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

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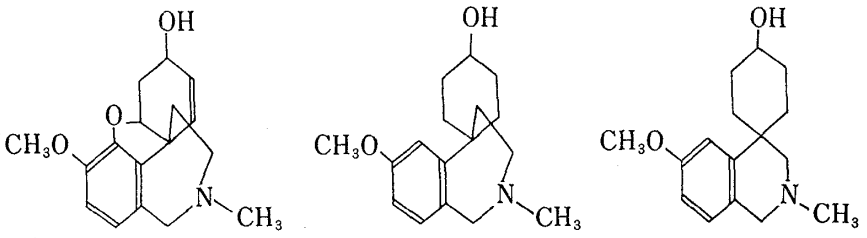
For the purpose of testing the biological activity, spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′H-isoquinoline] (III) was synthesized by a sequence of reactions including the Schmidt reaction on the indanone (XIV). The compound (III) was found to have a considerably lower anti-cholinesterase activity than galanthamine (I).

In an earlier publication[3)] we have reported the synthesis of spiro[1,2,3,4-tetrahydro-7-methoxy-2-methyl-5H-2-benzazepine-5,1′-4′-hydroxycyclohexane] (II) which is structurally related to galanthamine (I), an Amaryllidaceae alkaloid. In continuation of this work we now wish to describe the synthesis of spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′H-isoquinoline] (III) which is a compound closely resembling the above compound (II), only differing in the size of the nitrogenous ring.



I II III

Chart 1

Reduction of 1-(*m*-methoxyphenyl)-4-oxocyclohexanecarbonitrile (IV)[3)] with sodium borohydride at room temperature gave 91% yield of the hydroxy-nitrile (V) in which the hydroxyl and nitrile groups must be *cis*-oriented since it is expected that the bulky benzene ring in compound (V) must be equatorial and the hydroxyl group takes also equatorial conformation. This assignment was confirmed by the fact that the corresponding hydroxy-carboxylic acid (VI) formed a lactone (VIII) on treatment of it with acetic anhydride.

Acetylation of the hydroxy-carboxylic acid (VI) with acetic anhydride in pyridine gave along with a small yield of the lactone (VIII) the acetoxy-carboxylic acid (VII) which was treated with thionyl chloride to give the acid chloride (IX). The Arndt–Eistert reaction[4)] with this acid chloride (IX) yielded, through the diazoketone (X), the acetoxy-acetate (XI) as an oil in *ca.* 50% over all yield based on the starting carboxylic acid (VII).

The ester (XI) was hydrolyzed in an alkaline solution to give 1-(*m*-methoxyphenyl)-4-hydroxycyclohexaneacetic acid (XII) which was reacetylated, giving the acetoxy-acetic

1) This work was presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.
2) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
3) S. Uyeo, H. Shirai, A. Koshiro, T. Yashiro, and K. Kagei, *Chem. Pharm. Bull.* (Tokyo), **14**, 1033 (1966).
4) F. Arndt and B. Eistert, *Chem. Ber.*, **68**, 200, 212 (1935).

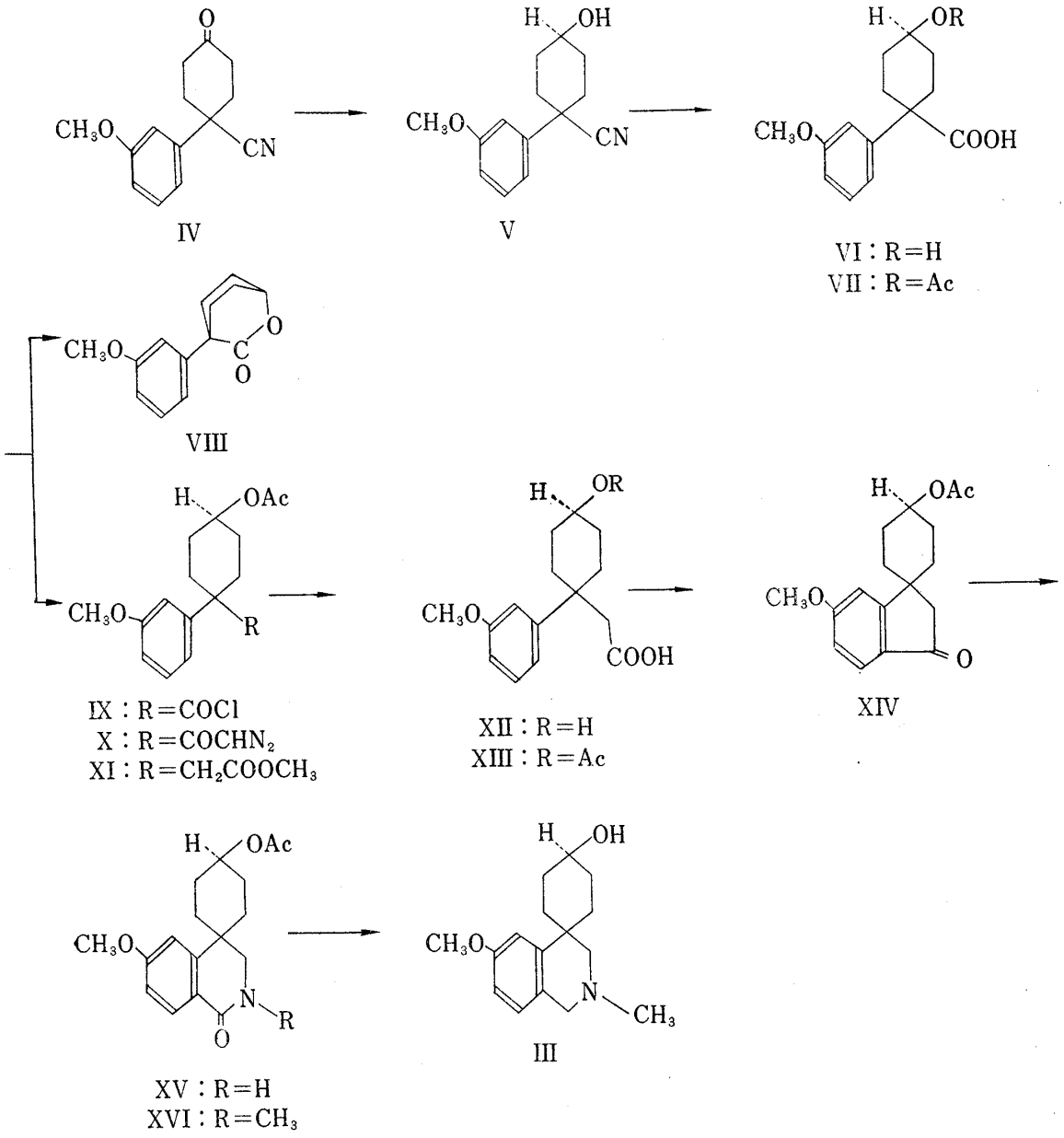


Chart 2

acid (XIII). The acid (XIII) was treated with phosphorus pentachloride to give the acid chloride which on Friedel–Crafts cyclization[5] using stannic chloride as a catalyst afforded the acetoxy-indanone (XIV). The infrared spectrum of XIV showed the conjugated carbonyl band at 1700 cm^{-1}, and the out-of-plane CH deformation vibration at 890 and 810 cm^{-1}, indicating that this compound was a 1:2:4-tri-substituted benzene derivative. The nuclear magnetic resonance spectrum (Fig. 1) showed a two protons singlet at 7.40 τ due to a methylene group adjacent to the carbonyl group and a one proton doublet at 2.34 τ (J=9.0 cps), two protons multiplet at 3.00—3.18 τ corresponding the phenyl protons in accord with the expected structure (XIV).

The Schmidt reaction[6] with this ketone (XIV) by the use of sodium azide in trichloroacetic acid gave solely the acetoxy-lactam (XV) of an isoquinoline type in 76% yield. The

5) C. Friedel and J.M. Crafts, *Compt. Rend.*, **84**, 1392, 1450 (1877); P.B. Talukdar, *J. Org. Chem.*, **21**, 506 (1956).
6) H.J. Schmidt, A. Hunger, and K. Hoffmann, *Helv. Chim. Acta*, **39**, 607 (1956); D.E. Evans and I.M. Lockhart, *J. Chem. Soc.*, **1965**, 4806.

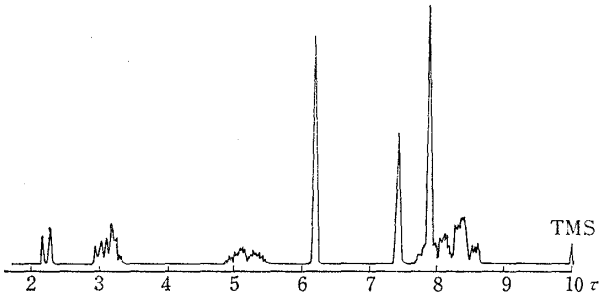


Fig. 1. Nuclear Magnetic Resonance Spectrum of Spiro[4-acetoxycyclohexane-1,1′-6′-methoxy-indan-3′-one] in $CDCl_3$

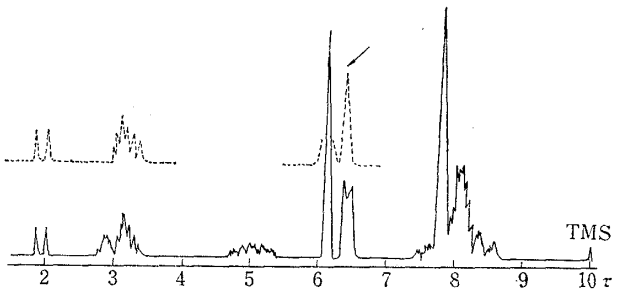


Fig. 2. Nuclear Magnetic Resonance Spectrum of Spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-3′H-isoquinoline-1′(2′H)-one]in $CDCl_3$

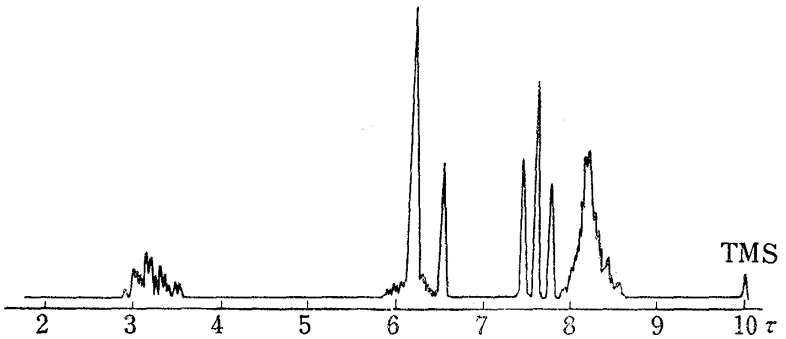


Fig. 3. Nuclear Magnetic Resonance Spectrum of Spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′H-isoquinoline] in $CDCl_3$

structure of this compound (XV) was established by its spectral properties. Thus the infrared spectrum exhibited a carbonyl band at 1665 cm^{-1} (arylic ketone) and the nuclear magnetic resonance spectrum showed two protons doublet at 6.48 τ (J=3.0 cps) which was sharpened on irradiation at the proton, attached to the nitrogen of the amino group adjacent to this methylene group (Fig. 2). Absence of isomeric compound to this lactam was shown by the single spot for XV on thin-layer chromatography of the mother liquor from crystallization of XV.

N-Methylation of XV with methyl iodide and subsequent reduction with lithium aluminum hydride gave the final product (III). The ultraviolet spectrum of III gave an absorption maximum at 279 mμ and no hypsochromic shift was observed in acidic ethanol solution, indicating that the structure of III is a benzylamino type. Infrared and nuclear magnetic resonance spectra gave data in agreement with the assigned structure (III).

The biological test was carried out at the Research Laboratory, Dainippon Pharmaceutical Co. in Osaka. It was found that the compound (III) has slightly less anti-cholinesterase activity than the compound (II) and far less than galanthamine. The ED_{50} of III and of galanthamine were more than 10^{-4}M and 3.5×10^{-6}M, respectively.

Experimental[7]

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanecarbonitrile (V)——To the ketonitrile (IV) (3.5 g) in THF (80 ml), was added $NaBH_4$ (0.45 g) in H_2O (4 ml). The mixture was stirred at room temperature for 6 hr and evaporated to dryness. The residue was taken up in H_2O (40 ml), acidified with dil. HCl, and extracted to dryness to give the *cis*-hydroxy-nitrile (V) (3.2 g), which was crystallized from ether as prisms, mp 69—71°. *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.69; H, 7.41; N, 6.05. Found: C, 72.75; H, 7.58; N, 6.10, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2260 (CN).

7) All melting points and boiling points were uncorrected. The NMR spectra were determined on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as internal standard.

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanecarboxylic Acid (VI)——A mixture of the hydroxy-nitrile (V) (1.5 g), diethylene glycol (60 ml) and 40% aqueous KOH (80 ml) was heated under reflux for 8 hr. The solution was diluted with H_2O (500 ml) and washed with ether. The aqueous layer was acidified with conc. HCl and extracted with AcOEt. Evaporation of the AcOEt extract, after being washed with H_2O and dried over Na_2SO_4 gave a crystalline mass which was recrystallized from AcOEt to give the hydroxy-carboxylic acid (VI) (1.51 g) as needles, mp 179.5—181°. *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.49; H, 7.28. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 3500—2500 (COOH), 1680 (CO).

1-(*m*-Methoxyphenyl)-4-acetoxycyclohexanecarboxylic Acid (VII)——A mixture of the hydroxy-carboxylic acid (VI) (1.29 g), pyridine (13 ml) and Ac_2O (6.5 ml) was allowed to stand at room temperature overnight, then diluted with H_2O, acidified with conc. HCl and extracted with ether. The ethereal extract was washed with H_2O, and extracted with 5% aqueous Na_2CO_3. The ether solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give the lactone (VIII) (0.11 g), mp 105—106°, which was identical in all respects with an authentic sample described below. The alkaline extract was acidified with conc. HCl and extracted with ether. The ether extract was washed with H_2O and dried over Na_2SO_4. Evaporation of the ether gave a residue which was crystallized from ether to give the acetoxy-carboxylic acid (VII) (1.29 g) as needles, mp 144.5—145.5°. *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.89. Found: C, 64.42; H, 7.17. IR ν_{max}^{KBr} cm^{-1}: 1740, 1700 (CO).

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanecarboxylic Lactone (VIII)——A mixture of the *cis*-hydroxy-carboxylic acid (VI) (60 mg) and Ac_2O (10 ml) was heated on a waterbath for 6 hr. Removal of the excess solvent by evaporation under reduced pressure gave a residue which was crystallized from EtOH to give the lactone (VIII) (50 mg) as needles, mp 105—106°. *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.38; H, 6.94. Found: C, 72.64; H, 7.24. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (CO).

Methyl 1-(*m*-Methoxyphenyl)-4-acetoxycyclohexaneacetate (XI)——The acetoxycarboxylic acid (VII) (0.78 g) and purified $SOCl_2$ (7 ml) were heated gently on the waterbath 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. A solution of the residual acid chloride (IX) in 5 ml dry benzene was added dropwise, with stirring and ice-cooling, to an ethereal solution of CH_2N_2 prepared from nitrosomethylurea (1.4 g). After the solution was allowed to stand overnight at room temperature, the solvent was removed under reduced pressure. The resulting diazoketone (X) was dissolved in dry MeOH (15 ml) and the freshly prepared Ag_2O (80 mg) was added. The mixture was refluxed for 2 hr, filtered and evaporated to dryness. Distillation of the residue gave the acetoxy-acetate (XI) (0.42 g) as a pale yellow oil, bp 193—200° (1.5 mmHg) (bath temp.). *Anal.* Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.11; H, 7.35. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO).

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexaneacetic Acid (XII)——The acetoxy-acetate (XI) (470 mg) was heated on a water bath in 4% ethanolic NaOH (15 ml) for 8 hr. EtOH was removed under reduced pressure, and the residue was diluted with H_2O and washed with ether. The aqueous solution was acidified with conc. HCl and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give oil which was chromatographed in $CHCl_3$ on SiO_2 gel. The $CHCl_3$–EtOH (10:1) eluate gave the hydroxy-acetic acid (XII) (235 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3500—2500 (COOH), 1715 (CO).

1-(*m*-Methoxyphenyl)-4-acetoxycyclohexaneacetic Acid (XIII)—— A mixture of the hydroxy-acetic acid (XII) (280 mg), dry pyridine (3 ml) and Ac_2O (1.5 ml) was allowed to stand at room temperature overnight. After the addition of H_2O, the mixture was acidified with conc. HCl and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. After purification of the residue by chromatography in $CHCl_3$ on SiO_2 gel, the acetoxy-acetic acid (XIII) (250 mg) was isolated as prisms, mp 183—184.5° (from ether). *Anal.* Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.38; H, 7.13. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1710 (CO).

Spiro[4-acetoxycyclohexane-1,1′-6′-methoxyindan-3′-one] (XIV)——To a mixture of the acetoxy-acetic acid (XIII) (600 mg) in dry benzene (30 ml) was added powdered PCl_5 (700 mg) with stirring and cooling in an ice bath. The mixture was stirred for 1 hr, then $SnCl_4$ (1.6 g) was added in one portion and the stirring was continued at 0° for 1 hr, and at room temperature for an additional 1 hr. The mixture was diluted with ice-cold conc. HCl and extracted with ether. The extract was washed with 5% aqueous Na_2CO_3 and H_2O, dried over Na_2SO_4 and evaporated to dryness to give the residue which was chromatographed in $CHCl_3$ on SiO_2 gel. The $CHCl_3$ eluate gave the acetoxy-indanone (XIV) (170 mg) as prisms, mp 174.5—176.5° (from ether). *Anal.* Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.74; H, 7.15. IR ν_{max}^{KBr} cm^{-1}: 1740, 1700 (CO), 890, 810 (CH). UV λ_{max}^{EtOH} $m\mu$ (log ε): 224.5 (4.26); 270.5 (4.17); 287 (4.06); 295 (shoulder 4.04). NMR (in $CDCl_3$) τ: 2.34 (1H, doublet, J=9.0 cps, aromatic proton), 3.00—3.18 (2H, multiplet, aromatic protons), 4.9—5.5 (1H, multiplet, >CH–OAc), 6.10 (3H, singlet, $-OCH_3$), 7.40 (2H, singlet, $-CO-CH_2-$), 7.93 (3H, singlet, $-OCOCH_3$), 7.75—8.67 (8H, multiplet, $-CH_2-CH_2-$).

Schmidt Reaction on the Acetoxy-indanone (XIV)——To a mixture of the acetoxy-indanone (XIV) (350 mg) and Cl_3CCOOH (5.94 g) was added NaN_3 (162 mg) with stirring at 60°. Stirring was continued at 65—68° for 6.5 hr. The mixture was poured into 30% aqueous NH_3 (30 ml) with cooling and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. A crystalline mass was thus obtained which was recrystallized from EtOH to give spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-

3′H-isoquinoline-1′(2′H)-one] (XV) (280 mg) as prisms, mp 224—225°. *Anal.* Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.20; H, 7.13; N, 4.78. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 3200 (NH), 1735, 1665 (CO). UV λ_{max}^{EtOH} mμ (log ε): 262.5 (4.14). NMR (in $CDCl_3$) τ: 1.95 (1H, doublet, J=9.0 cps, aromatic proton), 3.00—3.30 (2H, multiplet, aromatic protons), 2.90 (1H, multiplet, NH), 4.95—5.50 (1H, multiplet, >CH–OAc), 6.15 (3H, singlet, $-OCH_3$), 6.48 (2H, doublet, J=3.0 cps, $-NH-CH_2-$), 7.95 (3H, singlet, $-OCOCH_3$), 7.70—8.60 (8H, multiplet, $-CH_2-CH_2-$).

Spiro[4-acetoxycyclohexane-1,4′-6′-methoxy-2′-methyl-3′H-isoquinoline-1′-(2′H)-one] (XVI)——A mixture of the acetoxy-lactam (XV) (100 mg) and NaH (105 mg) (50% in mineral oil) in dry toluene (40 ml) was heated under reflux for 12 hr. After cooling, CH_3I (1 ml) was added to the mixture and the whole was stirred at room temperature for 1 hr and heated under reflux for a further 2 hr. After decomposition of the excess NaH with AcOH, the mixture was diluted with benzene, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Crystallization of the residue from ether gave the N-methyl-acetoxy-lactam (XVI) (84 mg) as prisms, mp 145—147°. *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 67.93; H, 7.38; N, 4.51. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1645 (CO). UV λ_{max}^{EtOH} mμ (log ε): 264 (4.07).

Spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′H-isoquinoline] (III)——A mixture of the N-methyl-lactam (XVI) (75 mg), $LiAlH_4$ (90 mg) and dry THF (34 ml) was heated under reflux for 16 hr. The excess reagent was decomposed by cautious addition of H_2O and the precipitate was filtered off and washed with THF. The filtrate and the washings 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 dil. HCl, the acidic extract was basified with 5% aqueous NH_3 and extracted with ether. The ethereal extract was washed with H_2O, dried over K_2CO_3 and evaporated to dryness to afford the hydroxy-isoquinoline (III) (33 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2780 (>N–CH_3). UV λ_{max}^{EtOH} mμ (log ε): 279 (3.29), 285 (shoulder 3.22). NMR (in $CDCl_3$) τ: 2.93—3.43 (3H, multiplet, aromatic protons), 5.90—6.40 (1H, multiplet, >CH–OH), 6.22 (3H, singlet, $-OCH_3$), 6.52 (2H, singlet, phenyl–CH_2–N<), 7.41 (2H, singlet, >N–CH_2), 7.75 (3H, singlet, >N–CH_3), 7.75 (1H, singlet, –OH), 7.83—8.67 (8H, multiplet, $-CH_2-CH_2-$). The Hydrochloride: prisms, mp 232—234° (from EtOH) *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, 64.18; H, 8.31; N, 4.84; Cl, 12.07. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 2650 (N^+–H). UV λ_{max}^{EtOH} mμ (log ε): 222 (3.89), 278 (3.34), 285 (shoulder 3.27).

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