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Constituents of Rhizoma *Nupharis*. XXVII.[1] Synthesis and Stereochemistry of 1- and 7-Methyl-4-phenylquinolizidin-2-one

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A stereoselective synthesis of 1-methyl(*e*)-4-phenyl(*e*)-*trans*-quinolizidin-2-one (**16a**) and 7-methyl(*e*)-4-phenyl(*e*)-*trans*-quinolizidin-2-one (**23a**) was accomplished during model studies for a stereoselective synthesis of quinolizidine-type *Nuphar* alkaloids. Condensation of ethylpyridine (**11**) with acetonitrile followed by ketalization gave the ketal (**13**), which was hydrogenated to afford two diastereoisomers (**14a** and **14b**) in a 1:1 ratio. Deketalization of **14a** or **14b** afforded a diastereoisomeric mixture (1:1 ratio) of the aminoketone (**15**), which was condensed with benzaldehyde to give two quinolizidin-2-ones (**16a** and **16b**) in 63 and 17% yields, respectively. The latter isomerized smoothly into the former on treatment with aqueous alkali in methanol. Similarly, the ketal (**20**) derived from 2,5-lutidine (**18**) was hydrogenated to give the *trans*- and *cis*-piperidines (**21a** and **21b**) in a 2:1 ratio. Treatment of both of them with hydrochloric acid effected deketalization and isomerization to yield a mixture of the *trans*- and *cis*-aminoketone (**22a** and **22b**) in a 6:1 ratio, whereas deketalization with aqueous acetic acid or *p*-toluenesulfonic acid gave the mixture in a 1:3 ratio. Condensation of the mixture of **22a** and **22b** (6:1 ratio) with benzaldehyde gave two quinolizidin-2-ones (**23a** and **23b**) in 65 and 10% yields, respectively. These were also obtained in 31 and 27% yields, respectively, from the mixture of **22a** and **22b** (1:3 ratio).

Keywords——quinolizidine-type *Nuphar* alkaloid; deoxynupharidine; quinolizidin-2-one; stereoselective synthesis; isomerization *via* amino-enone

Deoxynupharidine (**1**), a representative quinolizidine-type *Nuphar* alkaloid,[3] had been synthesized by several groups[4] without consideration of stereoselectivity. Recently, **1** and its stereoisomers, 7-epideoxynupharidine (**2**),[5] 1-epideoxynupharidine (**3**), and 1-epi-7-epideoxynupharidine (**4**), were isolated from scent glands of the Canadian beaver.[6]

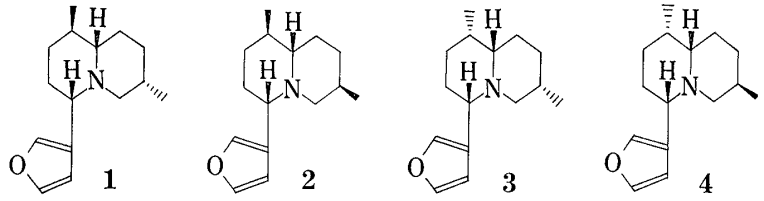

Chart 1

1) Part XXVI: Y. Itatani, S. Yasuda, M. Hanaoka, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **24**, 2521 (1976).
2) Location: *13-1, Takara-machi, Kanazawa, 920, Japan.*
3) J.T. Wróbel, "The Alkaloids," Vol. IX, ed. by R.H.F. Manske, Academic Press, New York, 1967, pp. 441—464.
4) *a*) F. Bohlmann, E. Winterfeldt, P. Studt, H. Laurent, G. Boroschewski, and K.-M. Kleine, *Chem. Ber.* **94**, 3151 (1961); *b*) Y. Arata, T. Ohashi, and Y. Asaoka, *Chem. Pharm. Bull.* (Tokyo), **10**, 675 (1962); *c*) I. Kawasaki, *Nippon Kagaku Zasshi*, **81**, 156 (1960); *d*) J.T. Wróbel and Z. Dabrowski, *Roczniki Chem.*, **39**, 1239 (1965) [*Chem. Abst.*, **64**, 15936 (1966)]; *e*) J. Szychowski, A. Leniewski, and J.T. Wróbel, *Chem. Ind.* (London), **1978**, 273.
5) This alkaloid was isolated from *Nuphar luteum* subsp. *variegatum*; C.F. Wong and R.T. LaLonde, *Phytochemistry*, **9**, 659 (1970).
6) B. Maurer and G. Ohloff, *Helv. Chim. Acta*, **59**, 1169 (1976).

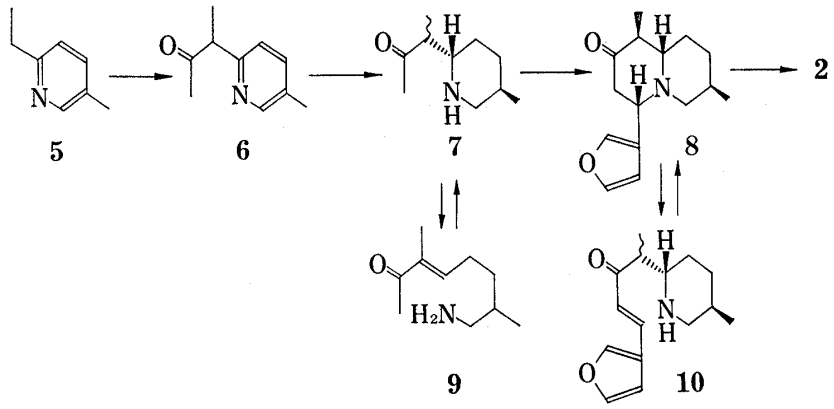

Chart 2

In order to develop a stereoselective synthesis of the *Nuphar* alkaloids, a synthesis of 7-epideoxynupharidine (**2**), the most stable isomer, was designed as shown in Chart 2.

The synthetic strategy was based on the assumption that the most stable aminoketones (**7** and **8**) should be preferentially synthesized through isomerization *via* the amino-enones (**9** and **10**), respectively. It was further expected that the stereochemistry of the 1-methyl group in **8** could be controlled *via* enolization of the carbonyl group. Preliminary experiments were carried out to investigate the validity of the above assumption.

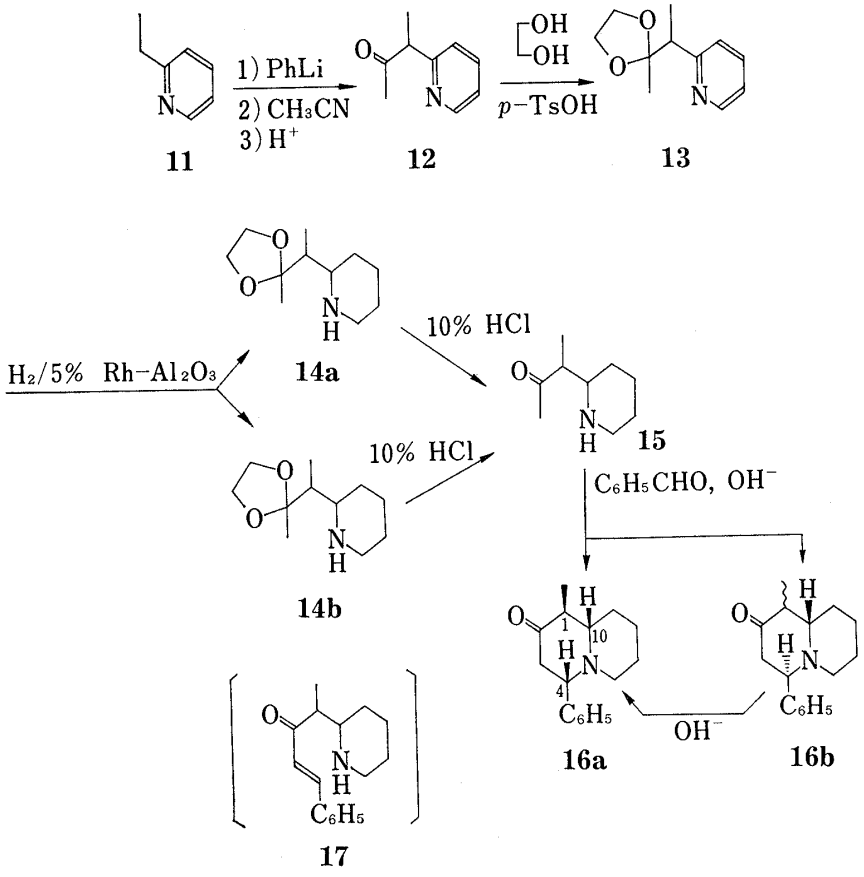

Chart 3

Initially, 1-methyl-4-phenylquinolizidin-2-one was synthesized according to the above synthetic route to check the stereoselectivity at C_1, C_4, and C_{10}.

Condensation of 2-ethylpyridine (**11**) with acetonitrile in the presence of phenyllithium, followed by acidic treatment, gave the ketone (**12**) [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O)] in 38% yield. Ketalization of **12** with ethylene glycol afforded the ketal (**13**) (76% yield), which was hydrogenated over 5% rhodium on alumina in acetic acid,[7] followed by chromatographic separation to give two diastereoisomers, **14a** [δ: 0.92 (3H, d, J=7.5 Hz, CHC$\underline{H}_3$), 1.26 (3H, s, CH_3)] and **14b** [δ: 0.99 (3H, d, J=7 Hz, CHC$\underline{H}_3$), 1.30 (3H, s, CH_3)] in a 1:1 ratio (89% yield). The stereochemistry of **14a** and **14b** remained undetermined. Deketalization of **14a** with 10% hydrochloric acid provided the aminoketone (**15**) in 87% yield; this was found to be a mixture on the basis of the appearance of two methyl signals at δ 1.08 (d, J=7 Hz, CHC$\underline{H}_3$) and δ 1.11 (d, J=7 Hz, CHC$\underline{H}_3$) in a 1:1 ratio in its nuclear magnetic resonance (NMR) spectrum. A similar mixture (1:1 ratio) was obtained from **14b** in 78% yield by acidic deketalization.

Condensation[8] of the aminoketone (**15**) with benzaldehyde in aqueous methanol in the presence of sodium hydroxide afforded two stereoisomeric quinolizidin-2-ones (**16a** and **16b**) in 63 and 17% yields, respectively. The *cis*-relationship between C_4–H and C_{10}–H in **16a** was confirmed by the presence of the Bohlmann bands at 2790 and 2750 cm^{-1} in its infrared (IR) spectrum and the appearance of the C_4–H signal at δ 3.24 (1H, d-d, J=11; 3.5 Hz) in its NMR spectrum.[9] The equatorial methyl group on C_1 in **16a** was suggested by the finding

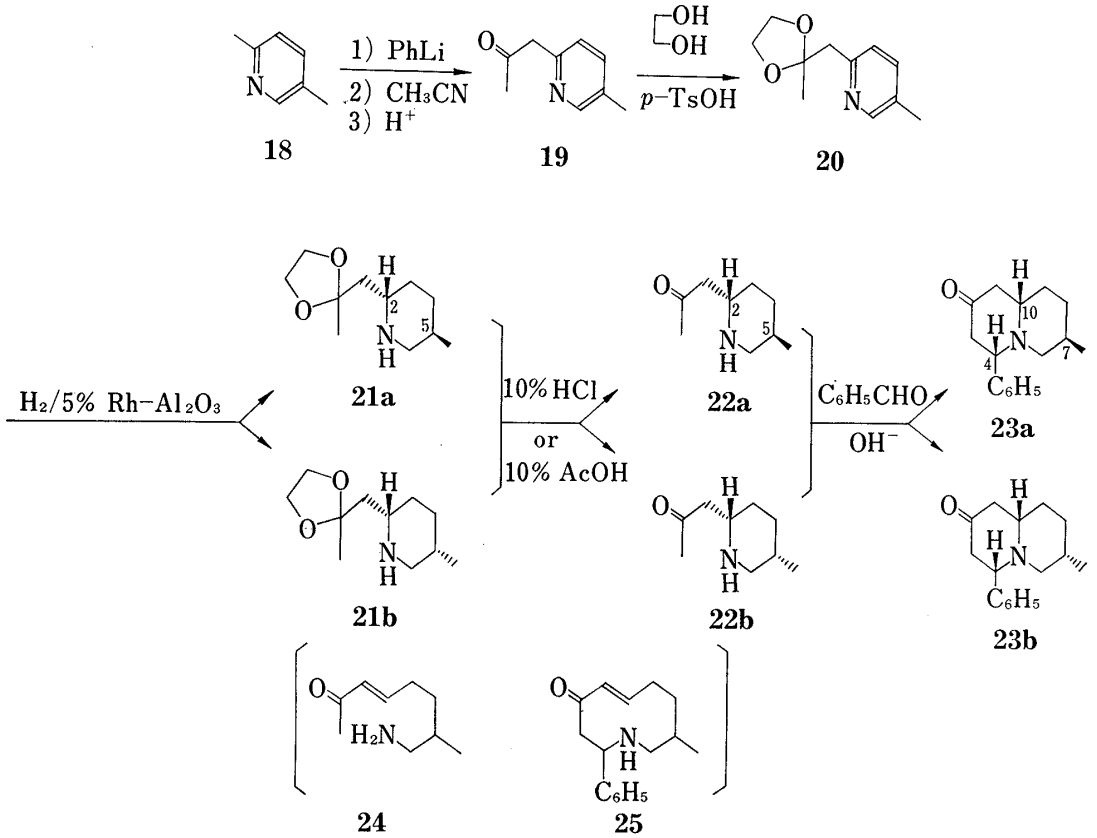

Chart 4

7) *cf.* M. Hanaoka, N. Ogawa, and Y. Arata, *Yakugaku Zasshi*, **94**, 531 (1974).
8) *cf.* M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **24**, 1045 (1976).
9) F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Lett.*, **1965**, 2705.

that no epimerization occurred at C_1 on treatment of **16a** with sodium methoxide in methanol. The presence of the *cis*-quinolizine ring in **16b** was confirmed by the lower chemical shift of the C_4–H signal at δ 4.20 (1H, d–d, J=6.5; 3.5 Hz) in its NMR spectrum[9] and the absence of a Bohlmann band in its IR spectrum. Treatment of **16b** with aqueous sodium hydroxide in methanol effected isomerization to give **16a** in 66% yield *via* the enone (**17**), as initially expected. Thus, stereoselective synthesis of the most stable aminoketone **16a** was accomplished.

Next, 7-methyl-4-phenylquinolizidin-2-one was synthesized according to the above synthetic method to check the stereoselectivity at C_4, C_7, and C_{10}.

Condensation of 2,5-lutidine (**18**) with acetonitrile afforded the ketone (**19**) [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O)] in 44% yield. Ketalization of **19** with ethylene glycol afforded the ketal (**20**) (84% yield), which was hydrogenated over 5% rhodium on alumina in acetic acid, followed by chromatographic separation to give the *trans*-piperidine (**21a**) [δ: 0.83 (3H, d, J=6.5 Hz, C_5–CH_3)] and the *cis*-piperidine (**21b**) [δ: 1.03 (3H, d, J=7 Hz, C_5–CH_3)] in a 2:1 ratio (84% yield). The higher chemical shift and the smaller coupling constant of the C_5-methyl signal of **21a** (δ: 0.83, J=6.5 Hz) in comparison with those of **21b** (δ: 1.03, J=7 Hz) in the NMR spectra[10] indicated that the C_5-methyl group in **21a** is equatorial and that in **21b** is axial. Deketalization of **21a** with 10% hydrochloric acid afforded a mixture of two isomeric aminoketones, *trans*[**22a**: δ 0.83 (d, J=6 Hz, C_5–CH_3)] and *cis* [**22b**: δ 1.01 (d, J=7 Hz, C_5–CH_3)] in a 6:1 ratio (91% yield). The same mixture was obtained from **21b** by deketalization with 10% hydrochloric acid in 78% yield. These findings suggested that the thermodynamically more stable isomer (**22a**) was mainly obtained from either **21a** or **21b** under the above deketalization reaction conditions, probably *via* **24**. Attempts to isolate the two isomers were unsuccessful. On the other hand, deketalization of **21b** with either 10% acetic acid or *p*-toluenesulfonic acid in acetone afforded a mixture of **22a** and **22b** in a 1:3 ratio in 95 or 82% yield, respectively. Thus, deketalization with 10% acetic acid or *p*-toluenesulfonic acid prevented the isomerization *via* **24** to a considerable extent.

Condensation of the mixture of the aminoketones [**22a** and **22b** (6:1)] with benzaldehyde in aqueous methanol in the presence of sodium hydroxide afforded two stereoisomeric quinolizidin-2-ones, **23a** [$\nu_{max}^{CHCl_3}$ cm^{-1}: 2775, 2745 (Bohlmann bands), 1715 (C=O), δ 0.76 (3H, d, J=6 Hz, C_7–CH_3), 3.27 (1H, d–d, J=11; 4 Hz, C_4–H), *m/e* 243 (M^+)] and **23b** [$\nu_{max}^{CHCl_3}$ cm^{-1}: 2780, 2750 (Bohlmann bands), 1715 (C=O), δ; 1.09 (3H, d, J=7 Hz, C_7–CH_3), 3.28 (1H, d–d, J=11.5; 4 Hz, C_4–H), *m/e*: 243 (M^+)] in 65 and 10% yields, respectively. The *cis*-relationship between C_4–H and C_{10}–H of **23a** and **23b** was confirmed by the presence of the Bohlmann bands in the IR spectra and the C_4–H signals in the NMR spectra.[9] The higher chemical shift and the smaller coupling constant of the C_7-methyl signal of **23a** in comparison with those of **23b** indicated that the C_7-methyl group in **23a** was equatorial and that in **23b** was axial. Condensation of the mixture of the aminoketones [**22a** and **22b** (1:3)] with benzaldehyde under the same reaction conditions afforded **23a** and **23b** in 31 and 27% yields, respectively.

Isomerization of **23b** to **23a** *via* **25** did not occur on treatment with sodium methoxide in methanol.

Thus, the stereoselective synthesis of the most stable aminoketone **23a** was accomplished. Further, the relatively unstable isomer **23b** was also obtained under suitable reaction conditions.

The initial expectation that the most stable aminoketones could be obtained according to our synthetic strategy (Chart 2) was thus correct, and this method appeared to be promising for a stereoselective synthesis of 7-epideoxynupharidine.

10) T.M. Moynehan, K. Schofield, R.A.Y. Jones, and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.

Experimental[11]

3-(2-Pyridyl)butan-2-one (12)——Bromobenzene (102 g) was added dropwise to a stirred suspension of lithium (8.2 g) in dry ether (250 ml) for 1.5 hr under an N_2 atmosphere with cooling in an ice bath. The reaction mixture was stirred for 1 hr at room temperature. 2-Ethylpyridine (23.2 g) was added dropwise to the reaction mixture with cooling in an ice bath, and the reaction mixture was then refluxed gently for 30 min. Acetonitrile (14.0 g) was added dropwise to the reaction mixture with cooling in an ice bath, and stirring was continued for 3 hr at room temperature. The reaction mixture was acidified to pH 1 with 4 N H_2SO_4 with cooling, then stirred for 2 hr at room temperature. The ethereal layer was separated. The aqueous layer was washed with ether, then made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and evaporated *in vacuo*. The residue was distilled to give **12** (12.2 g, 38%) as a yellow oil, bp 115—117°/17 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O). NMR δ: 1.44 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 2.10 (3H, s, $COCH_3$), 3.97 (1H, q, J=7 Hz, $C\underline{H}CH_3$).

Picrate: Yellow needles, mp 112—114° (EtOH). *Anal.* Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.63; H, 3.73; N, 14.81. Found: C, 47.76; H, 3.74; N, 14.86.

3-(2-Pyridyl)butan-2-one Ethylene Acetal (13)——A mixture of the ketone (**12**) (10.90 g) ethylene glycol (10.1 g), and *p*-toluenesulfonic acid monohydrate (18.23 g) in benzene (100 ml) was refluxed for 10 hr with stirring in a flask equipped with a Dean-Stark water separator. Water was added to the cooled reaction mixture and the benzene layer was separated. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and concentrated *in vacuo*. The residue was distilled to give **13** (10.75 g, 76%) as a colorless oil, bp 130—133°/17 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1150, 1070, 1050 (C–O). NMR δ: 1.26 (3H, s, CH_3), 1.38 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 3.23 (1H, q, J=7 Hz, $CHC\underline{H}_3$), 3.85 (4H, m, OCH_2CH_2O).

Picrate: Yellow needles, mp 119—120° (EtOH). *Anal.* Calcd. for $C_{17}H_{18}N_4O_9$: C, 48.35; H, 4.30; N, 13.27. Found: C, 48.41; H, 4.28; N, 13.24.

3-(2-Piperidyl)butan-2-one Ethylene Acetal (14a and 14b)——A solution of the ketal (**13**) (23.12 g) in acetic acid (60 ml) was hydrogenated over 5% Rh-Al_2O_3 (5 g) at room temperature under atmospheric pressure until no more hydrogen was observed, then the catalyst was filtered off. The filtrate was evaporated *in vacuo*. The residue was made alkaline with aq. K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried, and concentrated *in vacuo*. The residue was distilled to give a colorless oil (21.23 g, 89%), bp 127—129°/17 mmHg. The oil (8.21 g) was chromatographed on Al_2O_3, using AcOEt as an eluent. The first fraction gave **14a** (4.12 g) as a colorless oil, bp 126—128°/17 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (NH), 1120, 1095, 1050 (C–O). NMR δ: 0.92 (3H, d, J=7.5 Hz, $CHC\underline{H}_3$), 1.26 (3H, s, CH_3), 2.82 (1H, s, NH, disappeared on addition of D_2O), 3.92 (4H, s, OCH_2CH_2O).

Picrate: Yellow cubes, mp 156—157° (EtOH). *Anal.* Calcd. for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.65; N, 13.08. Found: C, 47.81; H, 5.60; N, 13.05.

The second fraction gave **14b** (3.23 g) as a colorless oil, bp 126—127°/17 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (NH), 1165, 1115, 1050 (C–O). NMR δ: 0.99 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 1.30 (3H, s, CH_3), 2.22 (1H, s, NH, disappeared on addition of D_2O), 3.90 (4H, m, OCH_2CH_2O).

Picrate: Yellow plates, mp 145.5—146.5° (EtOH). *Anal.* Calcd. for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.65; N, 13.08. Found: C, 47.76; H, 5.80; N, 12.83.

3-(2-Piperidyl)butan-2-one (15)——1) A solution of the ketal (**14a**) (3.74 g) in 10% HCl (35 ml) was heated at 80—85° for 10 hr with stirring. After cooling, the reaction solution was made alkaline with 20% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and evaporated *in vacuo*. The residue was distilled to give **15** (2.53 g, 87%) as a colorless oil, bp 105—108°/17 mmHg (under an N_2 atmosphere). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1705 (C=O). NMR δ: 1.08 (3/2H, d, J=7 Hz, $CHC\underline{H}_3$), 1.11 (3/2H, d, J=7 Hz, $CHC\underline{H}_3$), 2.18 (3H, s, $COCH_3$).

2) A solution of the ketal (**14b**) (2.85 g) in 10% HCl (30 ml) was heated at 90° for 12 hr with stirring. The reaction solution was treated by the procedure described in 1) to give **15** (1.74 g, 78%) as a colorless oil, bp 105—108°/17 mmHg; this was identical with **15** obtained in 1) by TLC, and from the IR and NMR spectra.

1-Methyl-4-phenylquinolizidin-2-one (16a and 16b)——A solution of the aminoketone (**15**) (420 mg), benzaldehyde (332 mg), and 5% aq. NaOH (6 ml) in MeOH (30 ml) was heated at 80—85° for 8 hr with stirring under an N_2 atmosphere. The reaction mixture was acidified with 10% HCl and MeOH was evaporated off *in vacuo*. The residue was washed with ether, made alkaline with K_2CO_3, and extracted with

11) All melting points were measured with a Yanagimoto micro melting point apparatus. Melting points and boiling points are uncorrected. Alumina (Brockmann grade II—III, Merck) was used for column chromatography, and alumina (GF_{254}, type 60/E, Merck) and silica gel (GF_{254}, type 60, Merck) for thin-layer chromatography (TLC). Extracts were dried over anhyd. Na_2SO_4. IR spectra were measured with an IR-G spectrophotometer, Japan Spectroscopic Co., NMR spectra in $CDCl_3$ with a PS-100 machine, Japan Electron Optics Lab. Co., using tetramethylsilane as an internal standard, and mass spectra (MS) with a JMS-01SG mass spectrometer, Japan Electron Optics Lab. Co.

$CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and concentrated *in vacuo*. The residue was chromatographed on Al_2O_3 using benzene as an eluent. The first fraction gave **16a** (417 mg, 63%) as colorless crystals, which were recrystallized from *n*-hexane to give colorless scales, mp 93—94°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2790, 2750 (Bohlmann bands), 1712 (C=O). NMR δ: 0.98 (3H, d, J=7.5 Hz, C_1–CH_3), 3.24 (1H, d-d, J=11; 3.5 Hz, C_4–H). MS *m/e*: 243 (M^+), 84 (base peak). *Anal.* Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.97; H, 8.83; N, 6.05.

The second fraction gave **16b** (115 mg, 17%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1708 (C=O). NMR δ: 1.15 (3H, d, J=6.5 Hz, C_1–CH_3), 4.20 (1H, d-d, J=6.5; 3.5 Hz, C_4–H). MS *m/e*: 243 (M^+), 84 (base peak).

Picrate: Yellow cubes, mp 170—171° (acetone). *Anal.* Calcd. for $C_{22}H_{24}N_4O_8$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.89; H, 5.00; N, 11.95.

Isomerization of 16b to 16a——A solution of *cis*-quinolizidin-2-one (**16b**) (111 mg) and 5% aq. NaOH (4 ml) in MeOH (15 ml) was refluxed for 6 hr with stirring. The reaction solution was acidified with 10% HCl and MeOH was evaporated off *in vacuo*. The residue was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and concentrated *in vacuo*. The residue was subjected to preparative TLC (p-TLC) (Al_2O_3, benzene) to give **16a** (73 mg, 66%) and **16b** (26 mg, 23%). The products were identical with the corresponding authentic specimens.

Reaction of 16a with Sodium Methoxide——A solution of **16a** (35 mg) and $NaOCH_3$ (10 mg) in anhyd. MeOH (5 ml) was refluxed for 6 hr. MeOH was removed *in vacuo*, then the residue was dissolved in $CHCl_3$ and the solution was washed with water, dried, and evaporated *in vacuo*. The residue (30 mg, 86%) was identical with **16a** (TLC and IR spectra).

1-(5-Methyl-2-pyridyl)propan-2-one (19)——Bromobenzene (36.5 g) was added dropwise to a stirred suspension of lithium (3.0 g) in anhyd. ether (200 ml) for 1 hr under an N_2 atmosphere with cooling in an ice bath, and stirring was continued for 1 hr at room temperature. 2,5-Lutidine (12.7 g) was added to the reaction mixture with cooling in an ice bath, then the reaction solution was refluxed gently for 30 min with stirring. Acetonitrile (5.5 g) was added dropwise to the reaction solution with cooling in an ice bath, then stirring was continued for 2.5 hr at room temperature. The reaction solution was acidified with 4 N H_2SO_4 with cooling, then stirred for 2 hr at room temperature. The reaction solution was treated by the procedure described for **12** to give **19** (7.8 g, 44%) as a yellow oil, bp 125—127°/19 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). NMR δ: 2.24 (3H, s, CH_3), 2.34 (3H, s, CH_3), 3.91 (2H, s, $COCH_2$).

Picrate: Yellow plates, mp 152—154° (EtOH). *Anal.* Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.63; H, 3.73; N, 14.81. Found: C, 47.83; H, 3.59; N, 15.00.

1-(5-Methyl-2-pyridyl)propan-2-one Ethylene Acetal (20)——A mixture of the ketone (**19**) (8.50 g), ethylene glycol (9.5 g), and *p*-toluenesulfonic acid monohydrate (18.0 g) in benzene (90 ml) was refluxed for 10 hr with stirring in a flask equipped with a Dean-Stark water separator. The reaction mixture was treated by the procedure described for **13** to give **20** (9.26 g, 84%) as a colorless oil, bp 135—136°/21 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1130, 1037 (C–O). NMR δ: 1.35 (3H, s, CH_3), 2.32 (3H, s, CH_3), 3.12 (2H, s, $-CH_2-$), 3.92 (4H, m, OCH_2CH_2O).

Picrate: Yellow needles, mp 142—143° (EtOH). *Anal.* Calcd. for $C_{17}H_{18}N_4O_9$: C, 48.35; H, 4.30; N, 13.27. Found: C, 48.32; H, 4.00; N, 13.27.

1-(5-Methyl-2-piperidyl)propan-2-one Ethylene Acetal (21a and 21b)——A solution of the ketal (**20**) (8.97 g) in acetic acid (60 ml) was hydrogenated over 5% Rh-Al_2O_3 (2 g) at room temperature under atmospheric pressure until no more hydrogen was absorbed. The mixture was treated by the procedure described for **14a** and **14b** to give a mixture (7.78 g, 84%) of **21a** and **21b** as a colorless oil, bp 130—132°/21 mmHg. This oil (1.21 g) was chromatographed on Al_2O_3 using $CHCl_3$ as an eluent. The first fraction gave **21a** (0.68 g, 56%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (NH), 1130, 1035 (C–O). NMR δ: 0.83 (3H, d, J=6.5 Hz, C_5–CH_3), 1.36 (3H, s, CH_3), 2.63 (1H, s, NH, disappeared on addition of D_2O), 3.97 (4H, s, OCH_2CH_2O).

Picrate: Yellow needles, mp 141—142° (EtOH). *Anal.* Calcd. for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.65; N, 13.08. Found: C, 47.81; H, 5.60; N, 13.05.

The second fraction gave **21b** (0.34 g, 28%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (NH), 1090, 1040 (C–O). NMR δ: 1.03 (d, J=7 Hz, C_5–CH_3), 1.40 (3H, s, CH_3), 2.43 (1H, s, NH, disappeared on addition of D_2O), 3.97 (4H, s, OCH_2CH_2O).

Picrolonate: Yellow prisms, mp 167—169° (EtOH). *Anal.* Calcd. for $C_{21}H_{29}N_5O_7$: C, 54.42; H, 6.31; N, 15.11. Found: C, 54.13; H, 6.31; N, 14.97.

1-(5-Methyl-2-piperidyl)propan-2-one (22a and 22b)——1) A solution of the ketal (**21a**) (2.49 g) in 10% HCl (35 ml) was heated at 100° for 9 hr with stirring and treated by the procedure described for **15** to give a mixture (1.77 g, 91%) of **22a** and **22b** in a 6 : 1 ratio as a pale yellow oil, bp 108—109°/19 mmHg (in N_2 atmosphere). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3310 (NH), 1710 (C=O). NMR δ: 0.83 (18/7H, d, J=6 Hz, C_5–CH_3), 1.01 (3/7H, d, J=7 Hz, C_5–CH_3), 2.16 (3H, s, $COCH_3$), 2.33 (1H, s, NH, disappeared on addition of D_2O).

2) A solution of the ketal (**21b**) (1.97 g) in 10% HCl (30 ml) was heated at 100° for 10 hr with stirring and treated by the procedure described for **15** to give a pale yellow oil (1.19 g, 78%), bp 109—110°/21 mmHg, which was found to be a mixture of **22a** and **22b** (*ca.* 6 : 1) on the basis of its NMR spectrum; it was identical with the mixture obtained in 1).

3) A solution of **21b** (109 mg) in 10% AcOH (10 ml) was heated at 95—97° for 24 hr with stirring and treated by the procedure described for **15** to give a mixture (81 mg, 95%) of **22a** and **22b** in a 1:3 ratio. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3310 (NH), 1710 (C=O). NMR δ: 0.83 (3/4H, d, J=6 Hz, C_5–CH_3), 1.01 (9/4H, d, J=7 Hz, C_5–CH_3).

4) A solution of **21b** (141 mg) and *p*-toluenesulfonic acid monohydrate (155 mg) in acetone (20 ml) was refluxed for 15 hr with stirring, then acetone was evaporated off *in vacuo*. The residue was treated by the procedure described for **15** to give a pale yellow oil (90 mg, 82%), which was found to be a mixture of **22a** and **22b** (1:3) on the basis of its NMR spectrum; it was identical with the mixture obtained in 3).

Isomerization of 22b to 22a——1) A solution of a mixture (136 mg) of **22a** and **22b** (1:3) in 10% HCl (5 ml) was heated at 90° for 12 hr. After cooling, the reaction solution was made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and concentrated *in vacuo* to give a mixture (109 mg, 80%) of **22a** and **22b** in a 6:1 ratio. NMR δ: 0.83 (18/7H, d, J=6 Hz, C_5–CH_3), 1.01 (3/7H, d, J=7 Hz, C_5–CH_3).

2) A solution of a mixture of **22a** and **22b** (1:3) (200 mg) and 5% aq. NaOH (3 ml) in MeOH (10 ml) was heated at 70° for 12 hr with stirring under an N_2 atmosphere. After cooling, the reaction solution was acidified with 10% HCl, and MeOH was evaporated off. The residue was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and concentrated *in vacuo* to give a mixture (195 mg, 97%) of **22a** and **22b** in a 6:1 ratio. NMR δ: 0.83 (18/7H, d, J=6 Hz, C_5–CH_3), 1.01 (3/7H, d, J=7 Hz, C_5–CH_3).

7-Methyl-4-phenylquinolizidin-2-one (23a and 23b)——1) A solution of the aminoketone [a mixture of **22a** and **22b** (6:1)] (854 mg), benzaldehyde (704 mg) and 5% aq. NaOH (10 ml) in MeOH (50 ml) was heated at 75—80° for 10 hr with stirring under an N_2 atmosphere and treated by the procedure described for **16a** and **16b** to give a crude product, which was chromatographed on alumina using benzene as an eluent. The first fraction gave **23b** (129 mg, 10%) as crystals, which were recrystallized from *n*-hexane to give colorless needles, mp 93°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2780, 2750 (Bohlmann bands), 1715 (C=O). NMR δ: 1.09 (3H, d, J=7 Hz, C_7–CH_3), 3.28 (1H, d-d, J=11.5; 4 Hz, C_4–H). MS *m/e*: 243 (M^+), 98 (base peak). *Anal.* Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.84; H, 8.75; N, 5.89.

The second fraction gave **23a** (873 mg, 65%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2775, 2745 (Bohlmann bands), 1715 (C=O). NMR δ: 0.76 (3H, d, J=6 Hz, C_7–CH_3), 3.27 (1H, d-d, J=11, 4 Hz, C_4–H). MS *m/e*: 243 (M^+), 98 (base peak).

Picrate: Yellow cubes, mp 181—183° (AcOEt). *Anal.* Calcd. for $C_{22}H_{24}N_4O_8$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.98; H, 5.06; N, 11.85.

2) A solution of the aminoketone [a mixture of **22a** and **22b** (1:3)] (259 mg), benzaldehyde (183 mg), and 5% aq. NaOH (3 ml) in MeOH (10 ml) was heated at 70° for 9 hr with stirring under an N_2 atmosphere. The reaction mixture was treated by the procedure described for **16a** and **16b** to give a crude product, which was subjected to p-TLC (SiO_2, $CHCl_3$) to afford **23a** (127 mg, 31%) and **23b** (109 mg, 27%). The products, **23a** and **23b** were identical with the corresponding authentic specimens by TLC, and from the IR and NMR spectra.

Reaction of 23b with Sodium Methoxide——A solution of **23b** (56 mg) and sodium methoxide (15 mg) in anhyd. MeOH (5 ml) was refluxed for 6 hr, then MeOH was evaporated off under reduced pressure. The residue was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and concentrated *in vacuo*. The residue (47 mg, 84%) was identical with **23b**.

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