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Synthesis of Spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′*H*-isoquinoline] and 4-Dimethylaminomethyl-4-(*m*-methoxyphenyl)cyclohexanol[1]

Tamotsu Yashiro, Kyoko Yamada, and Hideaki Shirai

Faculty of Pharmaceutical Sciences, Nagoya City University[2]

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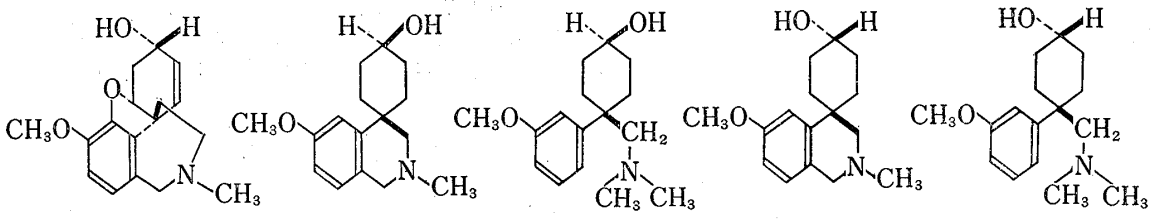
For the purpose of testing the biological activity, spiro-[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′*H*-isoquinoline] (IV) was synthesized by cyclization of 1-(*m*-methoxyphenyl)-4-hydroxycyclohexanemethylamine (XIII), which was obtained from the *trans*-acetoxy-amide(XII), in the presence of excess formic acid and formaldehyde under the conditions of Eschweiler-Clarke reaction.

4-Dimethylaminomethyl-4-(*m*-methoxyphenyl)cyclohexanol (V) was synthesized by reduction of 1-(*m*-methoxyphenyl)-4-acetoxycyclohexanecarbonyl dimethylamide (XIV), which was obtained from the *trans*-acetoxy-acid chloride (XI), with lithium aluminum hydride.

In earlier publications, we have reported the synthesis of spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′*H*-isoquinoline] (II)[3,4] and 4-dimethylaminomethyl-4-(*m*-methoxyphenyl)cyclohexanol (III),[5] which are structurally related to galanthamine (I), an Amaryllidaceae alkaloid. We now wish to report the synthesis of the *trans*-hydroxy-spiroisoquinoline compound (IV) and the *trans*-hydroxy-dimethylamine compound (V) which are closely resembling to the above compounds (II and III), except the configuration of the hydroxyl group.



I II III IV V

Chart 1

For the synthesis of the compound (IV), reduction of 1-(*m*-methoxyphenyl)-4-oxocyclohexanecarbonitrile (VI)[6] in propan-2-ol with aluminum isopropoxide was first carried out to give the known epimeric alcohols, 1-(*m*-methoxyphenyl)-4-hydroxycyclohexanecarbonitriles (VIIa, b). The relationship between the hydroxyl and nitrile group in VIIa and VIIb has been previously established to be *trans* and *cis* (29.7: 70.3), respectively by gas chromatography.[7] The *cis*-relationship of the hydroxyl and nitrile groups in VIIb was proved by the fact that the corresponding hydroxy-acid (VIIIb) formed a lactone (X).[3]

1) In these compounds, the hydroxyl group is *trans*-oriented with respect to the aminomethyl moiety.
2) Location: *3-1, Tanabe-dori, Mizuho-ku, Nagoya.*
3) H. Shirai, T. Yashiro, and T. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1564 (1969).
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5) T. Yashiro, *Yakugaku Zasshi*, **92**, 141 (1972).
6) S. Uyeo, H. Shirai, A. Koshiro, T. Yashiro, and K. Kagei, *Chem. Pharm. Bull.* (Tokyo), **14**, 1033 (1966).
7) H. Shirai, T. Yashiro, T. Sato, T. Aoyama, and T. Kuwayama, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo*, **20**, 26 (1972).

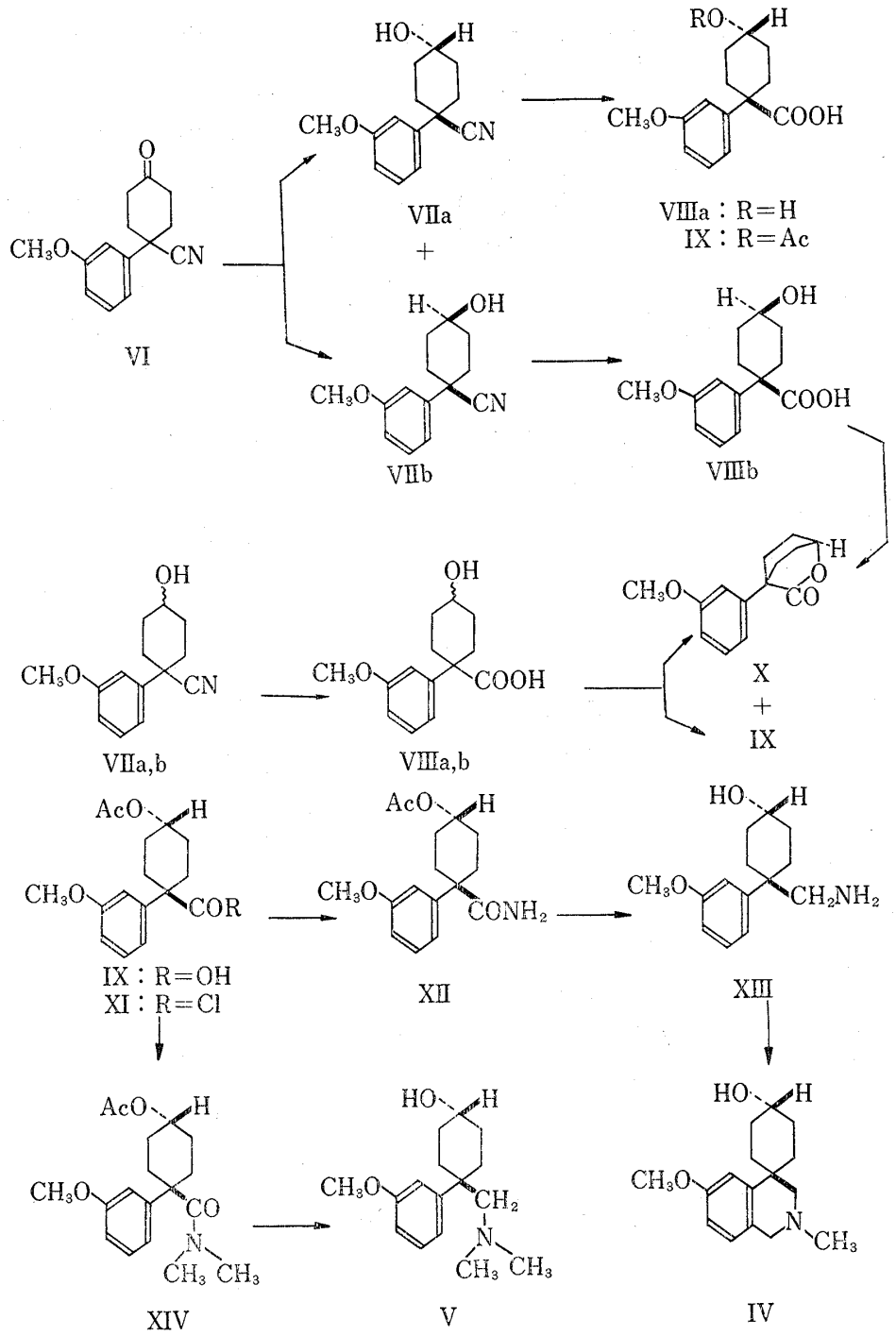

Chart 2

The isomeric hydroxy-nitriles (VIIa, b) were separated by chromatography on silica gel. The epimeric nature of the hydroxyl groups was confirmed by reoxidation with chromic acid-pyridine to the starting keto-nitrile (VI). Alkaline hydrolysis of VIIa gave the *trans*-hydroxy-acid (VIIIa), which was then treated with acetic anhydride in pyridine to give the 1-(*m*-methoxyphenyl-4-acetoxycyclohexanecarboxylic acid (IX).

On the other hand, a mixture of two hydroxy-nitriles (VIIa, b) was hydrolyzed in an alkaline solution to give a mixture of two hydroxy-acids (VIIIa, b), which was then acetylated with acetic anhydride, giving the lactone (X) and the *trans*-acetoxy-acid (IX) in a ratio of 7 : 3. Treatment of the *trans*-acetoxy-acid (IX) with thionyl chloride gave the acid chloride (XI).

The compound (XI) was treated with ammonia in benzene to give 1-(*m*-methoxyphenyl)-4-acetoxycyclohexanecarboxamide (XII).

Reduction of the *trans*-acetoxy-amide (XII) with lithium aluminum hydride in tetrahydrofuran gave the *trans*-hydroxy-amine (XIII). The Eschweiler-Clarke reaction on XIII with formic acid and formaldehyde afforded spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′*H*-isoquinoline] (IV) in 60% yield. The cyclization of XIII to IV was proved by the following facts: The empirical formula of this compound was in satisfactory agreement with $C_{16}H_{23}O_2N \cdot HCl$ corresponding to IV and its infrared (IR) spectrum displayed a band at 2780 cm^{-1} due to the methyl group. The nuclear magnetic resonance (NMR) spectrum showed signals assignable to the 1′-methylene protons of the isoquinoline ring at 6.53 τ as singlet and to the methyl protons of 2′-position at 7.96 τ as singlet.

The compound (V) was also synthesized from XI as a starting compound. Dimethylamidation of the *trans*-acetoxy-acid chloride (XI) with dimethylamine in benzene followed by subsequent reduction with lithium aluminum hydride gave 4-dimethylaminomethyl-4-(*m*-methoxyphenyl)cyclohexanol (V).

The pharmacological activities of the compounds (IV and V) obtained in this study are under investigation.

Experimental[8]

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanecarbonitrile (VIIa, b)——Freshly prepared aluminum isopropoxide (1.34 g) was added to a solution of the keto-nitrile (VI) (3.0 g) in propan-2-ol(150 ml), and the whole was fractionally distilled for 13 hr. During this time, the volume of the reaction mixture was kept at *ca.* 150 ml by the occasional additions of propan-2-ol. After 130 ml of distillate was collected, the residual mixture was concentrated under reduced pressure to *ca.* 5 ml, diluted with ice-water, and extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness to leave an oil (2.94 g) which was chromatographed on silica gel. The first elution with $CHCl_3$ gave the *trans*-hydroxy-nitrile (VIIa) (0.85 g) as an oil, bp 165—170° (0.015 mmHg) (bath temp.). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.69; H, 7.41; N, 6.05. Found: C, 72.71; H, 7.48; N, 6.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 2240 (CN).

Further elution with $CHCl_3$–EtOH (100: 1) afforded the *cis*–hydroxy–nitrile (VIIb) (2.01 g) as prisms, mp 69—71° (ether). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.69; H, 7.41; N, 6.05. Found: C, 72.77; H, 7.48; N, 6.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 2240 (CN). Both of the hydroxy–nitriles (VIIa, b) were oxidized with CrO_3-pyridine complex to give the same keto-nitrile (VI).

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanecarboxylic Acid (VIIIa)——A mixture of the *trans*-hydroxy-nitrile (VIIa) (2.10 g), diethylene glycol (80 ml) and 40% aqueous KOH (100 ml) was heated under reflux for 8 hr. The solution was diluted with H_2O (700 ml) and washed with ether. The aqueous layer was acidified with concentrated HCl and extracted with AcOEt. Evaporation of the AcOEt extract after washing with H_2O and drying over Na_2SO_4, gave a crystalline mass which was recrystallized from AcOEt to give the *trans*-hydroxy-carboxylic acid (VIIIa) (2.12 g) as needles, mp 109—111°. *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.22; H, 7.26. IR ν_{max}^{KBr} cm^{-1}: 3340 (OH), 3500—2500 (COOH), 1690 (CO).

1-(*m*-Methoxyphenyl)-4-acetoxycyclohexanecarboxylic Acid (IX)——i) A mixture of the *trans*-hydroxy-carboxylic acid (VIIIa) (1.12 g), dry pyridine (12 ml) and Ac_2O (5.6 ml) was allowed to stand overnight at room temperature, diluted with H_2O, acidified with concentrated HCl, and then extracted with ether. The ether extract was washed with H_2O and dried over Na_2SO_4. Evaporation of ether gave a residue which was recrystallized from ether to give the *trans*-acetoxy-carboxylic acid (IX) (1.11 g) as needles, mp 106—107°. *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.89. Found: C, 65.51; H, 7.02. IR ν_{max}^{KBr} cm^{-1}: 1740, 1700 (CO).

ii) The hydroxy-nitriles (VIIa, b) (2.77 g) was heated under reflux in diethylene glycol (100 ml) and 40% aqueous KOH (125 ml) for 8 hr. The solution was diluted with H_2O (900 ml) and acidified with concentrated HCl under cooling. The acidic aqueous solution was extracted with AcOEt and the AcOEt extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give the hydroxy-carboxylic acid (VIIIa, b) (2.72 g). IR ν_{max}^{KBr} cm^{-1}: 3340 (OH), 3500—2500 (COOH), 1690 (CO).

The hydroxy-carboxylic acid (VIIIa, b) (2.72 g) and Ac_2O (20 ml) were heated at 100—110° for 9.5 hr. The Ac_2O solution was concentrated under reduced pressure. Dry pyridine (30 ml) and Ac_2O (15 ml) were

8) All melting points were measured on a Yanagimoto micromelting point determination apparatus, and all melting and boiling points were uncorrected. NMR spectra were measured with Spectrometer JNM-MH-100, Japan Electron Lab. Co., using tetramethylsilane as an internal standard, and IR spectra with a Spectrometer A-2, Japan Electron Lab. Co.

added to the residue, and the mixture was allowed to stand overnight at room temperature. After the addition of ice-water (50 ml), the mixture was acidified with concentrated HCl and extracted with ether. The ether extract was washed with H_2O, and extracted with 5% aqueous Na_2CO_3. The alkaline extract was acidified with concentrated HCl and reextracted with ether. The ether extract was washed with H_2O and dried over Na_2SO_4 and evaporated to dryness to give the *trans*-acetoxy-carboxylic acid (IX) (0.87 g), mp 106—107°, which was identical in all respects with an authentic sample described above. The ether solution separated from the alkaline solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give the lactone (X) (1.71 g), mp and mixed mp being 105—106°.

1-(*m*-Methoxyphenyl)-4-acetoxycyclohexanecarboxamide (XII)——The *trans*-acetoxy-carboxylic acid (IX) (300 mg) and purified $SOCl_2$ (4 ml) were heated at 40—50° for 1 hr. Excess of $SOCl_2$ was evaporated under reduced pressure. Dry benzene was added to the residue, and the mixture was again evaporated to dryness. In a solution of the residual acid chloride (XI) in dry benzene (20 ml), dry NH_3 gas was let absorb under cooling in an ice bath for 2 hr and the mixture was stirred at room temperature for 30 min. The benzene solution was washed with 5% aqueous Na_2CO_3 and H_2O, dried over Na_2SO_4 and evaporated to dryness to give the *trans*-acetoxy-carboxamide (XII) (266 mg) as prisms, mp 126—127.5° (benzene). *Anal.* Calcd. for $C_{16}H_{21}O_4N$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.87; H, 7.48; N, 4.85. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 3400 (NH), 1726, 1677 (CO).

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanemethylamine (XIII)——A mixture of the *trans*-acetoxy-carboxamide (XII) (223 mg), $LiAlH_4$ (350 mg) and dry tetrahydrofuran (100 ml) was heated under reflux for 40 hr. A small amount of water was added to the mixture and the precipitate formed was removed by filtration. The filtrate was evaporated to dryness to give a residue which was taken up in $CHCl_3$. The $CHCl_3$ solution was extracted with dilute HCl. The acidic aqueous layer was basified with 5% aqueous NH_3 and extracted with ether. The ether extract was washed with H_2O, dried over K_2CO_3 and evaporated to dryness to give the *trans*-hydroxy-amine (XIII) (128 mg) as an oil, bp 100—102° (0.005 mmHg) (bath temp.). *Anal.* Calcd. for $C_{14}H_{21}O_2N$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.72; H, 8.87; N, 6.02. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3370, 3210 (NH).

Spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′*H*-isoquinoline (IV)——A mixture of the *trans*-hydroxy-amine (XIII) (100 mg), 80% HCOOH (190 mg), and 37% HCHO (180 mg) was heated in an oil bath (140°) for 6 hr. After cooling, concentrated HCl (0.2 ml) was added and evaporated under reduced pressure. A crystalline mass thus obtained was recrystallized from EtOH–ether to give the *trans*-hydroxy-isoquinoline (IV) HCl (82 mg) as prisms, mp 220—222°. *Anal.* Calcd. for $C_{16}H_{23}O_2N \cdot HCl$: C, 64.52; H, 8.12; N, 4.70; Cl, 11.91. Found: C, 64.66; H, 7.91; N, 4.58; Cl, 12.05. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 2650 (N^+–H). NMR (in $CDCl_3$) τ: 2.69—3.28 (3H, multiplet, aromatic protons), 5.18—5.24(1H, multiplet, >CH–OH), 6.16 (3H, singlet, $-OCH_3$), 6.53 (2H, singlet, phenyl-CH_2–N<), 6.85 (2H, singlet, >N–CH_2), 7.92 (1H, singlet, –OH), 7.96 (3H, singlet, >N–CH_3), 7.48—8.72 (8H, multiplet, $-CH_2-CH_2-$).

1-(*m*-Methoxyphenyl)-4-acetoxycyclohexanecarbonyl Dimethylamide (XIV)——The *trans*-acetoxy-carboxylic acid (IX) (400 mg) and purified $SOCl_2$ (5 ml) were heated gently on a water bath (40—50°) for 1 hr. Excess of $SOCl_2$ was evaporated under reduced pressure. The residue, acid chloride (XI), was dissolved in dry benzene (20 ml), filtered and added with a solution of 5% Me_2NH (4 ml) in dry benzene. The mixture was refluxed for 3 hr and the resultant Me_2NH–HCl was dissolved by adding H_2O (10 ml). The organic layer was dried over $MgSO_4$ and evaporated to dryness to give the *trans*-acetoxy-dimethylamide (XIV) (366 mg) as prisms, mp 124—125° (EtOH). *Anal.* Calcd. for $C_{18}H_{25}O_4N$: C, 67.49; H, 7.89; N, 4.39. Found: C, 67.56; H, 7.99; N, 4.26. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1630 (CO).

4-Dimethylaminomethyl-4-(*m*-methoxyphenyl)cyclohexanol (V)——A mixture of the *trans*-acetoxy-dimethylamide (XIV) (300 mg), $LiAlH_4$ (400 ml) and dry tetrahydrofuran (100 ml) was heated under reflux for 30 hr. The excess $LiAlH_4$ was decomposed by cautious addition of H_2O and the precipitate was filtered off and washed with tetrahydrofuran. The filtrate and the washing were combined and concentrated to dryness under reduced pressure to give a residue which was taken up in $CHCl_3$. The $CHCl_3$ solution was extracted with diluted HCl. The acidic extract was basified with 5% aqueous NH_3 and extracted with ether. The ether extract was washed with H_2O, dried over K_2CO_3 and evaporated to dryness to afford the *trans*-hydroxy-dimethylamine (V) (185 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3420 (OH), 2780 (>N–CH_3). NMR (in $CDCl_3$) τ: 2.64—3.26 (4H, multiplet, aromatic protons), 5.25—5.41 (1H, multiplet, >CH–OH), 6.21 (3H, singlet, $-OCH_3$), 6.54 (2H, singlet, $-CH_2$–N<), 7.65 (1H, singlet, –OH), 7.98 (6H, singlet, $-N-(CH_3)_2$), 7.72—8.78 (8H, multiplet, $-CH_2-CH_2-$). The Hydrochloride: mp 123—125° (EtOH–ether). *Anal.* Calcd. for $C_{16}H_{25}O_2N \cdot HCl$: C, 64.05; H, 8.74; N, 4.67; Cl, 11.82. Found: C, 64.11; H, 8.64; N, 4.56; Cl, 11.81. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 2650 (N^+–H).

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