# Synthesis of $\Delta^{1[9]}$- and/or $\Delta^{8[9]}$-Dehydroindolizidines and Related Compounds (1)

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A facile synthesis of $\Delta^{1[9]}$- and/or $\Delta^{8[9]}$-dehydroindolizidine and related compounds, consisting of dry distillation of γ-(*N*-2-piperidinonyl)butyric acid over soda-lime, is described. Reductions of these dehydroindolizidines and stereochemistry of 1-methylindolizidine are also described.

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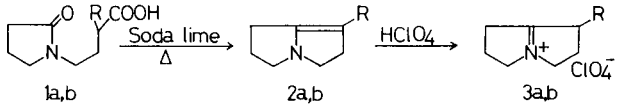
The preparation of heteroyclic enamines of 1-azabicycloalkanes, useful intermediates for organic synthesis, is usually achieved by hydrogenation of the corresponding 1-azabicycloalkanes with mercury(II) acetate (2-4). Recently, we have shown that the dry distillation of γ-(*N*-2-pyrrolidinonyl)butyric acids (**1**) over soda lime followed by treatment with perchloric acid affords $\Delta^{4[8]}$-dehydropyrrolizidinium perchlorate (**3**) *via* the corresponding heterocyclic enamine (**2**) (5-7), in good yields.

SCHEME 1



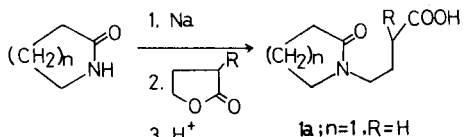

1a,b 2a,b 3a,b

a;R=H , b;R=$CH_3$

The present work was undertaken to extend the application of the cyclization procedure for the synthesis of $\Delta^{1[9]}$- and/or $\Delta^{8[9]}$-dehydroindolizidines and related compounds.

In a preliminary report dealing with pyrrolizidine system (5), we had prepared the starting butyric acid **1a** by the reaction of γ-butyrolactone with KOCN according to Reppe's procedure (8) which, however, suffers from the disadvantage of limited scope. In the present paper we wish to demonstrate a simple and convenient synthesis of compound **1a** and its analogues, which are the key compounds in the procedure. The method consists of the ring-cleavage at the C-5 position of γ-butyrolactones brought about with interaction of a sodium salt derived from a lactam such as 2-pyrrolidinone or 2-piperidinone.

SCHEME 2



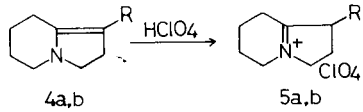

1a;n=1,R=H
1b;n=1,R=$CH_3$
1c;n=2,R=H
1d;n=2,R=$CH_3$

This procedure is quite simple and the yields are high. Thus, the compounds **1a, 1b, 1c**, and **1d** were obtained in 79, 95, 68, and 83% yields, respectively. The structures of these products could be easily confirmed by elemental and spectroscopic analyses (see Experimental).

The fact that dry distillation of butyric acids **1a** and **1b** over soda lime affords the corresponding dehydropyrrolizidine **2a** and **2b**, respectively (5-6) has already been reported by us. We now demonstrate here that our procedure is successfully applicable also to $\Delta^{1[9]}$- and/or $\Delta^{8[9]}$-dehydroindolizidine system. Thus, γ-(*N*-2-piperidinonyl)-butyric acid (**1c**) and its γ-methyl derivative (**1d**) could be transformed into the corresponding $\Delta^{1[9]}$- and/or $\Delta^{8[9]}$-dehydroindolizidines (**4a** and **4b**) by the analogous procedure for **1a-b**, in 46 and 54% yields, respectively.

The structures of the enamines **4a** and **4b** were readily confirmed by spectroscopic analysis (4) and transformation to the corresponding known iminium perchlorates **5a** and **5b** (4).

SCHEME 3




4a,b 5a,b

a;R=H , b;R=$CH_3$

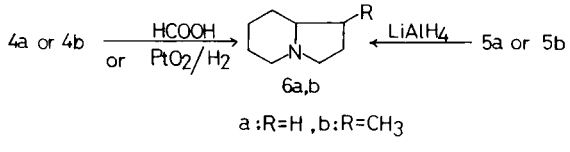
Taking advantage of the ready availability of dehydroindolizidines, reductions of them to indolizidines were successfully carried out and this provided another new route leading to indolizidines.

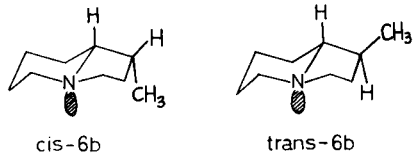
The dehydroindolizidines **4a** and **4b** were easily reduced upon treatment with formic acid to afford the corresponding indolizidine (**6a**, δ-coniseine) (9) and 1-methylindolizidine (**6b**) (10-11) in 52% and 54% yields, respectively. The nmr spectrum of **6b** in deuteriochloroform showed two characteristic signals at δ 0.97 (d, J = 6.7 Hz) and at δ 0.90 (d, J = 6.2 Hz) ppm, being assignable to each methyl protons on C-1 carbon of the indolizidine ring of the two diasteromers (*cis*- and *trans*-**6b**), and the ratio of

the integrations (δ 0.97/δ 0.90) being *ca* 2/1. Compound **6b** shows prominent Bohlmann bands in its ir spectrum in the region of 2700-2800 $cm^{-1}$, attributed to α-hydrogens oriented *trans* antiperiplanar to the nitrogen lone pair (12-13). This result indicates that the indolizidine ring is *trans*-fused. These spectroscopic results, together with the deshielding effect of the nitrogen lone pair (14), allow us to assign the signal at low field (δ 0.97 ppm) to the protons of the methyl group in *trans*-**6b** having the *trans*-1,9-hydrogen configuration, on the other hand, the signal at δ 0.90 can be assigned to those of the methyl group in *cis*-**6b**. By gas chromatographic analysis, the isomer *trans*-**6b** had a shorter retention time than that of *cis*-**6b** and the ratio of the isomers (*cis*-**6b**/*trans*-**6b**) was 34/66 (15).

The catalytic hydrogenation (platinum oxide as the catalyst) of the enamine **4b** at atmospheric pressure also afforded a mixture, in which *cis*-**6b** was predominant (with 83% of the isomeric ratio). This result is thought to reconfirm the stereochemical assignment regarding the configuration of **6b** described above. Thus, no isomerization in the catalytic hydrogenation process takes place it would

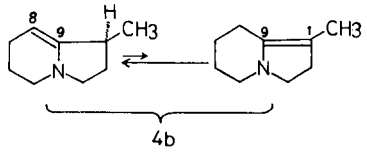
SCHEME 4




allow one easily to prepare that *cis*-hydrogenation of the $\Delta^{1[9]}$-isomer in **4b** might afford *cis*-**6b** and also that the catalytic hydrogenation of the $\Delta^{8[9]}$-isomer from the sterically least hindered side of the molecule (16) would result in the formation of *cis*-**6b**.

SCHEME 5




The reduction of the iminium perchlorate **5b** with LAH in anhydrous ether also gave a diastereomeric mixture in which the isomeric ratio of the products (*cis*-**6b**/*trans*-**6b**) was 56/44 by gas chromatography.

It appears that the described reactions, together with our previous work (5-7), provide an atrractive method for the synthesis of some heterocyclic enamines and related 1-azabicycloalkanes in terms of readily available starting materials and simple manipulations. It is especially noteworthy that the heterocyclic enamines were directly produced *via* cyclization in contrast to the known preparation of heterocyclic enamines which have uniformly consisted of mercury(II) acetate oxidations of the corresponding 1-azabicycloalkanes. Quite recently, McIntosh has shown that our method is more attractive for the preparation of $\Delta^{5[10]}$-dehydroquinolizidinium perchlorate rather than the preparation of this compound by the mercury(II) acetate oxidation of quinolizidine (17).

## EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were recorded on a Hitachi R-22 instrument, using tetramethylsilane as an internal standard. The ir spectra were measured on a Hitachi-EPI-G-3 instrument. High-resolution mass spectra were obtained with a JEOL-01 SG instrument with a direct inlet system at 75 eV. Gas chromatographic analyses were performed on a Yanako-G180 instrument, using a 1.5 m × 3 mm column (10% Themon-1000 + 3% potassium hydroxide Chromosorb W 80/100 AW-DMCS) at 0.8 $kg/cm^2$ nitrogen flow pressure, and at 75° column temperature.

General Procedure for γ-(*N*-2-Pyrrolidinonyl or *N*-2-Piperidinonyl)-butyric Acid (**1a-d**).

To 2-pyrrolidinone (25 g) or 2-piperidinone (25 g) was added metallic sodium (2.6-3.6 g) at 90-120°. To this solution was added dropwise the equivalent amount of butyrolactone or α-methyl-γ-butyrolactone, under a nitrogen stream and the mixture was stirred for 4-24 hours at 120-130° in an oil bath. After addition of 5% aqueous sodium hydroxide (15-20 ml) to the reaction mixture, the resulting solution was washed with dichloromethane (90-150 ml). The aqueous layer was acidified with concentrated hydrochloric acid (*ca* 15 ml), and then extracted with dichloromethane (100-150 ml). The exctract was washed with saturated aqueous sodium chloride (40-60 ml). After drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure to give the butyric acids **1a-d**.

γ-(*N*-2-Pyrrolidinonyl)butyric Acid (**1a**).

This compound was obtained in 79% yield as colorless prisms, mp 89.5-90° (from ethyl acetate), the ir spectrum of which was identical with that of the authentic sample prepared by Reppe's method (8).

γ-(*N*-2-Pyrrolidinonyl)-α-methylbutyric Acid (**1b**).

This compound was obtained in 95% yield as colorless flakes, mp 99.5-10.5° (from ethyl acetate), the spectroscopic data of which has already been reported (6).

γ-(*N*-2-Piperidinonyl)butyric Acid (**1c**).

This compound was obtained in 68% yield as colorless prisms, mp 89.5-90° (from diisopropyl ether); ir (potassium bromide): 1730 (acid C=O), and 1595 $cm^{-1}$ (amide C=O); ms: m/e 185.1040 ($M^+$, $C_9H_{15}NO_3$); nmr (deuteriochloroform): δ 1.6-2.1 (m, 6H, aliphatic protons), 2.2-2.55 (m, 4H, -C*H*$_2$-CON= and -C*H*$_2$-COOH), 3.18-3.56 (m, 4H, -C*H*$_2$-N-C*H*$_2$-), and 10.26 (bs, 1H, -COO*H*, disappeared by the treatment with deuterium oxide) ppm.

*Anal.* Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.40; H, 8.33; N, 7.47.

γ-(*N*-2-Piperidinonyl)-α-methylbutyric Acid (**1d**).

This compound was obtained in 83% yield as colorless prisms, mp 82-84° (from diisopropyl ether); ir (potassium bromide): 1717 (acid C=O) and 1595 $cm^{-1}$ (amide C=O); ms: m/e 199.1216 ($M^+$, $C_{10}H_{17}NO_3$); nmr (deuteriochloroform): δ 1.21 (d, 3H, J = 7.5 Hz, $CH_3$), 1.5-2.6 (m, 9H, aliphatic protons and =C*H*-COOH), 3.1-3.73 (m, 4H, -C$H_2$-n-C$H_2$), and 11.69 (bs, 1H, -COO*H*, disappeared by the treatment with deuterium oxide) ppm.

*Anal.* Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.98; H, 8.88; N, 6.99.

$\Delta^{1[9]}$- And/or $\Delta^{8[9]}$-Dehydroindolizidine (**4a**) and Its Perchlorate (**5a**).

A mixture of the butyric acid **1c** (25 g) and finely powdered soda-lime (25 g) was subjected to a dry distillation to afford the crude enamine **4a** in quantitative yield (fraction boiling between 145-165°). Redistillation of this material under a nitrogen stream gave **4a** as a colorless oil in 46% yield, bp 131-132.5°/218 mm; ms: m/e 123.1057 ($M^+$, $C_8H_{13}N$); ir (film): 1677 $cm^{-1}$ (enamine C=C), the nmr spectrum of which was identical with that of the authentic sample reported as a mixture of $\Delta^{1[9]}$ and $\Delta^{8[9]}$-isomers (4).

To a solution of the freshly distilled enamine **4a** (2.03 g, 0.016 mole) in ethanol (20 ml) was added an equivalent molar amount of perchloric acid (70%) dropwise under ice cooling. After addition of ethanol (50 ml) to the mixture, the resulting mixture was refluxed for 1 hour. After cooling, the precipitated crystals were collected by filtration, and recrystallization of the crude perchlorate from isopropyl alcohol afforded the pure perchlorate **5a** in 67% yield as colorless flakes, mp 223-226° dec [lit mp 218-219° dec (4)]; ir (potassium bromide): 1703 $cm^{-1}$ (iminium), the nmr spectrum of which was identical with that of the authentic sample (4).

*Anal.* Calcd. for $C_8H_{14}ClNO_4$: C, 42.96; H, 6.31; N, 6.26. Found: C, 42.66; H, 6.53; N, 6.12.

1-Methyl- $\Delta^{1[9]}$- and/or $\Delta^{8[9]}$-Dehydroindolizidine (**4b**) and Its Perchlorate (**5b**).

By using a similar procedure as described for the preparation of the enamine **4a**, **4b** (7.38 g, 54%) was obtained from **1d** (20 g) and finely powdered soda-lime (20 g) as a colorless oil, bp 119-121°/107 mm; ir (film): 1680 $cm^{-1}$ (enamine C=C), the nmr spectrum of which could be identical with that of the authentic sample, being indicated that this enamine exists as a 2:1 mixture of the $\Delta^{1[8]}$- and $\Delta^{1[9]}$-isomers (4).

The perchlorate **5b** was easily obtained by the treatment of the freshly distilled **4b** (6.02 g, 0.044 mole) with an equivalent molar amount of perchloric acid (70%) (6.30 g, 0.044 mole) in 73% yield as colorless flakes mp 239-241° dec (from ethanol) [lit mp 235-237° dec (4)]; ir (potassium bromide): 1700 $cm^{-1}$ (iminium), whose nmr spectrum was identical with that of the authentic sample (4).

*Anal.* Calcd. for $C_9H_{16}ClNO_4$: C, 45.48; H, 6.79; N, 5.89. Found: C, 45.29; H, 7.05; N, 5.71.

Reduction of **4a** with Formic Acid.

To the enamine **4a** (2.46 g, 0.02 mole) was added formic acid (99%) (1.86 g, 0.04 mole) with stirring under ice cooling. After being stirred for 1 hour at room temperature, the mixture was kept at 60-70° for 1 hour. To the mixture was added 40% aqueous sodium hydroxide (5 ml), and the resulting mixture was extracted with ether (30 ml). The ether extract was washed with saturated sodium chloride and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to give indolizidine **6a** in 52% yield as a colorless oil, bp 80-82°/64 mm; ms: m/e 125.1219 ($M^+$, $C_8H_{15}N$). The picrate of this base melted at 224-229° dec, and could be identified with that of δ-conisene (= indolizidine) (9).

*Anal.* Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.46; H, 5.22; N, 15.71.

Reduction of **4b** with Formic Acid.

By using a similar procedure to that described above, 1-methylindolizidine **6b** (5.23 g, 54%), bp 88-91°/53 mm, was obtained as a mixture of *cis* and *trans* isomers from **4b** (9.55 g) and formic acid (6.47 g). The picrate of this base melted at 189-190° dec (from ethanol), and could be resolved for satisfactory identification as authentic 1-methylindolizidine (10-11).

*Anal.* Calcd. for $C_{15}H_{10}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.78; H, 5.59; N, 14.96.

The following spectroscopic data of the free base **6b** were obtained; ms: m/e 139.1340 ($M^+$, $C_9H_{17}N$); ir (film): 2730 and 2790 $cm^{-1}$ (Bohlmann bands); nmr (deuteriochloroform): δ 0.90 (*ca.* 1H, d, J = 6.7 Hz, C-1 methyl protons of *cis*-**6b**), 0.97 (d, J = 6.2 Hz, methyl protons of *trans*-**6b**) [other singals (δ 1.05-3.25) appeared as multiplets owing to contamination by *cis*-**6b**]. Isomeric ratio fo this base (*trans*-**6b**/*cis*-**6b**) was 66/34 by gas chromatography. The *cis*-**6b** had a longer retention time (508 seconds) than that of *trans*-**6b** (444 seconds).

Repeated fractional recrystallization of the hydrobromide of this base gave the hydrobromide of *trans*-**6b**, mp 222-223.5° dec (from isopropyl alcohol), the purity of which was 100% by gas chromatographic analysis.

*Anal.* Calcd. for $C_9H_{18}BrN$: C, 49.10; H, 8.24; N, 6.36. Found: C, 48.79; H, 8.52; N, 6.11.

Catalytic Hydrogenation of **4a**.

A mixture of **4a** (3.07 g, 0.025 mole) and platinum oxide (0.02 g) as catalyst in anhydrous ether (30 ml) was placed under a hydrogen atmosphere at atmospheric pressure. After absorption of *ca* 560 ml of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give indolizidine **6a**, the yield of which was 94% as the picrate.

Catalytic Hydrogenation of **4b**.

By using the similar procedure as described above, 1-methylindolizidine **6b** (2.02 g, 52%) was obtained as a mixture of cis and trans isomers from the catalytic hydrogenation of **4b** (2.74 g). Gas chromatographic analysis of the product indicated that the ratio of the stereoisomers (*cis*-**6b**/*trans*-**6b**) was 83/17. The picrate of this base melted at 198-200° dec.

*Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.78; H, 5.62; N, 15.16.

Reduction of the Perchlorate **5a** with Lithium Aluminum Hydride.

To a suspension of lithium aluminum hydride (0.57 g, 0.015 mole) in anhydrous ether (40 ml) was added the perchlorate **5a** (1.12 g, 0.005 mole) with stirring. The mixture was kept at room temperature with stirring for 10 hours. After decomposition of the remaining lithium aluminum hydride by addition of 40% aqueous sodium hydroxide (10 ml), the resulting mixture was extracted with ether (100 ml) and the extract was washed with saturated sodium chloride (30 ml). After being dried over magnesium sulfate, the solvent was evaporated under reduced pressure to afford indolizidine **6a**. The yield was 83% as the picrate.

Reduction of the Perchlorate **5b** with Lithium Aluminum Hydride.

Analogous treatment of the perchlorate **5b** (1.188 g, 0.005 mole) with lithium aluminum hydride in anhydrous ether gave a mixture of *cis* and *trans*-**6b** in 92% yield. The ratio fo the stereoisomers (*cis*-**6b**/*trans*-**6b**) of the product was 56/44 by gas chromatographic analysis. The picrate of this base melted at 195-197° dec.

*Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 48.84; H, 5.54; N, 15.09.

## REFERENCES AND NOTES

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(11) 1-Methylindolizidine (**6b**) has already been reported as a diastereomeric mixture (see reference 10), in which the stereochemical analysis, however, has remained unexplored, so far.

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(13) For a review, see T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971) and related references cited therein.

(14) K. Yoshikawa and I. Morishima, *J. Synth. Org. Chem. Japan*, **35**, 83 (1977); *Chem. Abstr.*, **87**, 4794f (1977) in which it is mentioned that the vertical direction towards the orientation of nitrogen lone pair, as shown in Figure A, is deshielded. Taking this idea, the pseudoequatorial methyl protons of *trans*-**6b** which coincides with this direction straight rather than pseudoaxial methyl protons of the corresponding diastereomer (*cis*-**6b**) might be observed at a lower field.

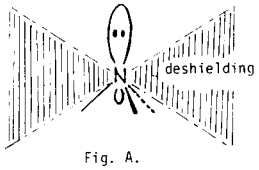


Fig. A.

(15) Evidently, *trans*-**6b** is the thermodynamically stable isomer [I. M. Skvortsov, *Russ. Chem. Rev.*, **48**, 262 (1979)]. In a pyrrolizidine ring system, a similar result has already been reported by us. Thus, the reduction of 1-methyl-$\Delta^{1(8)}$-dehydropyrrolizidine with formic acid gives the thermodynamically stable *trans*-1-methylpyrrolizidine (= pseudoheliotridane) as the main product (see reference 6).

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