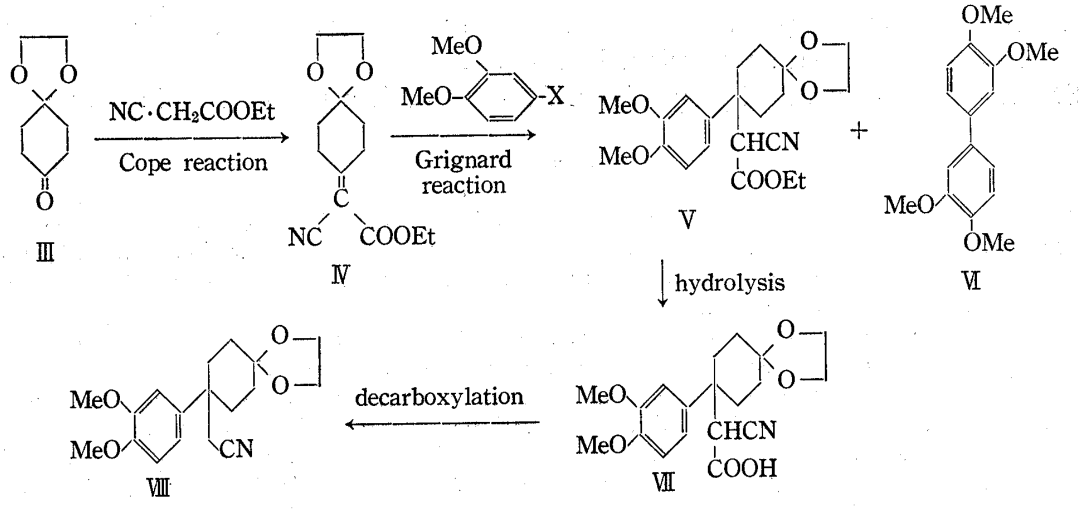


Chart 2

The yield of V was 22.6% when 4-bromo-1,2-dimethoxybenzene was used, but it increased to 33.2% when 4-iodo-1,2-dimethoxybenzene was employed instead of 4-bromo-1,2-dimethoxybenzene. Moreover, addition of catalytic amount of cuprous chloride increased7) the yield to 49.5%. Hydrolysis of V followed by purification by means of silica gel column chromatography gave 8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decane-8-cyanoacetic acid (VII) in

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4) M. Shamma and H.R. Rodriquez, *Tetrahedron Letters*, **52**, 4847 (1965); T.J. Curpher and H.L. Kim, *Tetrahedron Letters*, **12**, 1441 (1968); R.V. Stevens and M.P. Wentland, *Tetrahedron Letters*, **22**, 2613 (1968); S.L. Keely and F.C. Tahk, *Chem. Comm.*, **1968**, 441; H. Taguchi, T. Ohishi, and H. Kugita, *Chem. Pharm. Bull.* (Tokyo), **18**, 1008 (1970); S. Yamada and G. Otani, *Tetrahedron Letters*, **16**, 1133 (1971).

5) M.P. Mertes, *J. Org. Chem.*, **26**, 5236 (1961); P. Courtot, *Bull. Soc. Chim. France.*, **1962**, 1493.

6) F.H. Howell and D.A.H. Taylor., *J. Chem. Soc.*, **1956**, 4252; E. Matarasso, *Ann. Chim.*, **3**, [13], 405 (1958).

7) M.S. Kharasch and P.O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941); A.J. Birch and R. Robinson, *J. Chem. Soc.*, **1943**, 501; G. Buchi, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948).

70.4% yield. Subsequent decarboxylation of VII in pyridine afforded 8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decane-8-acetonitrile (VIII) in 72.5% yield. In the IR spectrum of VIII absorptions of carboxylic acid disappeared, and in the NMR spectrum a new methylene signal at δ 2.53 ppm was observed.

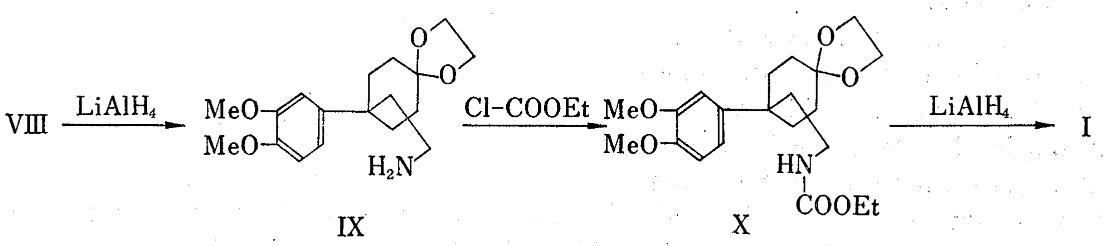


Chart 3

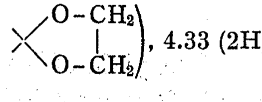
Reduction of VIII with lithium aluminum hydride in ether was carried out smoothly and furnished 2-[8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decan-8-yl]ethylamine (IX) in a good yield (93.4%). IR spectrum of IX confirmed its structure: new absorptions at 3360 cm^{-1} and 3290 cm^{-1} which are attributable to a primary amine appeared and a signal of a nitrile was not observed. Treatment of IX with ethyl chloroformate in pyridine produced ethyl 2-[8-(3,4-dimethoxyphenyl)-1,4-dioxaspiro[4,5]decan-8-yl]ethylcarbamate (X) in 81.9% yield, whose IR and NMR spectra were consistent with the assigned structure.

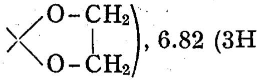
Reduction of X with lithium aluminum hydride afforded I in 73.2% yield as a colorless viscous oil, whose IR spectrum represented a signal of a secondary amine at 3290 cm^{-1}. Its NMR spectrum did not show any absorptions of ethyl ester, and a new signal of an N-methyl was observed at δ 2.30 ppm. Elementary analysis of its hydrochloride [mp 199—201° (decomp.)] agreed well with the assigned structure.

Studies on the chiroptical properties of I and its derivatives are now in progress.

Experimental

All the melting points were determined on a Yanagimoto Micro Melting Point apparatus and are not corrected. The IR spectra were measured with a Nihon Bunko Spectroscopic Co., Ltd. Model IR-S. The NMR spectra were measured with a Japan Electron Optics Laboratory Co. JNM-MH-60 spectrometer using tetramethylsilane as internal standard.

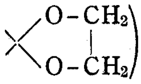
Ethyl 1,4-Dioxaspiro[4,5]decan-8-ylidene Cyanoacetate (IV)——A mixture of III[5] (5 g), benzene (30 ml), ethyl cyanoacetate (3.66 g), acetic acid (3.6 g), and ammonium acetate (0.23 g) was refluxed for 6 hr in a flask equipped with a water separator. The mixture was washed with water, and the benzene-layer was dried over Na_2SO_4. Benzene was distilled, and the residue was rectified to obtain bp$_{0.3}$ 120—140°, which crystallized on standing. Colorless needles of mp 83—84° (from ether-petroleum ether). Yield 2.15 g (26%). *Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.00; H, 6.85; N, 5.70. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2250 (C≡N), 1740 (C=O), 1600 (C=C). NMR $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 1.36 (3H, triplet, J=7.2 Hz, $-O-CH_2-\underline{CH_3}$), 1.19—2.09 and 2.75—3.40 (8H, multiplet, cyclohexane protons), 4.05 (4H singlet,  $\gt\!\begin{matrix}O-CH_2\\ |\\ O-CH_2\end{matrix}$), 4.33 (2H, quartet, J=7.2 Hz, $-O-\underline{CH_2}-CH_3$).

Ethyl 8-(3,4-Dimethoxyphenyl)-1,4-dioxaspiro[4,5]decane-8-cyanoacetate (V)——i) To a mixture of tetrahydrofuran (3 ml), magnesium turnings (150 mg), and a catalytic amount of iodine, 4-bromo-1,2-dimethoxybenzene (1.04 g) was added dropwise under mechanical stirring for 6 hr at 50—60°. Then IV (1.2 g) in tetrahydrofuran solution was added and the mixture was refluxed for 24 hr. The reaction mixture was poured into ice-water containing ammonium chloride, and extracted with ether. The ether-extracts were dried over Na_2SO_4, and solvent was distilled. The residue was purified by the silica gel column chromatography. From the chloroform-eluate pale yellow pillars of mp 40—42° (from ether-petroleum ether) were isolated. Yield 0.42 g (22.6%). *Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.47; H, 7.21; N, 3.87. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 890, 812 (1,2,4-trisubstituted benzene), 1752 (C=O), 2250 (C≡N). NMR $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 1.07 (3H, triplet, J=7.2 Hz, $-O-CH-\underline{CH_{23}}$), 1.30—2.50 (8H, multiplet, cyclohexane protons), 3.90 (3H, singlet, $-OCH_3$), 3.95 (3H, singlet, $-OCH_3$), 4.05 (2H, quartet, $-O-\underline{CH_2}-CH_3$), 4.05 (4H, singlet,  $\gt\!\begin{matrix}O-CH_2\\ |\\ O-CH_2\end{matrix}$), 6.82 (3H, singlet, aromatic protons).

ii) To a mixture of tetrahydrofuran (3 ml), magnesium turnings (150 mg), and a catalytic amount of iodine, 4-iodo-1,2-dimethoxybenzene (1.60 g) was added dropwise at room temperature under mechanical stirring for 6 hr. IV (1.0 g) in tetrahydrofuran solution was added to the above mixture and the mixture was stirred for 16 hr at room temperature. The mixture was treated as for the method (i). Yield 0.52 g (33.2%).

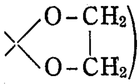
iii) To a mixture of tetrahydrofuran (3 ml), magnesium turnings (150 mg) and a catalytic amount of iodine, 4-iodo-1,2-dimethoxybenzene (1.60 g) was added dropwise at room temperature under mechanical stirring for 6 hr. IV (1 g) in tetrahydrofuran solution and 50 mg of Cu_2Cl_2 were added to the above mixture and the mixture was stirred for 16 hr at room temperature. The mixture was treated as for the method (i). Yield 0.76 g (49.5%).

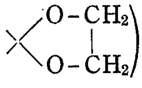
8-(3,4-Dimethoxyphenyl)-1,4-dioxaspiro[4,5]decane-8-cyanoacetic Acid (VII)——V (1.15 g) was dissolved in 10% methanolic potassium hydroxide, and the solution was stood overnight at 40—50°. Solvent was distilled under reduced pressure. Water was added to the residue, and the solution was made acid (pH 3—2) with 5% sulfuric acid to obtain precipitates which were extracted with chloroform. Solvent was distilled, and the residue was dissolved in $NaHCO_3$ solution, treated with activated charcoal, made acid with 5% sulfuric acid, and extracted with chloroform. The chloroform-extracts were dried over Na_2SO_4 and condensed. Purification by silica gel colmn chromatography furnished colorless pillars of mp 74—75° (recrystallized from CCl_4). Yield 0.75 g (70.4%). *Anal.* Calcd. for $C_{19}H_{23}O_6N$: C, 63.15; H, 6.42; N, 3.88. Found: C, 62.80; H, 6.19; N, 3.61. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3440 (OH), 1750 (C=O).

8-(3,4-Dimethoxyphenyl)-1,4-dioxaspiro[4.5]decane-8-acetonitrile (VIII)——VII (2 g) was dissolved in 10 ml of pyridine and the solution was refluxed for 9 hr. Pyridine was distilled and the residue was purified by alumina coloum chromatography to obtain colorless pillars of mp 123—124° (recrystallized from ether). Yield 1.27 g (72.5%). *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.04; H, 7.15; N, 4.19. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2250 (C≡N). NMR $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 1.50—2.35 (8H, multiplet, cyclohexane protons), 2.53 (2H, singlet, $-CH_2CN$), 3.95 and 3.98 (10H, two singlets, $-OCH_3$,  $>\begin{matrix}O-CH_2\\ \vert\\ O-CH_2\end{matrix}$), 6.95 (3H, singlet, aromatic protons).

2-[8-(3,4-Dimethoxyphenyl)-1,4-dioxaspiro[4,5]decan-8-yl]ethylamine (IX)——To a suspension of lithium aluminum hydride (500 mg) in 50 ml of ether, a solution of VIII (1 g) in tetrahydrofuran was added dropwise under stirring. The stirring was continued for 24 hr. Water was added to the reaction mixture, which was made alkaline, and filtered. The filtrate was extracted with ether. The extracts were dried over Na_2SO_4. Ether was evaporated and the residue was purified by silica gel colmn chromatography. From chloroform-eluate colorless viscous oil 0.94 g (93.4%) was obtained. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3360, 3290 (NH_2).

Hydrochloride of IX: Colorless scales of mp 198—200° (decomp.). *Anal.* Calcd. for $C_{18}H_{27}O_4N \cdot HCl$: C, 60.41; H, 7.89; N, 3.91. Found: C, 60.22; H, 7.83; N, 3.81.

Ethyl 2-[8-(3,4-Dimethoxyphenyl)-1,4-dioxaspiro[4.5]decan-8-yl]ethylcarbamate (X)——To a solution of IX (200 mg) in 5 ml of pyridine, ethyl chloroformate (43 mg) was added. The mixture was stood overnight at room temperature. Water was added to the reaction mixture which was evaporated to dryness. The residue was extracted with chloroform. The extracts were dried over Na_2SO_4. Chloroform was evaporated and the residue was purified by colmn chromatography on silica gel. From benzene-eluate colorless viscous oil 200 mg (81.9%) was obtained. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3300 (NH), 1710 (C=O). NMR $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 1.19 (3H, triplet, $J=7.2$ Hz, $-COOCH_2\underline{CH_3}$), 1.40—2.30 (12H, multiplet, cyclohexane and ethylene protons), 3.80—4.20 (12H, $-OCH_3 \times 2$, $-COO\underline{CH_2}CH_3$,  $>\begin{matrix}O-CH_2\\ \vert\\ O-CH_2\end{matrix}$), 6.78 (3H, singlet, aromatic protons).

N-Methyl-2-[8-(3,4-Dimethoxyphenyl)-1,4-dioxaspiro[4,5]decan-8-yl]ethylamine (I)——To a suspension of lithium aluminum hydride (500 mg) in ether, a solution of X (500 mg) in ether was added dropwise under reflux and stirring. The reflux and stirring were continued for 24 hr. Water was added to the reaction mixture, which was made alkaline and filtered. The filtrate was extracted with ether. The ether-extracts were dried over Na_2SO_4. Ether was evaporated and the residue was purified by alumina colmn chromatography. From chloroform-eluate colorless oil was obtained. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3290 (NH). NMR $\delta_{\text{ppm}}^{\text{CDCl}_3}$: 1.30—2.50 (12H, multiplet, cyclohexane and ethylene protons), 2.30 (3H, singlet, $N-CH_3$), 3.07 (1H, broad singlet, -NH-, erased on deuteration), 3.85 and 3.90 (10H, two singlets, $2\times -OCH_3$,  $>\begin{matrix}O-CH_2\\ \vert\\ O-CH_2\end{matrix}$), 6.75 (3H, singlet, aromatic protons).

Hydrochloride of I: Colorless pillars of mp 199—201° (decomp.). Yield 316 mg (73.2%). *Anal.* Calcd. for $C_{19}H_{29}O_4N \cdot HCl$: C, 61.36; H, 8.13; N, 3.77. Found: C, 61.22; H, 8.28; N, 3.67.

Acknowledgement The authors wish to express their appreciation to Professor Emeritus S. Sugasawa of the University of Tokyo for his encouragement during this work. The microanalyses and the measurements of NMR spectra were carried out by the members of the Microanalytical Center of this Faculty to whom the authors are grateful.