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

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A stereoerective 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 stereoerective 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 amino- ketone (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; stereoerective 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](image)

2) Location: 13-1, Takara-machi, Kanazawa, 920, Japan.
5) This alkaloid was isolated from Nuphar luteum subsp. variegatum; C.F. Wong and R.T. LaLonde, Phytochemistry, 9, 659 (1970).
In order to develop a stereoselective synthesis of the *Nuphar* alkaloids, a synthesis of 7-epideoxyxnupharidine (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.
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) \( \nu_{\text{max}} \text{ cm}^{-1}: 1715 \text{ (C=O)} \) 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 \( \delta: 0.92 \text{ (3H, d, } J=7.5 \text{ Hz, CHCH}_3) \), 1.26 (3H, s, CH\_3) and 14b \( \delta: 0.99 \text{ (3H, d, } J=7 \text{ Hz, CHCH}_3) \), 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 \( \delta 1.08 \text{ (d, } J=7 \text{ Hz, CHCH}_3) \) and \( \delta 1.11 \text{ (d, } J=7 \text{ Hz, CHCH}_3) \) 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\textsuperscript{9} of the aminoketone (15) with benzaldehyde in aqueous methanol in the presence of sodium hydroxide afforded two stereoismeric 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 \( \delta 3.24 \text{ (1H, d-d, } J=11; 3.5 \text{ Hz) in its NMR spectrum.}\textsuperscript{9} The equatorial methyl group on C_1 in 16a was suggested by the finding

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that no epimerization occurred at C₁ 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 C₄–H signal at δ 4.20 (1H, d-d, J=6.5; 3.5 Hz) in its NMR spectrum⁹ and the absence of a Bohllmann 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 C₄, C₅, and C₁₀.

Condensation of 2,5-lutidin (18) with acetonitrile afforded the ketone (19) [νCH₃ cm⁻¹: 1710 (C=O)] in 44% yield. Ketolization 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: 0.88 (3H, d, J=6.5 Hz, C₅–CH₃)] and the cis-piperidine (21b) [δ: 1.03 (3H, d, J=7 Hz, C₅–CH₃)] in a 2:1 ratio (84% yield). The higher chemical shift and the smaller coupling constant of the C₅-methyl signal of 21a (δ: 0.88, J=6.5 Hz) in comparison with those of 21b (δ: 1.03, J=7 Hz) in the NMR spectra⁹ indicated that the C₄-methyl group in 21a is equatorial and that in 21b is axial. Deketolization of 21a with 10% hydrochloric acid afforded a mixture of two isomeric aminoketones, trans[22a: δ 0.83 (d, J=6 Hz, C₅–CH₃)] and cis [22b: δ 1.01 (d, J=7 Hz, C₅–CH₃)] in a 6:1 ratio (91% yield). The same mixture was obtained from 21b by deketolization 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 deketolization reaction conditions, probably via 24. Attempts to isolate the two isomers were unsuccessful. On the other hand, deketolization 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, deketolization 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 [νCH₃ cm⁻¹: 2775, 2745 (Bohllmann bands), 1715 (C=O), δ 0.76 (3H, d, J=6 Hz, C₅–CH₃), 3.27 (1H, d-d, J=11; 4 Hz, C₄–H), m/e 243 (M⁺)] and 23b [νCH₃ cm⁻¹: 2780, 2750 (Bohllmann bands), 1715 (C=O), δ 1.09 (3H, d, J=7 Hz, C₅–CH₃), 3.28 (1H, d-d, J=11.5; 4 Hz, C₄–H), m/e 243 (M⁺)] in 65 and 10% yields, respectively. The cis-relationship between C₄–H and C₃p–H of 23a and 23b was confirmed by the presence of the Bohllmann bands in the IR spectra and the C₄–H signals in the NMR spectra.⁹ The higher chemical shift and the smaller coupling constant of the C₄-methyl signal of 23a in comparison with those of 23b indicated that the C₄-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.

Experimental\)

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 N₂ 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 H₂SO₄ 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 K₂CO₃ and extracted with CHCl₃. The CHCl₃ 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 νmax cm⁻¹: 1715 (C=O). NMR δ: 1.44 (3H, d, J = 7 Hz, CH₃), 2.10 (3H, s, COCH₃), 3.97 (1H, q, J = 7 Hz, CH₂CH₃). Ficar: Yellow needles, mp 114—114° (EtOH). Anal. Calcd. for C₁₅H₁₄N₂O₄: C, 74.63; H, 3.73; N, 14.81. Found: C, 74.76; H, 3.74; N, 14.86.

3-(2-Pyridyl)butan-2-one Ethylene Acetal (13) — A mixture of the ketone (12) (10.9 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 K₂CO₃ and extracted with CHCl₃. The CHCl₃ 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 νmax cm⁻¹: 1150, 1070, 1050 (C-O). NMR δ: 1.26 (3H, s, CH₃), 1.38 (3H, d, J = 7 Hz, CH₂CH₃), 3.23 (1H, q, J = 7 Hz, CH₂CH₃), 3.85 (4H, m, OCH₂CH₂O). Ficar: Yellow needles, mp 119—120° (EtOH). Anal. Calcd. for C₁₇H₂₆N₂O₄: 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 ketone (13) (23.12 g) in acetic acid (60 ml) was hydrogenated over 5% Rh-Al₂O₃ (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 withaq. K₂CO₃ and extracted with CHCl₃. The CHCl₃ 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 Al₂O₃ using AcOEt as an eluent. The first fraction gave 14a (4.12 g) as a colorless oil, bp 126—128°/17 mmHg. IR νmax cm⁻¹: 3340 (NH), 1120, 1095, 1050 (C-O). NMR δ: 0.92 (3H, d, J = 7.5 Hz, CH₂CH₃), 1.26 (3H, s, CH₃), 2.82 (1H, s, NH, disappeared on addition of D₂O), 3.92 (4H, m, OCH₂CH₂O). Ficar: Yellow cubes, mp 156—157° (EtOH). Anal. Calcd. for C₁₇H₂₆N₂O₄: C, 74.66; H, 5.65; N, 13.08. Found: C, 74.76; H, 5.60; N, 13.05.

The second fraction gave 14b (3.23 g) as a colorless oil, bp 126—127°/17 mmHg. IR νmax cm⁻¹: 3350 (NH), 1165, 1115, 1050 (C-O). NMR δ: 0.99 (3H, d, J = 7 Hz, CH₂CH₃), 1.30 (3H, s, CH₃), 2.22 (1H, s, NH, disappeared on addition of D₂O), 3.90 (4H, m, OCH₂CH₂O). Ficar: Yellow plates, mp 145.5—146.5° (EtOH). Anal. Calcd. for C₁₇H₂₆N₂O₄: C, 74.66; H, 5.65; N, 13.08. Found: C, 74.76; H, 5.60; N, 12.83.

3-(2-Piperidyl)butan-2-one (15) — A solution of the ketone (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 CHCl₃. The CHCl₃ extract was washed with water, dried, and evaporated in vacuo. The residue was distilled to give 15 (5.53 g, 87%) as a colorless oil, bp 105—108°/17 mmHg (under an N₂ atmosphere). IR νmax cm⁻¹: 3300 (NH), 1705 (C=O). NMR δ: 1.08 (3/2H, d, J = 7 Hz, CH₂CH₃), 1.11 (3/2H, d, J = 7 Hz, CH₂CH₃), 2.18 (3H, s, COCH₃).

2) A solution of the ketone (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-phenylquinolizinid-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 N₂ 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 K₂CO₃, 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 (GF₂₅₄, type 60/E, Merck) and silica gel (GF₂₅₄, type 60, Merck) for thin-layer chromatography (TLC). Extracts were dried over anhyd. Na₂SO₄. IR spectra were measured with an IR-G spectrophotometer, Japan Spectroscopic Co., NMR spectra in CDCl₃ with a FS-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.
CHCl₃. The CHCl₃ extract was washed with water, dried, and concentrated in vacuo. The residue was chromatographed on Al₂O₃ 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°C. IR νmax cm⁻¹: 2790, 2750 (Bolhmann bands), 1712 (C=O). NMR δ: 0.98 (3H, d, J = 7.5 Hz, C₆H₅CH₃), 3.24 (1H, d-d, J = 11; 3.5 Hz, C₆H₅). MS m/e: 243 (M⁺), 84 (base peak). Anal. Calcd. for C₁₆H₁₄NO₂: 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 νmax cm⁻¹: 1708 (C=O). NMR δ: 1.15 (3H, d, J = 6.5 Hz, C₆H₅CH₃), 4.20 (1H, d-d, J = 6.5; 3.5 Hz, C₆H₅). MS m/e: 243 (M⁺), 84 (base peak).


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 K₂CO₃ and extracted with CHCl₃. The CHCl₃ extract was washed with water, dried, and concentrated in vacuo. The residue was subjected to preparative TLC (p-TLC) (Al₂O₃, 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 NaOCH₃ (10 mg) in anhyd. MeOH (5 ml) was refluxed for 6 hr. MeOH was removed in vacuo, then the residue was dissolved in CHCl₃ 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 (9.0 g) in anhyd. ether (200 ml) for 1 hr under an N₂ 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 acetylated with 4 N H₂SO₄ 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°C/19 mmHg. IR νmax cm⁻¹: 1710 (C=O). NMR δ: 2.24 (3H, s, CH₃), 2.34 (3H, s, CH₃), 3.91 (2H, s, COCH₃).

Pircrate: Yellow plates, mp 152–154°C (EtOH). Anal. Calcd. for C₁₆H₁₄N₂O₂: 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°C/21 mmHg. IR νmax cm⁻¹: 1130, 1037 (C–O). NMR δ: 1.35 (3H, s, CH₃), 2.32 (3H, s, CH₃), 3.12 (2H, s, –CH₂–), 3.92 (4H, m, OCH₂CH₂O).

Pircrate: Yellow needles, mp 142–143°C (EtOH). Anal. Calcd. for C₁₅H₁₆O₄: 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 ketone (20) (8.97 g) in acetic acid (60 ml) was hydrogenated over 5% Rh-Al₂O₃ (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°C/21 mmHg. This oil (1.21 g) was chromatographed on Al₂O₃ using CHCl₃ as the eluent. The first fraction gave 21a (0.68 g, 56%) as a colorless oil. IR νmax cm⁻¹: 3320 (NH), 1130, 1055 (C–O). NMR δ: 0.83 (3H, d, J = 6.5 Hz, C₆H₅CH₃), 1.36 (3H, s, CH₃), 2.63 (1H, s, NH, disappeared on addition of D₂O), 3.97 (4H, s, OCH₂CH₂O).

Pircrate: Yellow needles, mp 141–142°C (EtOH). Anal. Calcd. for C₁₇H₂₂N₂O₄: 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 νmax cm⁻¹: 3320 (NH), 1090, 1040 (C–O). NMR δ: 1.03 (d, J = 7 Hz, C₆H₅CH₃), 1.40 (8H, s, CH₂), 2.43 (1H, s, NH, disappeared on addition of D₂O), 3.97 (4H, s, OCH₂CH₂O).


1-[5-Methyl-2-piperidyl]propan-2-one (22a and 22b)—1. A solution of the ketone (21a) (2.49 g) in 10% HCl (35 ml) was heated at 100°C 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°C/19 mmHg (in N₂ atmosphere). IR νmax cm⁻¹: 3310 (NH), 1710 (C=O). NMR δ: 0.83 (18H, d, J = 6 Hz, C₆H₅CH₃), 1.01 (3H, d, J = 7 Hz, C₆H₅CH₃), 2.16 (3H, s, COCH₃), 2.33 (1H, s, NH, disappeared on addition of D₂O).

2) A solution of the ketone (21b) (1.97 g) in 10% HCl (30 ml) was heated at 100°C 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°C/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 ν_{max} cm⁻¹: 3310 (NH), 1710 (C=O). NMR δ: 0.83 (3/4H, d, J = 6 Hz, C₃-C₂H₃), 1.01 (9/4H, d, J = 7 Hz, C₈-C₃H₁₂).

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——I) 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 K₂CO₃ and extracted with CHCl₃. The CHCl₃ 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, C₈-C₃H₁₂), 1.01 (3/7H, d, J = 7 Hz, C₈-C₃H₁₂).

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 N₂ atmosphere. After cooling, the reaction solution was acidified with 10% HCl, and MeOH was evaporated off. The residue was made alkaline with K₂CO₃ and extracted with CHCl₃. The CHCl₃ 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, C₈-C₃H₁₂), 1.01 (3/7H, d, J = 7 Hz, C₈-C₃H₁₂).

7-Methyl-4-phenylquinolinizidin-2-one (23a and 23b)——I) 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 N₂ 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 ν_{max} cm⁻¹: 2780, 2750 (Bohmian bands), 1715 (C=O). NMR δ: 1.09 (3H, d, J = 7 Hz, C₈-C₃H₁₂), 3.28 (1H, d-d, J = 11.5; 4H, C₄H₆). MS m/e: 243 (M⁺), 98 (base peak). Anal. Calcd. for C₉H₁₄NO: 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 ν_{max} cm⁻¹: 2775, 2745 (Bohmian bands), 1715 (C=O). NMR δ: 0.76 (3H, d, J = 6 Hz, C₈-C₃H₁₂), 3.27 (1H, d-d, J = 11, 4 Hz, C₄H₆). MS m/e: 243 (M⁺), 98 (base peak).


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 N₂ 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 (SiO₂, CHCl₃) to afford 23a (127 mg, 51%) 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 CHCl₃. The CHCl₃ extract was washed with water, dried, and concentrated in vacuo. The residue (47 mg, 84%) was identical with 23b.

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