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Synthesis of Octahydroindole Derivatives[1]

Hiroyasu Taguchi, Tokuro Oh-ishi
and Hiroshi Kugita

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd.[2]

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Some mesembrine type (3a-aryl-*cis*-octahydroindol-6-one) compounds (VIII—X) were synthesized from benzyl nitriles (I) by the six-step sequence of the reactions involving an acid-catalyzed cyclization of 3a-aryl-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-pyrroline (VI). Pictet-Spengler reaction of XVIII and XIX, which were derived from N-benzyl derivative (Xb), gave dihydrocrinine models (XX and XXI) in good yields. The stereochemistry of two epimeric 3a-phenyl-*cis*-octahydroindol-6-ols (XIVa and XVIa) was determined on the basis of infrared and nuclear magnetic resonance spectral data.

Our interests in mesembrine (3a-(3,4-dimethoxyphenyl)-1-methyl-*cis*-octahydroindol-6-one) type compounds[3] with respect to yet unspecified physiological activities and possible transformation to tetracyclic compounds, such as XX and XXI, basic structure of which is

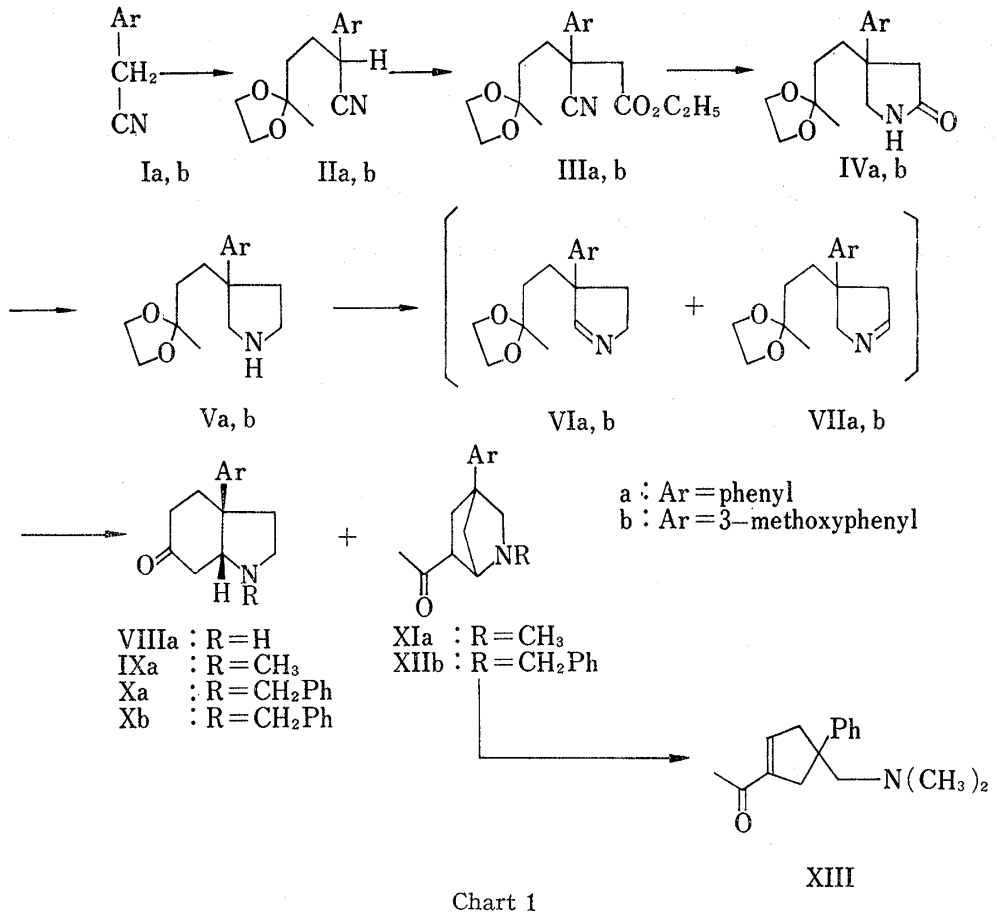


Chart 1

1) Preliminary communication of this work has appeared: H. Taguchi, T. Oh-ishi and H. Kugita, *Tetrahedron Letters*, **1968**, 5763.
2) Location: *No. 2-50, Kawagishi 2-Chome, Toda, Saitama.*
3) A. Popelak and G. Lettenbauer, "The Alkaloids," Vol. IX, ed. by R.H.F. Manske, Academic Press, New York and London, 1967, Chapter 11.

common to some Amaryllidaceae alkaloids, prompted us to explore a general approach to 3a-aryl-octahydroindol-6-one derivatives (VIII—X).

Benzyl cyanide (Ia) was alkylated with 1-bromo-2-(2-methyl-1,3-dioxolan-2-yl)ethane to give 4-(2-methyl-1,3-dioxolan-2-yl)-2-phenylbutyronitrile (IIa), which gave ethyl 3-cyano-5-(2-methyl-1,3-dioxolan-2-yl)-3-phenylpentanoate (IIIa) by the second C-alkylation with ethyl bromoacetate. Reductive cyclization of IIIa on Raney-Co yielded 4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-4-phenyl-2-pyrrolidinone (IVa) and subsequent reduction of IVa with lithium aluminum hydride (LAH) afforded 3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3-phenylpyrrolidine (Va) in good yield. The amine (Va) was dehydrogenated with manganese dioxide in chloroform to give an oily mixture of 3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3-phenyl-1-pyrroline (VIa) and a small quantity of 4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-4-phenyl-1-pyrroline (VIIa). Hydrogenation of the mixture on Pd–C gave the starting amine (Va) as a sole product, indicating that the mixture consisted of VIa and a double bond isomer, VIIa.[4] Recrystallization of the crystalline hydrochloride of the mixture from ethanol–ether gave pure VIa-hydrochloride, but failed to give VIIa-hydrochloride in pure form.

The above pyrroline mixture of VIa and VIIa, without further separation, was quarternized with methyl iodide and treated with 10% hydrochloric acid at room temperature to give 1-methyl-3a-phenyl-*cis*-octahydroindol-6-one (IXa) in 34.9% overall yield from Va, together with 6-acetyl-2-methyl-4-phenyl-2-azabicyclo-[2,2,1]heptane (XIa).

The compound (IXa), which was recently reported by Stevens, *et al.*,[5] exhibited a characteristic nuclear magnetic resonance (NMR) pattern of *cis*-fused 3a-aryl-octahydroindol-6-ones, and the melting point of IXa-picrate, mp 169—170° (decomp.), was identical with that recorded in the literature.[5]

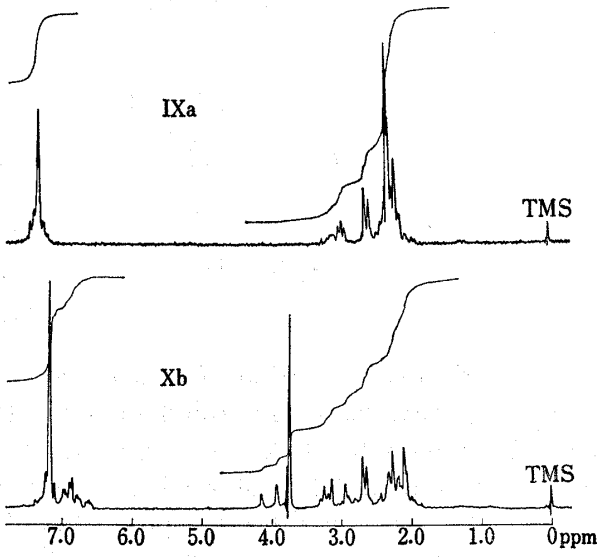


Fig. 1. NMR Spectra of IXa and Xb

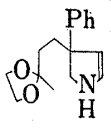
The structure of XIa, which was obviously derived from VIIa, was determined on the basis of spectral and chemical properties. Hofmann degradation of XIa-methiodide gave 1-acetyl-4-dimethylaminomethyl-4-phenylcyclopent-1-ene (XIII) in 75.2% yield.

In a similar way, 1-benzyl-3a-phenyl-*cis*-octahydroindol-6-one (Xa) was synthesized in 21.7% yield from Va, and hydrogenolysis of Xa-hydrochloride gave 3a-phenyl-*cis*-octahydroindol-6-one (VIIIa) in 68.0% yield.

The structure and stereochemistry of VIIIa were confirmed by its conversion to IXa on N-methylation with methyl iodide and potassium carbonate.

Direct cyclization of the pyrroline mixture (VIa and VIIa) in 10% hydrochloric acid gave VIIIa only in 3% yield from Va.

4) The NMR spectrum of the pyrroline mixture showed a weak singlet peak of the tertiary methyl group of VIIa at 1.18 ppm besides a strong peak at 1.26 ppm due to that of VIa, and a peak at 7.64 ppm due to C-2 proton of VIa as a triplet ($J=2$ cps). Unfortunately, the signal of C-2 proton of VIIa could not be clearly observed, which appeared to be overlapped with those of the aromatic protons (7.0—7.5 ppm). However, the absence of singals in the region (3.0—5.0 ppm) expected for –N–CH=CH– excluded an alternative structure VIIa′ for the double bond isomer.



VII′a

5) R.V. Stevens and M.P. Wentland, *Tetrahedron Letters*, **1968**, 2613.

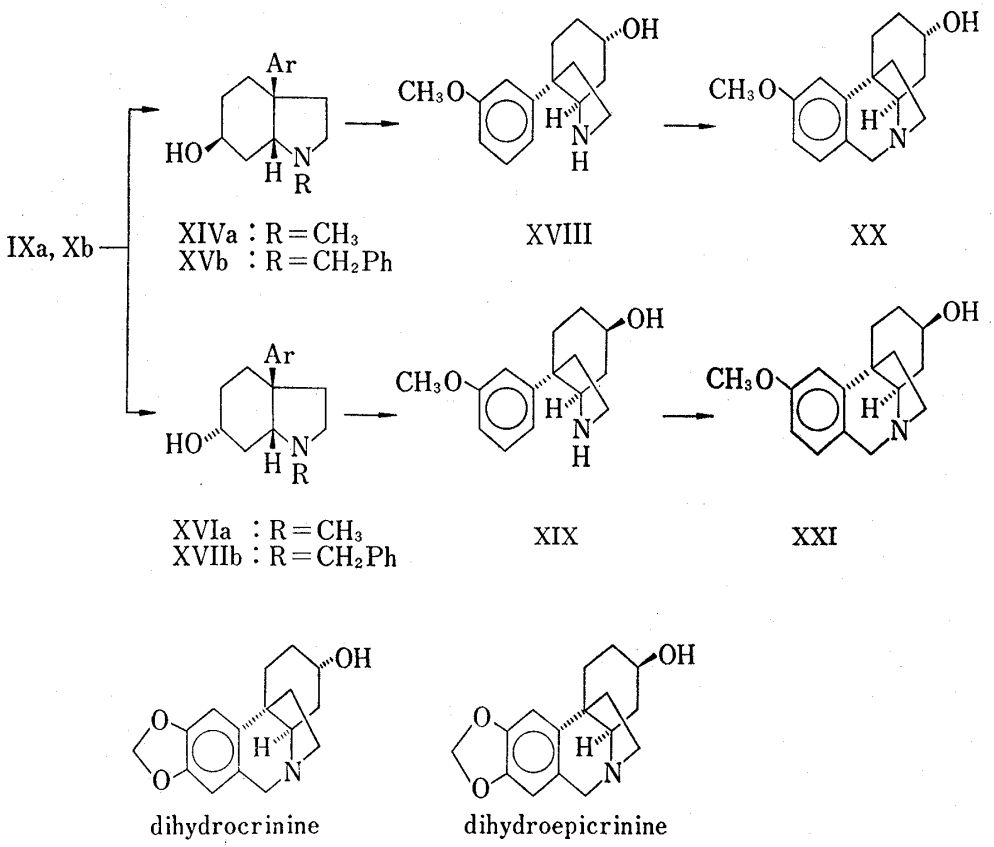


Chart 2

Catalytic hydrogenation of IXa in isopropanol over Pt gave stereoisomeric alcohols, 1-methyl-3a-phenyl-*cis*-octahydroindol-6β-ol (XIVa),[6] mp 110—111°, and 1-methyl-3a-phenyl-*cis*-octahydroindol-6α-ol (XVIa),[6] mp 62—63°, in 56.7% and 24.6% yield, respectively. The major product XIVa showed a widely spread signal of C-6 proton at 3.60—4.20 ppm (axial proton), whereas the minor product XVIa showed the signal at 3.29 ppm with half-band width of *ca.* 8 cps (equatorial proton) in NMR spectra. This most probably indicates the presence of an equatorial hydroxyl group for the former and axial one for the latter. Infrared spectrum (IR spectrum) of XVIa showed a significant intramolecular hydrogen bond (OH···N, ν_{max} 3320 cm^{-1}, remained unchanged on dilution to 1.0×10^{-2}M in CCl_4). On the other hand, XIVa revealed only a band due to free OH (ν_{max} 3590 cm^{-1} 1.0×10^{-2}M in CCl_4).

This observation, coupled with the NMR data, confirmed the stereochemistry[7] of XIVa and XVIa as XIVa and XVIa respectively, precluding alternative conformation XVI'a and XVI'a in Fig. 3.

3-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-3-(3-methoxyphenyl)pyrrolidine (Vb) was similarly prepared from 3-methoxybenzyl cyanide (Ib) in four steps.

Dehydrogenation of Vb with mangenese dioxde in chloroform yielded a pyrroline mixture, 3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-3-(3-methoxyphenyl)-1-pyrroline (VIb) and 4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-4-(3-methoxyphenyl)-1-pyrroline (VIIb). Quaternization of the mixture with benzyl iodide followed by treatment with 10% hydrochloric acid afforded 1-benzyl-3a-(3-methoxyphenyl)-*cis*-octahydroindol-6-one (Xb) in 32.5% yield from Vb, and 6-acetyl-2-benzyl-4-(3-methoxyphenyl)-2-azabicyclo[2,2,1]heptane (XIIb) was also obtained

6) The prefixes "α" and "β" are used to designate relative stereochemistry; β-substituents are *cis* to C-3a aryl group and α-substituents are *trans*.

7) Stereochemistry of mesembrine and mesembrinol has recently been reported: P.W. Jeffs, R.L. Hawks and D.S. Farrier, *J. Am. Chem. Soc.*, **91**, 3831 (1969).

as a by–rpoduct in 7.2% yield from Vb. Reduction of Xb with LAH in ether gave stereosiomeric alcohols, 1-benzyl-3a-(3-methoxyphenyl)-*cis*-octahydroindol-6β-ol (XVb)[6] and 1-benzyl-3a-(3-methoxyphenyl)-*cis*-octahydroindol-6α-ol (XVIIb)[6] in 40.0% and 39.6% yield respectively. Stereochemistry of these alcohols was determined by spectral evidences as mentioned for XIVa and XVIa, that is, XVIIb has an equatorial proton at C-6 and shows intramolecular hydrogen bonding between hydroxyl group and nitrogen, whereas XVb has an axial proton at C-6 and does not show intramolecular hydrogen bonding in a dilute solution. These observations indicate that XVIIb exists in conformation XVIa and XVb in conformation XIVa.

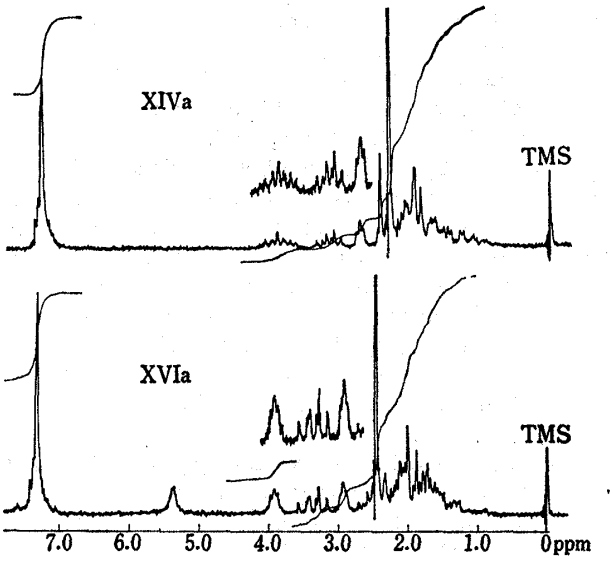
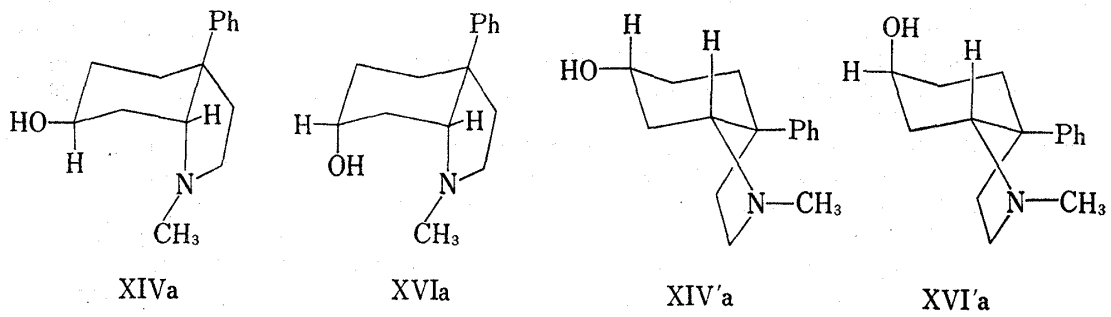


Fig. 2. NMR Spectra of XVIa and XVIa



XIVa XVIa XIV'a XVI'a

Fig. 3. Conformations of XIVa and XVIa

On hydrogenolysis of XVb on Pd–C, the objective amine, 3a-(3-methoxyphenyl)-*cis*-octahydroindol-6β-ol (XVIII)[6] was obtained in 94.6% yield, and similarly, its epimer, 3a-(3-methoxyphenyl)-*cis*-octahydroindol-6α-ol (XIX)[6] was obtained from XVIIb in 82.8% yield.

Transformation to tetracyclic compounds by Pictet-Spengler reaction was successfully carried out under the condition described by Whitlock, Jr., *et al.*[8] The amine (XVIII) was cyclized to 5,10b-ethano-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridin-3-ol (XX) in 77.2% yield and its epimer (XXI) was likewise obtained from XIX in 76.4% yield. In NMR spectra, AB type signals of benzyl protons at 3.73 and 4.33 ppm for XX, and at 3.73 and 4.34 ppm for XXI certify the tetracyclic structure of these compounds. XX, obtained from XVb, has the same hydroxyl configuration as dihydrocrinine,[9] while XXI, obtained from XVIIb, has the same one as dihydroepicrinine.[9]

Experimental[10]

4-(2-Methyl-1,3-dioxolan-2-yl)-2-phenylbutyronitrile (IIa)——A solution of Ia (34.0 g) in benzene (200 ml) was added with stirring to $NaNH_2$ (11.3 g), under a nitrogen atmosphere and ice cooling. The mixture was stirred for 1.5 hr at room temperature, and then refluxed for 2 hr. After cooling, a solution of 1-bromo-

8) H.W. Whitlock, Jr. and G.L. Smith, *J. Am. Chem. Soc.*, **89**, 3600 (1967).
9) W.C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).
10) All melting and boiling points are uncorrected. IR spectra were measured on a Nippon Bunko Model IR-E spectrophotometer. NMR spectra were determined on a Japan Electron Optics Co. JNM C-60 Spectrometer with tetramethylsilane as an internal standard.

2-(2-methyl-1,3-dioxolan-2-yl)ethane (57.4 g) in benzene (100 ml) was added to the mixture. Stirring was continued at room temperature for 16 hr and finally under refluxing for 1.5 hr, and water (200 ml) was added under cooling. The organic layer was taken to benzene, washed with water, and dried over K_2CO_3. After removal of benzene, the residue was distilled under reduced pressure to give IIa (44.8 g, 67.9%), bp 162—164° (3 mmHg). IR ν_{max}^{film} cm^{-1}: 2260 (C≡N). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.88; H, 7.48; N, 5.98.

Ethyl 3-Cyano-5-(2-methyl-1,3-dioxolan-2-yl)-3-phenylpentanoate (IIIa)——A solution of IIa (43.9 g) in benzene (100 ml) was added with stirring to $NaNH_2$ (8.16 g), under a nitorgen atmosphere and ice cooling. The mixture was stirred for 1 hr at room temperature and then refluxed for 2 hr. To the mixture, a solution of ethyl bromoacetate (38.1 g) in benzene (90 ml) was added under cooling. Stirring was continued at room temperature for 14 hr and finally under refluxing for 1.5 hr. After cooling, water (100 ml) was added. The organic layer was washed with water and dried over K_2CO_3. After removal of the solvent, the residue was distilled to give IIIa (53.2 g, 88.7%), bp 156—168° (0.1 mmHg), which was crystallized on standing. Recrystallization from iso-propyl ether and hexane gave pure IIIa (38.4 g, 64.1%), mp 54.5—55°. IR ν_{max}^{Nujol} cm^{-1}: 2270 (C≡N), 1735 (C=O). *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.32; H, 7.45; N, 4.23.

4-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-4-phenyl-2-pyrrolidinone (IVa)——A solution of IIIa (36.3 g) in EtOH (300 ml) was hydrogenated over Raney-Co (20 ml) under 98 atm of hydrogen pressure at 80—100°. The reaction mixture was filtered and evaporated to leave a crystalline residue. Recrystallization from EtOH gave IVa (28.2 g, 90.0%), mp 132—133°. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1680 (lactam). *Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.72; H, 7.45; N, 5.24.

3-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-3-phenylpyrrolidine (Va)——A solution of IVa (43.0 g) in tetrahydrofuran (600 ml) was added to a solution of LAH (19.0 g) in tetrahydrofuran (200 ml) and heated to reflux for 24 hr with stirring. After cooling, the excess of reagent was decomposed by addition of water (50 ml). The inorganic substances were filtered off. The filtrate was dried over K_2CO_3 and evaporated to give crude Va (36.4 g, 91.0%), mp 40°. Distillation gave a pure sample of Va, bp 132—134° (0.1 mmHg). Va-hydrochloride, mp 166—167°. *Anal.* Calcd. for $C_{16}H_{24}O_2NCl$: C, 64.53; H, 8.12; N, 4.70. Found: C, 64.04; H, 8.26; N, 4.57.

Reaction of Va with MnO_2——A mixture of Va (16.7 g), MnO_2 (111.4 g) and $CHCl_3$ (1000 ml) was stirred at room temperature for 3 days and filtered. The filtrate was concentrated at reduced pressure. The residue was distilled to give a mixture (14.2 g, 85.6%) of VIa and VIIa, bp 145—152° (0.4 mmHg). This oily mixture (Va and VIIa) was used in the next step without further separation to each component.

To an ethereal solution of the mixture was added an alcoholic solution of hydrogenchloride. The precipitate was recrystallized from ethanol–ether to give pure VIa-hydrochloride in 23.8% yield, mp 84—86° (decomp.). IR ν_{max}^{film} cm^{-1} (free base): 1620 (C≡N). NMR (free base in $CDCl_3$): 7.64 ppm (1H, triplet, $J=2$ cps, C<u>H</u>=N–).

Cyclization Reaction of the Pyrroline Mixture, VIa and VIIa, to IXa and XIa——The above pyrroline mixture (1.04 g) of VIa and VIIa was added to methyl iodide (2.84 g) and allowed to stand overnight at room temperature. After removal of excess methyl iodide, the resulting oil was dissolved in 10% hydrochloric acid (10 ml) and kept standing overnight at room temperature. The acidic solution was washed with ether, neutralized with K_2CO_3 and extracted with ether. The extract was washed with water, dried over K_2CO_3 and evaporated to give a mixture of IXa and XIa as an oil. Treatment of the oily mixture with HCl–iso-PrOH and recrystallization from iso-PrOH gave pure IXa-hydrochloride (320 mg), mp 204—205° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{15}H_{20}ONCl$ (IXa-hydrochloride): C, 67.78; H, 7.59; N, 5.27; Cl, 13.34. Found: C, 67.91; H, 7.82; N, 5.22; Cl, 13.43.

The mother liquor was neutralized with K_2CO_3 and chromatographed on silica gel. A fraction eluted with $CHCl_3$ gave further IXa, which was converted to the hydrochloride (90 mg). The total yield of IXa-hydrochloride was 410 mg (34.9% from Va).

A fraction eluted with 5% MeOH in $CHCl_3$ gave XIa as an oil. XIa-hydrochloride (100 mg, 8.5% from Va) was prepared by treatment of the oil with HCl gas in EtOH and ether, mp 191—193° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{15}H_{20}ONCl$ (XIa-hydrochloride): C, 67.78; H, 7.59; N, 5.27; Cl, 13.34. Found: C, 67.62; H, 7.71; N, 5.15; Cl, 13.58. NMR (XIa in $CDCl_3$): 2.17 ppm (3H, singlet, –COC<u>H</u>$_3$), 2.42 ppm (3H, singlet, N–C<u>H</u>$_3$).

1-Benzyl-3a-phenyl-*cis*-octahydroindol-6-one (Xa)——The mixture (480 mg) of VIa and VIIa was dissolved in benzyl iodide (1.0 g) and allowed to stand overnight. After removal of excess benzyl iodide by washing with ether, the ether-insoluble residue was dissolved in EtOH (4 ml) and conc. hydrochloric acid (2 ml). The mixture was allowed to stand for 2 days. Working up as described for IXa gave Xa-hydrochloride (160 mg, 25.4%), mp 189—190° (decomp.) as crystals. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{21}H_{24}ONCl$: C, 73.77; H, 7.08; N, 4.10; Cl, 10.37. Found: C, 73.77; H, 7.22; N, 3.92; Cl, 10.54. NMR spectrum ($CDCl_3$) of the free base (Xa) exhibited an AB quartet ($J=12$ cps) at 3.06 and 4.06 ppm due to benzyl protons.

Debenzylation of Xa——A solution of Xa-hydrochloride (170 mg) in EtOH (20 ml) was shaken in a hydrogen atmosphere in the presence of 10% Pd–C (100 mg). After removal of the catalyst by filtration,

the filtrate was concentrated and the residue was purified by recrystallization from iso-PrOH to give VIIIa-hydrochloride (85 mg, 68.0%), mp 173—176° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O). VIIIa-picrate, mp 169—170° (decomp.). *Anal.* Calcd. for $C_{20}H_{20}O_8N_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.26; H, 4.59; N, 12.65.

N-Methylation of VIIIa——A mixture of VIIIa-hydrochloride (30 mg), K_2CO_3 (90 mg), methyl iodide (30 mg), EtOH (0.2 ml) and water (0.2 ml) was stirred overnight at room temperature, and extracted with ether. The organic layer was washed with water and dried over K_2CO_3. Removal of ether gave IXa (20 mg, 74.1%). The melting point of its hydrochloride was not depressed on admixture with the sample prepared previously, and the IR spectra of them were also identical.

Cyclization Reaction of the Pyrroline Mixture, VIa and VIIa, with 10% Hydrochloric Acid——A solution of the mixture (1.03 g) of VIa and VIIa in 10% hydrochloric acid (10 ml) was allowed to stand overnight and worked up in the usual manner to give VIIIa-hydrochloride (30 mg, 3.0%).

Hofmann Degradation of XIa——A solution of XIa (290 mg) in methyl iodide (3 ml) was allowed to stand overnight. After removal of excess methyl iodide, the residue was recrystallized from EtOH to give the methiodide of XIa (430 mg, 82.0%), mp 113—115° (decomp.).

To a solution of the methiodide of XIa (190 mg) in water (4 ml) was added 10% aqueous NaOH (2 ml) at 70—80°. A separated oil was crystallized soon on standing. Filtration gave XIII (110 mg, 91.7%), mp 75—76°. IR ν_{max}^{Nujol} cm^{-1}: 1645, 1615. NMR ($CDCl_3$): 1.91 ppm (6H, singlet, $-N(C\underline{H}_3)_2$), 2.34 ppm (3H, singlet, $-COC\underline{H}_3$), 2.40 ppm (2H, singlet, $-C\underline{H}_2-N$), 2.7—3.1 ppm (4H, $-C\underline{H}_2-C=$), 6.6—6.9 ppm (1H, $=CH-$). XIII-methiodide, mp 139—140° (decomp.) from iso-PrOH. *Anal.* Calcd. for $C_{17}H_{24}ONI \cdot \frac{1}{2}C_3H_7OH$: C, 53.50; H, 6.80; N, 3.37. Found: C, 53.55; H, 6.81; N, 3.28.

Reduction of IXa——IXa (1.35 g) in iso-PrOH (50 ml) was hydrogenated with PtO_2 (150 mg) at 3 atm for 3 hr. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. Trituration of the residue with ethyl acetate gave a crystalline solid, which was recrystallized from iso-propyl ether giving a β-isomer (XIVa) (640 mg, 47.4%), mp 110—111°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3590, 3300 (OH); the peak at 3300 cm^{-1} was diminished on dilution to 1.0×10^{-2}M solution. NMR ($CDCl_3$): 2.31 ppm (3H, singlet, $N-C\underline{H}_3$), 3.60—4.20 ppm (1H, broad multiplet, C_6-axial proton). *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.98; H, 9.33; N, 5.67.

The mother liquor was concentrated and the residue was chromatographed on alumina. Elution with hexane–ether (20:1) gave an α-isomer (XVIa) (335 mg, 24.6%) as crystals, mp 62—63°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3320 (OH); this associated OH absorption peak remained unchanged in 1.0×10^{-2}M solution. NMR ($CDCl_3$): 2.46 ppm (3H, singlet, $N-C\underline{H}_3$), 3.92 ppm (1H, half-band width=8 cps, C_6-equatorial proton). XVIa-picrate, mp 173.5—175° (decomp.). *Anal.* Calcd. for $C_{21}H_{24}O_8N_4$ (picrate): C, 54.78; H, 5.25; N, 12.17. Found: C, 54.86; H, 5.32; N, 12.10.

From a fraction eluted with ether, the further crop of β-isomer (XIVa) (125 mg, 9.3%) was obtained.

2-(3-Methoxyphenyl)-4-(2-methyl-1,3-dioxolan-2-yl)butyronitrile (IIb)——Reaction of Ib (60.0 g), $NaNH_2$ (17.5 g) and 1-bromo-2-(2-methyl-1,3-dioxolan-2-yl)ethane (85.0 g) in benzene (400 ml) under the same condition as with IIa gave IIb (80.1 g, 77.0%), bp 150—153° (0.3 mmHg). IR ν_{max}^{film} cm^{-1}: 2270 (C≡N). *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.94; H, 7.40; N, 5.54.

Ethyl 3-Cyano-3-(3-methoxyphenyl)-5-(2-methyl-1,3-dioxolan-2-yl)pentanoate (IIIb)——Reaction of IIb (77.0 g), $NaNH_2$ (13.0 g) and ethyl bromoacetate (60.0 g) gave IIIb (80.8 g, 79.2%), bp 176—180° (0.4 mmHg). IR ν_{max}^{film} cm^{-1}: 2270 (C≡N), 1730 (C=O).

4-(3-Methoxyphenyl)-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-pyrrolidinone (IVb)——A solution of IIIb (74.6 g) in MeOH (600 ml) was hydrogenated with Raney-Co at 100° and 110 atm to yield IVb (42.6 g, 65.0%), mp 137—137.5°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1695 (lactam). *Anal.* Calcd. for $C_{17}H_{23}O_4N$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.14; H, 7.67; N, 4.61.

3-(3-Methoxyphenyl)-3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]pyrrolidine (Vb)——Reduction of IVb (30.2 g) with LAH (11.4 g) in refluxing tetrahydrofuran (700 ml) for 41 hr yielded Vb (25.7 g, 89.1%), bp 165—171° (0.5 mmHg). Vb-picrate, mp 191.5—192.5° (decomp.). *Anal.* Calcd. for $C_{23}H_{28}O_{10}N_4$: C, 53.07; H, 5.42; N, 10.77. Found: C, 53.28; H, 5.49; N, 10.66.

Reaction of Vb with MnO_2——Dehydrogenation of Vb (19.0 g) with MnO_2 (113 g) in $CHCl_3$ (1000 ml) at room temperature for 3 days gave a mixture of VIb and VIIb (17.5 g, 93.0%), bp 166—168° (0.4 mmHg). The mixture was used in the next step without further separation.

Cyclization Reaction of the Pyrroline Mixture, VIb and VIIb, to Xb and XIIb——The above pyrroline mixture (10.1 g) of VIb and VIIb was dissolved in benzyl iodide (23.0 g) and allowed to stand overnight. After removal of excess benzyl iodide by washing with ether, the residue was dissolved in EtOH (30 ml) and 10% hydrochloric acid (100 ml). After standing for 12 hr at room temperature, the solution was made alkaline with K_2CO_3 and extracted with benzene. Working up as described for IXa and XIa gave Xb-hydrochloride (4.55 g, 32.5%), mp 171.5—172.5° (decomp.) and XIIb-hydrochloride (1.00 g, 7.2%), mp 162.5—163.5° (decomp.). The yields were calculated from Vb.

NMR (Xb in $CDCl_3$): AB quartet (J=12 cps) at 3.06 and 4.06 ppm due to benzyl protons. Xb-hdyrochloride, IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{22}H_{26}O_2NCl$: C, 71.05; H, 7.05; N, 3.77; Cl, 9.53. Found: C, 71.34; H, 7.18; N, 3.92; Cl, 9.77.

NMR (XIIb in $CDCl_3$): 2.08 ppm (3H, singlet, $-COCH_3$). XIIb-hydrochloride. IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O). *Anal.* Calcd. for $C_{22}H_{26}O_2NCl$: C, 71.05; H, 7.05; N, 3.77; Cl, 9.53. Found: C, 70.84; H, 7.09; N, 3.83; Cl, 9.58.

Reduction of Xb——To a suspension of LAH (0.16 g) in ether (10 ml) was added dropwise Xb (1.34 g) in ether (30 ml). The mixture was stirred for 45 min at room temperature and then refluxed for 25 min. Excess LAH was decomposed by addition of water (1 ml) with cooling. The inorganic substances were removed by filtration. The filtrate was dried over K_2CO_3 and evaporated. The residue was subjected to alumina chromatography. XVIIb was eluted with hexane–ether (4:1) and purified as the hydrochloride (590 mg, 39.6%), mp 197—199° (decomp.). *Anal.* Calcd. for $C_{22}H_{28}O_2NCl$ (XVIIb-hydrochloride): C, 70.67; H, 7.55; N, 3.75; Cl, 9.48. Found: C, 70.60; H, 7.63; N, 3.74; Cl, 9.69. IR $\nu_{max}^{CCl_4}$ cm^{-1} (free base): 3320. This peak remained unchanged on dilution to 0.02M solution. NMR (free base in $CDCl_3$): 3.97 ppm (1H, half-band width = 8 cps, C_6-equatorial proton).

From a fraction eluted with hexane–ether (1:1) XVb was obtained (540 mg, 40.0%), mp 95.5—96°. *Anal.* Calcd. for $C_{22}H_{27}O_2N$ (XVb): C, 78.30; H, 8.07; N, 4.15. Found: C, 78.55; H, 8.18; N, 4.20. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3590, 3300; the latter peak diminished on dilution to 0.02M solution. In NMR spectrum ($CDCl_3$) of the free base, C_6-axial proton appeared at 3.6—4.4 ppm as a broad multiplet, partly obscured by benzyl (4.19 ppm) and methoxyl (3.78 ppm) protons.

Debenzylation of XVb——To a solution of XVb (370 mg) in EtOH (40 ml) was added a few drops of HCl–EtOH. The mixture was shaken for 3 hr in a hydrogen atmosphere in the presence of 10% Pd–C (200 mg). After removal of the catalyst, the filtrate was evaporated to give XVIII-hydrochloride (295 mg, 94.6%), mp 213—214° (decomp.). *Anal.* Calcd. for $C_{15}H_{22}O_2NCl$: C, 63.48; H, 7.82; N, 4.93; Cl, 12.49. Found: C, 63.76; H, 7.92; N, 5.06; Cl, 12.51. IR $\nu_{max}^{CCl_4}$ cm^{-1} (free base): 3600, 3280.

Debenzylation of XVIIb——To a solution of XVIIb-hydrochloride (450 mg) in EtOH (40 ml) was added 10% Pd–C (200 mg), and the mixture was shaken for 3 hr in a hydrogen atmosphere. After removal of the catalyst, the solvent was evaporated. The residue was dissolved in water. The aqueous solution was made alkaline with K_2CO_3 and extracted with ether. The ether extract was washed with water, dried over K_2CO_3 and filtered. The filtrate was evaporated and the residue was recrystallized from benzene–hexane to give XIX (245 mg, 82.8%), mp 111—112°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3280. *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.80; H, 8.66; N, 5.81.

Pictet-Spengler Reaction of XVIII——To a solution of XVIII (105 mg) in MeOH (1 ml) was added 37% formalin (1.2 ml) at room temperature. After 10 min, the mixture was poured into 6N hydrochloric acid (40 ml) and stirred for 17 hr at room temperature. After treatment with decolourising charcoal, the solution was neutralized with aqueous ammonia solution and extracted with chloroform. The chloroform extract was washed with water and dried over Na_2SO_4. Evaporation and recrystallization of the residue from EtOH–ether gave XX (80 mg, 77.2%), mp 207.5—208°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH). NMR ($CDCl_3$): AB quartet (J = 17 cps) at 3.73 and 4.33 ppm due to benzyl protons. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.32; H, 8.33; N, 5.47.

Pictet-Spengler Reaction of XIX——To a solution of XIX (100 mg) in MeOH (1 ml) was added 37% formalin (1.2 ml) at room temperature. After 10 min, the mixture was poured into 6N hydrochloric acid and stirred for 17 hr at room temperature. After treatment with charcoal, the solution was neutralized with aqueous ammonia solution and extracted with chloroform. The chloroform extract was washed with water, dried over Na_2SO_4 and evaporated to give an oily residue. The residue was dissolved in ether and added HCl–EtOH to give XXI-hydrochloride (90 mg, 76.4%) as crystals, mp 248—249.5° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_2NCl$: C, 64.97; H, 7.50; N, 4.74; Cl, 11.99. Found: C, 64.74; H, 7.58; N, 4.76; Cl, 11.94. IR $\nu_{max}^{CCl_4}$ cm^{-1} (free base): 3600 (OH). NMR (free base in $CDCl_3$): AB quartet (J = 17 cps) at 3.73 and 4.34 ppm due to benzyl protons.

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