[Chem. Pharm. Bull. 20(1) 41—46 (1972)]
UDC 547.833.9.057

Synthesis of Spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-substituted-2′-methyl-1′*H*-isoquinoline]

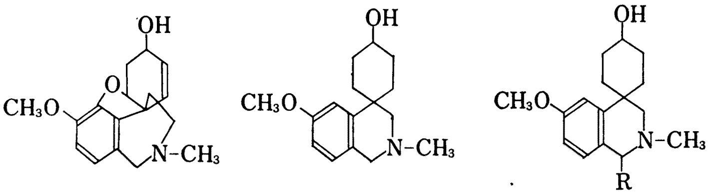
Hideaki Shirai, Tamotsu Yashiro, and Taiki Aoyama

Faculty of Pharmaceutical Sciences, Nagoya City University[1]

(Received April 13, 1971)

For the purpose of testing the biological activity, some galanthamine related compounds, spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-substituted-2′-methyl-1′*H*-isoquinoline] (IIIa, b,c) were synthesized by the application of the Bischler–Napieralski cyclization on the N-acyl compounds (VIIa,b,c).

In an earlier publication,[2] we have reported the synthesis of spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′*H*-isoquinoline] (II), which is structurally related to galanthamine (I), an alkaloid from Amaryllidaceae. As a part of further synthetic studies on galanthamine related compounds, this paper deals with the synthesis of three 1′-substituted II derivatives; spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′,2′-dimethyl-1′*H*-isoquinoline] (IIIa), spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-phenyl-2′-methyl-1′*H*-isoquinoline] (IIIb), and spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-benzyl-2′-methyl-1′*H*-isoquinoline] (IIIc). As substituents, the methyl, phenyl, and benzyl groups were selected at our present investigation.



I II

IIIa : R=CH_3
IIIb : R=C_6H_5
IIIc : R=$CH_2C_6H_5$

Chart 1

For the synthesis of the compound (IIIa), reduction of 1-(*m*-methoxyphenyl)-4-oxocyclohexanecarbonitrile (IV)[3] with lithium aluminium hydride was first carried out to give the known methylamine compound, 1-(*m*-methoxyphenyl)-4-hydroxycyclohexanemethylamine (V).[4] The configuration between the hydroxy and aminomethyl groups in V has been previously established to be *cis*.[5] Acetylation of the *cis*-hydroxy-amine (V) with acetic anhydride in pyridine afforded N-acetyl-1-(*m*-methoxyphenyl)-4-acetoxycyclohexanemethylamine (VIIa) as a colorless oil, bp 149—151° (2.5 mmHg).

Alternative acetylation of V with acetyl chloride by the Schotten–Baumann condensation, however, yielded pale yellow pillars, mp 48—49°, together with VIIa. This crystal-

---

[1] Location: *3-1, Tanabe-dori, Mizuho-ku, Nagoya.*
[2] H. Shirai, T. Yashiro, and T. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1564 (1969).
[3] S. Uyeo, H. Shirai, A. Koshiro, T. Yashiro, and K. Kagei, *Chem. Pharm. Bull.* (Tokyo), **14**, 1033 (1966).
[4] H. Shirai, T. Yashiro, and T. Aoyama, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo*, **17**, 33 (1969).
[5] H. Shirai, T. Yashiro, and T. Aoyama, *Yakugaku Zasshi*, **90**, 1135 (1970).

line compound was assigned to be N-acetyl-1-(*m*-methoxyphenyl)-4-hydroxycyclohexanemethylamine (VIa) from its empirical formula and its infrared spectrum which displayed the OH band at 3400 cm^{-1} and amido carbonyl band at 1668 cm^{-1}. Further acetylation of VIa with acetic anhydride in pyridine afforded VIIa.

Next the diacetyl compound (VIIa) was submitted to the Bischler–Napieralski reaction by use of phosphorus oxychloride in chloroform to give spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-methyl-3′*H*-isoquinoline] (VIIIa), colorless prisms, mp 139—140°. The cyclization of VIIa to VIIIa was proved by the following facts: The empirical formula of this compound was in satisfactory agreement with $C_{18}H_{23}O_3N$ corresponding to VIIIa and its infrared spectrum displayed the band at 1630 cm^{-1} due to the imino group. The nuclear magnetic resonance spectrum showed signals assignable to the 3′-methylene protons of the isoquinoline ring at 6.32 τ as singlet and the methyl protons of 1′-position at 7.63 τ as singlet.

The spiro-compound (VIIIa) thus obtained was converted to the corresponding methiodide (IXa), which was subsequently reduced with sodium borohydride in methanol to the tertiary base spiro[4-acetoxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′,2′-dimethyl-1′*H*-isoquinoline] (XIa). Alternatively XIa was obtained by the methylation of the secondary base (X) derived from VIIIa by reduction with sodium borohydride. The infrared spectra of the above two compounds (X and XIa) exhibited no longer the imino band (C=N), while X showed a band at 3420 cm^{-1} due to amino group. The ultraviolet spectra of X and XIa showed the hypsochromic shift and their extinction coefficients were decreased compared

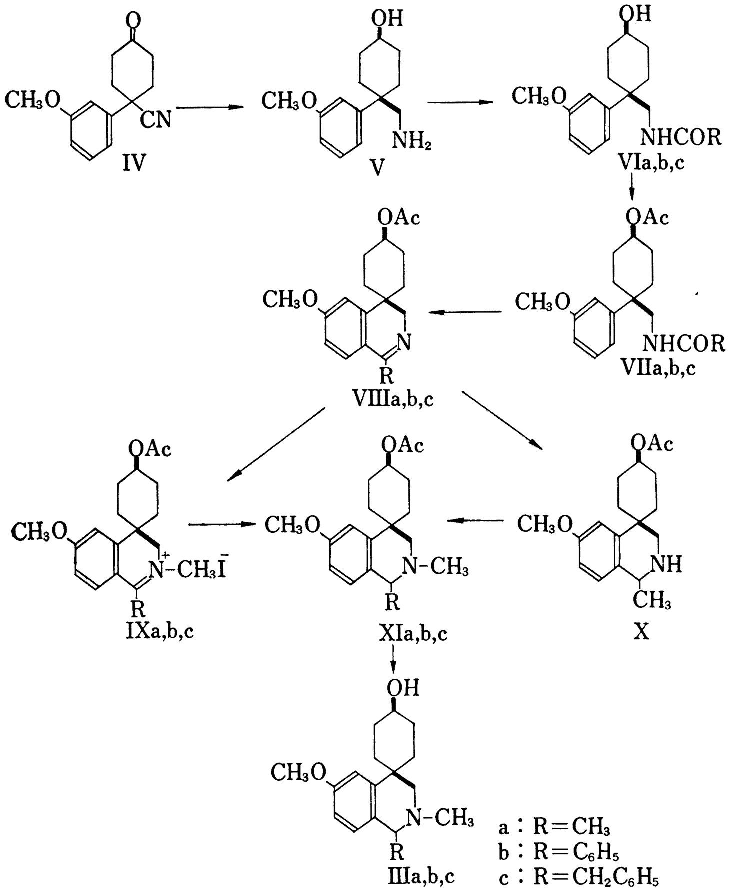


Chart 2

with that of VIIIa. These data of ultraviolet spectra supported the view that the conjugated double bond of VIIIa was saturated by the above reduction. Hydrolysis of XIa with ethanolic sodium hydroxide gave a colorless oil (IIIa), which was converted to its crystalline hydrochloride, whose structure was confirmed by the data of its ultraviolet, infrared, and nuclear magnetic resonance spectra.

Similarly two other spiro[cyclohexane-isoquinoline]compounds, (IIIb) and (IIIc), were synthesized starting from V. The Bischler–Napieralski reaction was also applied to obtain 1′-substituted isoquinoline derivatives with the phenyl or the benzyl group as showing in Chart 2.

In the first step, the Schotten–Baumann condensation of the *cis*-hydroxy-amine (V) with benzoyl chloride or phenylacetyl chloride afforded the N-acylcompounds, (VIb) and (VIc) respectively. Infrared spectra of both compounds exhibited the amido carbonyl band at 1655 cm^{-1}. Acetylation of VIb and VIc with acetic anhydride in pyridine gave colorless oils, (VIIb) and (VIIc), which were treated with phosphours oxychloride in benzene to give spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-phenyl-3′*H*-isoquinoline] (VIIIb) and spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-benzyl-3′*H*-isoquinoline] (VIIIc) respectively. The former (VIIIb) exhibited in infrared spectra the carboxyl band at 1725 cm^{-1} and the imino (C=N) band at 1603 cm^{-1} (VIIIb) and the latter (VIIIc) exhibited at 1730 cm^{-1} and 1620 cm^{-1} respectively.

Reduction of the methiodides, (IXb) and (IXc), derived from VIIIb and VIIIc with sodium borohydride in methanol gave tertiary bases, XIb and XIc respectively. Their structures were confirmed by the absence of the imino band in their infrared spectra and their ultraviolet spectra exhibited the hypsochromic shift and decrease in extinction coefficiency compared the with those of VIIIb and VIIIc. These compound (XIb, c) were hydrolized with ethanolic sodium hydroxide to give spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-phenyl-2′-methyl-1′*H*-isoquinoline] (IIIb), mp 128—129° and spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-benzyl-2′-methyl-1′*H*-isoquinoline] (IIIc), mp 140—142°. Physical data and the elementary analyses supported the structures of IIIb and IIIc.

The pharmacological activities of the compounds obtained in this study are under investigation.

Experimental[6]

Acetylation of 1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanemethylamine (V)——i) A mixture of the *cis*-hydroxy-amine (V) (240 mg), Ac$_2$O (1 ml) and dry pyridine (1.8 ml) was allowed to stand overnight at room temperature and then diluted with ice-water. The resulting precipitate was extracted with ether. The ethereal extract was washed with H$_2$O, dried over anhydrous Na$_2$SO$_4$ and evaporated to dryness to give the residue, which was chromatographed on silica gel. The CHCl$_3$ eluate gave N-acetyl-1-(*m*-methoxyphenyl)-4-acetoxycyclohexanemethylamine (VIIa) (249 mg) as a colorless oil, bp 149—151° (2.5 mmHg). *Anal.* Calcd. for C$_{18}$H$_{25}$O$_4$N: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.74; H, 8.04; N, 4.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3445 (NH), 1735 (acetyl C=O), 1665 (amide C=O).

ii) Acetyl chloride (0.2 ml) dissolved in dry ether was added dropwise with stirring to a mixture of V (300 mg) in tetrahydrofuran (10 ml) and 5% aq. NaOH (10 ml) cooled in an ice-bath. After the reaction mixture was stirred for 30 min, ether (10 ml) was added in one portion to the mixtute. The ether layer separated was washed with 5% aq. NaOH and H$_2$O, dried over anhydrous K$_2$CO$_3$, and evaporated to dryness to give the residue which was chromatographed on silica gel. The first CHCl$_3$ eluate gave VIIa (260 mg) as a colorless oil, bp 149—151° (2.5 mmHg). *Anal.* Calcd. for C$_{18}$H$_{25}$O$_4$N: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.72; H, 7.99; N, 4.42. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3445 (NH), 1735 (C=O), 1665 (C=O). The second CHCl$_3$ eluate gave N-acetyl-1-(*m*-methoxyphenyl)-4-hydroxycyclohexanemethylamine (VIa)(37 mg) which

---

6) All melting points were measured on a Yanagimoto micromelting point determination apparatus, and all melting and boiling points were uncorrected. Nuclear magnetic resonance spectra were taken on a Varian associate A-60 spectrometer with tetramethylsilane as internal standard.

was crystallized from petroleum ether as pale yellow pillars, mp 48—49°. *Anal.* Calcd. for $C_{16}H_{23}O_3N$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.34; H, 8.51; N, 5.11. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (NH), 3400 (OH), 1668 (C=O). A mixture of VIa, Ac_2O and pyridine was left overnight at room temperature and was worked up in the same manner described above in i) to give a colorless oil (32 mg), bp 149—151° (2.5 mmHg). The boiling point and infrared spectrum of this oil were identical with those of the sample (VII a) described above.

Spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-methyl-3′*H*-isoquinoline] (VIIIa)——A mixture of VIIa (200 mg) and $POCl_3$ (300 mg) in dry $CHCl_3$ (3 ml) was heated under reflux for 3 hr and the solvent was evaporated to dryness. The residue was washed with ether, and then taken up in H_2O, which was alkalized with 10% aq. NaOH, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over anhydrous K_2CO_3, and evaporated to give colorless crystals (170 mg) which were recrystallized from petroleum ether as colorless prisms, mp 139—140°. *Anal.* Calcd. for $C_{13}H_{23}O_3N$; C, 71.73; H, 7.69; N, 4.65. Found: C, 71.69; H, 7.72; N, 4.61. IR ν_{max}^{KBr} cm^{-1}: 1745 (C=O), 1630 (C=N). UV λ_{max}^{EtOH} $m\mu$ ($\log \varepsilon$): 230 (3.90), 249 (3.51), 325 (3.83). NMR (in $CDCl_3$) τ: 2.45—3.42 (3H, multiplet, aromatic protons), 5.14—5.50 (1H, multiplet, $>C\underline{H}\text{-}OAc$), 6.15 (3H, singlet, $\text{-}OCH_3$), 6.32 (2H, singlet, $\text{-}CH_2\text{-}N\langle$), 7.63 (3H, singlet, $CH_3\text{-}C\langle_{C_6H_5}$), 7.92 (3H, singlet, $\text{-}O\text{-}COCH_3$), 8.01—8.55 (8H, multiplet, $\text{-}CH_2\text{-}CH_2\text{-}$).

Spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-methyl-3′*H*-isoquinoline] Methiodide (IXa)——To an ice-cooled soultion of VIIIa (200 mg) in dry MeOH (8 ml) was added CH_3I (0.1 ml) with stirring. The mixture was stirred at room temperature for 1 hr and was heated under gentle reflux for 2 hr. The crystals deposited after cooling with ice were collected by filtration and recrystalized from EtOH to afford 250 mg of IXa as yellow needles, mp 246.5—248.5°. *Anal.* Calcd. for $C_{19}H_{26}O_3NI$: C, 51.49; H. 5.86; N, 3.16. Found: C, 51.50; H, 5.89; N, 3.16.

Spiro[4-acetoxycyclohexanc-1,4′-2′,3′-dihydro-6′-methoxy-1′-methyl-1′*H*-isoquinoline] (X)——To a solution of VIIIa (350 mg) in MeOH (5 ml), $NaBH_4$ (200 mg) suspended in MeOH (3 ml) was added. The mixture was stirred at room temperature for 1 hr and the solvent was evaporated to dryness. The residue was taken up in 2% aq. NaOH, which was extracted with $CHCl_3$. The $CHCl_3$, extract was washed with H_2O and dried over anhydrous K_2CO_3 and evaporated to dryness to give a brown oil (250 mg). IR $\lambda_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 1730 (C=O).

Spiro[4-acetoxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′,2′-dimethyl-1′*H*-isoquinoline] (XIa)——i) To a solution of IXa (190 mg) in MeOH (4 ml), $NaBH_4$ (100 mg) suspended in MeOH (2 ml) was added with stirring. The mixture was stirred at room temperature for 1 hr and the solvent was evaporated to dryness. The residue was taken up in 2% aq. NaOH, which was extracted with ether, and the ethereal solution was washed with H_2O and dried over anhydrous K_2CO_3. Removal of the solvent gave a brown oil, XIa (130 mg), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2780 (CH), 1735 (C=O).

ii) A mixture of X (150 mg) and NaH (150 mg)(50% in mineral oil) in dry toluene (70 ml) was heated under reflux for 12 hr and then cooled in an ice bath. After addition of CH_3I (2 ml), the mixture was stirred at room temperature for 1 hr, and then heated under reflux for 2 hr. After decomposition of excess NaH with AcOH, the mixture was diluted with benzene, which was washed with H_2O, dried over anhydrous Na_2SO_4 and then evaporated to dryness to give a brown oil XIa (120 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2780 (CH), 1735 (C=O). The infrared spectrum of this oil was identical with the sample described above in i).

Spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′,2′-dimethyl-1′*H*-isoquinoline] (IIIa)——A mixture of XIa (100 mg) and 5% ethanolic NaOH (10 ml) was heated under reflux for 1 hr. Evaporation of EtOH under reduced pressure gave the residue which was extracted with ether. The ethereal extract was washed with H_2O, dried over anhydrous K_2CO_3 and evaporated to dryness. Purification of the residue by chromatography in $CHCl_3$ on Al_2O_3 gave a colorless oil, IIIa (56 mg). UV λ_{max}^{EtOH} $m\mu$ ($\log \varepsilon$): 230 (3.70), 280 (3.11), 287 (shoulder 3.03). NMR (in $CDCl_3$) τ: 2.86—3.42 (3H, multiplet, aromatic protons), 5.99—6.18 (1H, multiplet, $>C\underline{H}\text{-}OH$), 6.20 (3H, singlet, $\text{-}OCH_3$), 6.52 (1H, quartet, $J=7.0$ cps, ${}_{C_6H_5}>C\underline{H}\text{-}CH_3$), 7.15 (2H, singlet, $\text{-}CH_2\text{-}N\langle$), 7.54 (3H, singlet, $>N\text{-}CH_3$), 7.72 (1H, singlet, -OH), 7.79—8.59 (8H, mutiplet, $\text{-}CH_2\text{-}CH_2\text{-}$), 8.69 (3H, dobulet, $J=7.0$ cps, ${}_{C_6H_5}>CH\text{-}C\underline{H}_3$). Hydrochloride of IIIa: colorless prisms, mp 235—238° (from MeOH–ether). *Anal.* Calcd. for $C_{17}H_{25}O_2N \cdot HCl$: C, 65.51; H, 8.34; N, 4.49; Cl, 11.37. Found: C, 65.79; H, 8.42; N, 4.49; Cl, 11.42. IR ν_{max}^{KBr} cm^{-1}: 3375 (OH), 2750 ($N^+\text{-}H$).

N-Benzoyl-1-(*m*-methoxyphenyl)-4-hydroxycyclohexanemethylamine (VIb)——Benzoyl chloride (0.5 ml) in dry tetrahydrofuran (25 ml) was added dropwise with stirring to a mixture of V (500 mg), tetrahydrofuran (5 ml), and 5% aq. NaOH (10 ml) cooled in an ice bath. After the reaction mixture was stirred for 30 min, ether (10 ml) was added in one portion to the mixture. The ethereal solution was washed with 5% aq. NaOH and H_2O, dried over anhydrous K_2CO_3 and evaporated to dryness to give the residue which was chromatographed in $CHCl_3$ on silica gel. The $CHCl_3$ eluate gave VIb as a colorless oil (650 mg). *Anal.* Calcd. for $C_{21}H_{25}O_3N$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.39; H, 7.37; N, 4.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3460 (NH), 1655 (C=O).

N-Benzoyl-1-(*m*-methoxyphenyl)-4-acetoxycyclohexanemethylamine (VIIb)——A mixture of VIb (600 mg), Ac_2O (2.5 ml) and dry pyridine (6 ml) was allowed to stand at room temperature for 24 hr and diluted with ice-water. The resulting precipitate was extracted with ether. The ethereal extract was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness. Purification of the residue by chromatography in AcOEt on silica gel gave VIIb (500 mg) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 1725 (acetyl C=O), 1655 (amide C=O).

Spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-phenyl-3′*H*-isoquinoline] (VIIIb)——A mixture of VIIb (560 mg), $POCl_3$ (1.5 ml), and dry benzene (25 ml) was heated under reflux for 3 hr and evaporated to dryness. The residue was taken up in H_2O, which was alkalized with 10% aq. NaOH, and the resulting product was extracted with ether. The ethereal extract was washed with H_2O and dried over anhydrous K_2CO_3, and then evaporated to give colorless crystals (420 mg), which were recrystallized from petroleum ether as colorless prisms VIIIb, mp 147—148°. *Anal.* Calcd. for $C_{23}H_{25}O_3N$: C, 76.00; H, 6.93; N, 3.85. Found: C, 76.12; H, 6.81; N, 3.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (C=O), 1603 (C=N). UV λ_{max}^{EtOH} mμ (log ε): 224 (shoulder 4.33), 252 (3.95), 283 (shoulder 3.82), 340 (4.12).

Spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-phenyl-3′*H*-isoquinoline] methiodide (IXb)——To an ice-cooled solution of VIIIb (400 mg) in dry MeOH (15 ml), CH_3I (0.2 ml) was added with stirring. The mixture was stirred at room temperature for 1 hr and then heated under gentle reflux for 2 hr. The crystals formed under cooling were collected by filtration and recrystallized from EtOH to afford IXb (440 mg) as yellow needles, mp 250—251.5°. *Anal.* Calcd. for $C_{24}H_{28}O_3NI$: C, 57.06; H, 5.54; N, 2.77. Found: C, 57.09; H, 5.60; N, 2.75.

Spiro[4-acetoxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-phenyl-2′-methyl-1′*H*-isoquinoline] (XIb)——To a mixture of VIIIb (200 mg) in dry MeOH (5 ml), $NaBH_4$ (100 mg) was added with stirring. The mixture was stirred at room temperature for 1 hr and the solvent was evaporated to dryness. Ether and H_2O were added to the residue. The ethereal solution was washed with H_2O and dried over anhydrous K_2CO_3. Removal of the ether gave XIb as a brown oil (139 mg). Hydrochloride of XIb: colorless prisms, mp 168—170° (from ether–EtOH). *Anal.* Calcd. for $C_{24}H_{29}O_3N \cdot HCl$: C, 69.33; H, 7.21; N, 3.37; Cl, 8.52. Found: C, 69.27; H, 7.13; N, 3.41; Cl, 8.49. IR ν_{max}^{KBr} cm^{-1}: 2649 (N^+-H), 1730 (C=O).

Spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-phenyl-2′-methyl-1′*H*-isoquinoline] (IIIb)——A mixture of XIb (150 mg) and 5% ethanolic NaOH (20 ml) was heated under reflux for 1 hr and the solvent was evaporated to dryness. Ether and H_2O were added to the residue and the ethereal extract was washed with H_2O and dried over anhydrous K_2CO_3 and evaporated to dryness. Purification of the residue by chromatography in $CHCl_3$ on Al_2O_3 gave IIIb as colorless prisms, mp 128—129° (from petroleum ether). *Anal.* Calcd. for $C_{22}H_{27}O_2N$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.37; H, 8.12; N, 4.11. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (OH). NMR (in $CDCl_3$) τ: 2.42—3.50 (8H, multiplet, aromatic protons), 5.91—6.18 (1H, multiplet, $>C\underline{H}$-OH), 6.26 (3H, singlet, $-OCH_3$), 6.59 (1H, singlet, $-CH\langle^{N}_{C_6H_5}$), 7.61 (2H, singlet, $-CH_2-N\langle$), 7.70 (1H, singlet, -OH), 7.83 (3H, singlet, $>N-CH_3$), 7.99—8.62 (8H, multiplet, $-CH_2-CH_2-$). UV λ_{max}^{EtOH} mμ (log ε): 233 (3.72), 288 (3.34). Hydrochloride of IIIb: colorless prisms, mp 188—191° (from petroleum ether). *Anal.* Calcd. for $C_{22}H_{27}O_2N \cdot HCl$: C, 70.70; H, 7.49; N, 3.74; Cl, 9.48. Found: C, 70.75; H, 7.45; N, 3.72; Cl, 9.41. IR ν_{max}^{KBr} cm^{-1}: 3430 (OH), 2550 (N^+-H).

N-Phenylacetyl-1-(*m*-methoxyphenyl)-4-hydroxycyclohexanemethylamine (VIc)——A mixture of phenylacetic acid (400 mg), $SOCl_2$ (1.5 ml), and benzene (4 ml) was heated under reflux for 1 hr. The solvent and the excess $SOCl_2$ were removed under reduced pressure and the residue was dissolved in dry ether. The ether solution was added dropwise to a mixture of V (400 mg), tetrahydrofuran (10 ml), ether (70 ml), and 3% aq. NaOH cooled in an ice bath. The reaction mixture was stirred at room temperature for 1 hr and the ethereal solution separated was washed with 3% HCl and H_2O, dried over anhydrous K_2CO_3 and evaporated to dryness to give brown crystals which were recrystallized from benzene as colorless prisms VIc, mp 102—104°. *Anal.* Calcd. for $C_{22}H_{27}O_3N$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.42; H, 7.51; N, 4.02. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425 (NH), 3380 (OH), 1655 (C=O).

N-Phenylacetyl-1-(*m*-methoxyphenyl)-4-acetoxycyclohexanemethylamine (VIIc)——A mixture of VIc (260 mg), Ac_2O (1.3 ml), and dry pyridine (2.6 ml) was allowed to stand at room temperature overnight and then diluted with ice-water. The resulting precipitate was extracted with ether. The ethereal extract was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness to give VIIc as a brown oil (270 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 1730 (acetyl C=O), 1655 (amide C=O).

Spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-benzyl-3′*H*-isoquinoline] (VIIIc)——A mixture of VIIc (270 mg), $POCl_3$ (1 ml), and dry benzene (10 ml) was heated under reflux for 3 hr and the solvent was evaporated to dryness. The residue, after washing with ether, was dissolved in H_2O, which was then alkalized with 10% aq. NaOH, the resulting product was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhydrous K_2CO_3, and evaporated to give brown crystals (180 mg) which were recrystallized from petroleum ether as colorless prisms VIIIc, mp 105—107°. *Anal.* Calcd. for $C_{24}H_{27}O_3N$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.25; H, 7.31; N, 3.69. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O), 1620 (C=N). UV λ_{max}^{EtOH} mμ (log ε): 222 (shoulder 4.32), 253 (4.06), 275 (3.94), 345 (3.91).

Spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-1′-benzyl-3′*H*-isoquinoline] Methiodide (IXc)——To a solution of VIIIc (200 mg) in dry MeOH (8 ml) cooled in an ice-bath, CH_3I (0.1 ml) was added. The mixture was stirred at room temperature for 1 hr and heated under gentle reflux for 2 hr. The crystals formed after cooling were collected by filtration, and recrystallized from EtOH to give IXc (210 mg) as yellow needles, mp>300°. *Anal.* Calcd. for $C_{25}H_{30}O_3NI$: C, 57.81; H, 5.78; N, 2.70. Found: C, 57.92; H, 5.81; N, 2.76.

Spiro[4-acetoxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-benzyl-2′-methyl-1′*H*-isoquinoline] (XIc)——To a solution of IXc (120 mg) in dry MeOH (4 ml), $NaBH_4$ (80 mg) was added with stirring. The mixture was stirred at room temperature for 1 hr and the solvent was evaporated to dryness. Ether and H_2O were added to the residue. The ethereal extract was washed with H_2O and dried over anhydrous K_2CO_3. Removal of the solvent gave XIc as a brown oil (94 mg). Hydrochloride of XIc: colorless prisms, mp 166—168° (from ether–MeOH). *Anal.* Calcd. for $C_{25}H_{31}O_3N \cdot HCl$: C, 69.83; H, 7.44; N, 3.26; Cl, 8.24. Found: C, 70.01; H, 7.31; N, 3.17; Cl, 8.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2545 (N^+-H), 1730 (C=O).

Spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-1′-benzyl-2′-methyl-1′*H*-isoquinoline](IIIc)——A mixture of XIc (100 mg) and 5% ethanolic NaOH (12 ml) was heated under reflux for 1 hr and the solvent was evaporated to dryness. Ether and H_2O were added to the residue and the ethereal extract was washed with H_2O, dried over anhydrous K_2CO_3, and evaporeted to dryness. Purification of the residue by chromatography in $CHCl_3$ on Al_2O_3 gave IIIc as colorless prisms, mp 140—142° (from ether). *Anal.* Calcd. for $C_{23}H_{29}O_2N$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.78; H, 8.35; N, 3.87. IR ν_{max}^{EtOH} cm^{-1}: 3370 (OH). UV λ_{max}^{EtOH} $m\mu$ (log ε): 227 (3.89), 278 (3.41), 286 (shoulder 3.37). NMR (in $CDCl_3$) τ: 2.68—3.75 (8H, multiplet, aromatic protons), 6.06—6.14 (1H, multiplet, $>C\underline{H}$-OH), 6.25 (3H, singlet, $-OCH_3$), 6.48 (1H, triplet, $J=7.0$ cps, ${}^{C_6H_5}{>}C\underline{H}-CH_2-$), 7.29 (2H, singlet, $-CH_2-N<$), 7.40 (2H, dobulet, $J=7.0$ cps, ${}^{C_6H_5}{>}CH-C\underline{H}_2-$), 7.48 (3H, singlet, $>N-CH_3$), 7.52—7.65 (1H, singliet, -OH), 7.89—8.40 (8H, multiplet, $-CH_2-CH_2-$). Hydrochloride of IIIc: colorless prisms, mp 201—204° (from ether–EtOH). *Anal.* Calcd. for $C_{23}H_{29}O_2N \cdot HCl$: C, 71.24; H, 7.73; N, 3.61; Cl, 9.14. Found: C, 71.31; H, 7.71; N, 3.59; Cl, 9.05. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 2650 (N^+-H).

Acknowledgement The authors are deeply indebted to Prof. S. Uyeo, Kyoto University, for his kind advice and encouragement on this work. Thanks are also due to Dr. T. Shingu for taking nuclear magnetic resonance spectra, and to the members of Microanalytical Center of Kyoto University and the analytical laboratory of this Faculty for elemental analysis.