A Convenient Synthesis of 1-Methylpyrrolizidines [(±)-Heliotridane and (±)-Pseudoheliotridane][1]

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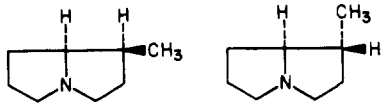
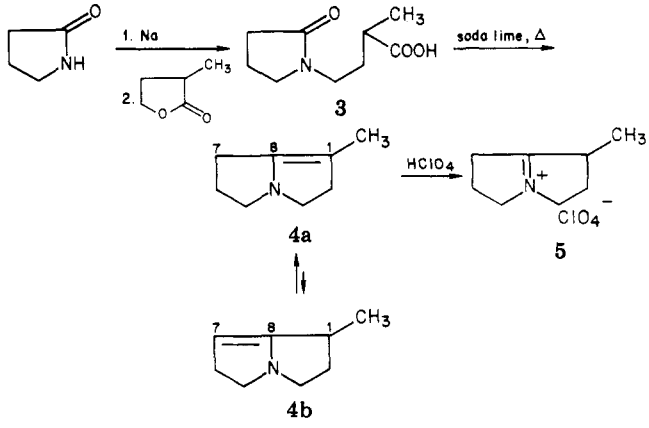
Pyrrolizidines and related compounds are attracting considerable attention because of their chemical and pharmacological interest.[2] So far, synthesis of 1-methylpyrrolizidines [(±)-heliotridane (1) and (±)-pseudoheliotridane (2)] has been achieved via various routes.[3,4] Among these procedures, Schweizer's[3a] or Skvortsov's method[3b] and Leonard's method[3c] are considered to be the most efficient for (±)-heliotridane (1) and (±)-pseudoheliotridane (2), respectively; however, these methods suffer from disadvantages such as many stages or low overall yields.



1 2

We now report a convenient synthesis of 1 and 2 via 1-methyl-$\Delta^{1(8)}$-dehydropyrrolizidine (4) which is readily available by the cyclization procedure described previously.[5] Thus, γ-(*N*-2-pyrrolidinonyl)-α-methylbutyric acid (3), which is easily obtained in 95% yield by the interaction of the sodium salt of 2-pyrrolidinone with α-methyl-γ-butyrolactone, was subjected to a dry distillation over soda lime to give the crucial intermediate 4. The heterocyclic enamine 4 was purified by distillation of the crude product and the yield was 73%. The distilled material, bp 94 °C (72 torr), as a colorless oil, is easily characterized as the enamine 4 by IR (1710 cm^{-1}, a typical heterocyclic enamine group[6]) and by conversion to 1-methyl-$\Delta^{4(8)}$-dehydropyrrolizidinium perchlorate (5) on the treatment of 4 with perchloric acid in ethanol. In the NMR spectrum of 4, only a small amount (ca. 10%) of the $\Delta^{7(8)}$ isomer (4b) was detectable by the presence of a signal at δ 4.40–4.53 (br), being assignable to the vinyl proton of heterocyclic enamines.[6,7] This fact also confirms that the 1-methyl substituent contributes to the stabilization of the $\Delta^{1(8)}$ isomer system (4a) rather than the $\Delta^{7(8)}$ isomer system (4b).[8] The similar effect of the methyl group has been observed in the isomerization of the 1-methyl-$\Delta^{1(10)}$- and/or -$\Delta^{9(10)}$-dehydroquinolizidine system,[7] in which the $\Delta^{1(10)}$ isomer is predominant.



3 4a 4b 5

Catalytic hydrogenation of enamine 4 resulted in the formation of 1-methylpyrrolizidine in quantitative yield with high stereoselectivity (90%), giving isomer 1[3] having cis 1,8-hydrogens. Redistillation of the product afforded (±)-heliotridane (1) with 93% isomeric purity, in 67% yield. In contrast, reduction of the enamine 4 with formic acid gave a mixture, in which the stereoselectivity was 66% isomer 2[3] having trans 1,8-hydrogens. Redistillation of the crude material gave (±)-pseudoheliotridane (2) in 68% yield, with 75% isomeric purity.

$$4 \xrightarrow[\text{or HCOOH}]{H_2/PtO_2} 1 + 2$$

To our knowledge, this method for the stereoselective synthesis of 1-methylpyrrolizidines (1 and 2) is the most attractive one in terms of easily available starting materials, high overall yields, and simple transformations.

It is expected that the intermediate cyclic enamine 4 may be converted into various pyrrolizidines the derivatives of which will be described in future communications.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Hitachi-MH-100 instrument, using tetramethylsilane as an internal standard. IR spectra were measured on a Hitachi-EPI-G-3 instrument. High-resolution mass spectra were obtained with a JEOL-JMS-OISG 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% Thermon-1000 + 3% KOH Chromosorb W 80/100 AW-DMCS) at 1.2 kg/cm^2 of N_2 flow pressure and at 98 °C column temperature.

γ-(*N*-2-Oxopyrrolidinyl)-α-methylbutyric Acid (3). To 2-pyrrolidinone (25 g) was added metallic sodium (3.6 g, 0.156 mol) at 90–120 °C. To this solution was added dropwise the equivalent amount of α-methyl-γ-butyrolactone (15.6 g, 0.156 mol), and the mixture was stirred for 4–5 h at 120–130 °C in an oil bath. After addition of 5% aqueous sodium hydroxide (15 mL) to the

(1) Part 3 in the series on studies of pyrrolizidines and related compounds.

(2) For example, see the following reviews: (a) Leonard, N. J. *Alkaloids (NY)* **1960**, *6*, 35. (b) Kochetkov, N. K.; Likhosherstov, A. M. *Adv. Heterocycl. Chem.* **1965**, *5*, 315. (c) Robins, D. J. *Ibid.* **1979**, *24*, 247.

(3) (a) Schweizer, E. E.; Light, K. K. *J. Org. Chem.* **1966**, *31*, 870. (b) Skvortsov, N. M.; Antipova, I. V. *Tr. Molodykh Uch., Sarat. Univ.*, **1971**, 158. (c) Leonard, N. J.; Felley, D. L. *J. Am. Chem. Soc.* **1950**, *72*, 2537. Leonard, N. J.; Burk, Jr, E. H. *Ibid.* **1950**, *72*, 2543.

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(6) (a) Leonard, N. J.; Hay, A. S.; Fulmer, R. W.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 439. (b) Cervinka, O. In "Enamines: Synthesis, Structures, and Reactions"; Cook, A. G., Ed.; Marcel Dekker: New York and London, 1969, p 253 and related references cited therein.

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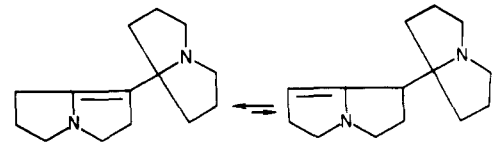
(8) The similar isomerization between the $\Delta^{1(8)}$ isomer (A) and $\Delta^{7(8)}$ isomer (B) has been observed, with isomer A in predominance (Sumoto, K.; Fuji, S.; Yamashita, O.; Somehara, T.; Miyano, S., in press).



A B

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reaction mixture, the resulting solution was washed with dichloromethane (150 mL). The aqueous layer was acidified with concentrated hydrochloric acid (10 mL) and extracted with dichloromethane (150 mL). The extract was washed with saturated aqueous sodium chloride (60 mL). After being dried over magnesium sulfate, the solvent was evaporated under reduced pressure to give butyric acid **3** in 95% yield: mp 99.5–100.5 °C (after recrystallization from ethyl acetate); mass spectrum, m/e 185.1039 (M^+, $C_9H_{15}NO_3$); IR (KBr) 1720 (s), 1630 (s), 1210 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.22 (3 H, d, J = 6.5 Hz, CH_3), 1.4–2.6 (7 H, m, aliphatic protons), 3.2–3.6 (4 H, m, aliphatic protons), 10.8 (1 H, br s, disappeared upon treatment with D_2O, COOH).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.15; H, 8.43; N, 7.41.

1-Methyl-$\Delta^{1(8)}$-dehydropyrrolizine (4) and Its Perchlorate (5). A mixture of butyric acid **3** (30 g) and finely powdered soda lime (30 g) was subjected to a dry distillation to afford the crude enamine **4** in quantitative yield (fraction boiling between 140 and 160 °C). Redistillation of this material under a nitrogen stream gave 14.6 g (73%) of 1-methyl-$\Delta^{1(8)}$-dehydropyrrolizidine (**4**) as a colorless oil: bp 94 °C (72 torr); mass spectrum, m/e 123.1095 (M^+, $C_8H_{13}N$), 246 (weak dimeric ion); IR (liquid film) 1710 cm^{-1} (s, enamine C=C); NMR (benzene-d_6) δ 4.40–4.53 (ca. 0.1 H, br s, vinyl proton of **4b**), 1.67 (br s, methyl protons of **4a**) [other signals (δ 0.7–3.5) appeared as complicated multiplets owing to contamination by **4b**].

To a solution of the freshly distilled enamine **4** (9.017 g, 0.073 mol) in ethanol (200 mL) was added an equivalent molar amount of perchloric acid (70%) dropwise with ice cooling. After addition of ethanol (300 mL) to the mixture, the precipitated crystals were collected by filtration, and recrystallization of the product from ethanol gave the perchlorate **5** in 88% yield as colorless flakes: mp 196–198 °C; IR (KBr) 1700 cm^{-1} (s, iminium =C=N$^+$=); NMR (pyridine-d_5) δ 3.87–4.20 (4 H, m, $^+NCH_2$), 1.9–3.7 (7 H, m, aliphatic protons), 1.20 (3 H, d, J = 7.5 Hz, CH_3).

Anal. Calcd for $C_8H_{14}ClNO_4$: C, 42.95; H, 6.30; N, 6.26. Found: C, 42.74; H, 6.58; N, 6.16.

Catalytic Hydrogenation of 4. Preparation of (±)-Heliotridane (1). A mixture of **4** (4.99 g, 0.04 mol) and platinum oxide (0.027 g) as catalyst in anhydrous ether (30 mL) was placed under a hydrogen atmosphere at atmospheric pressure. After absorption of ca. 900 mL of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Distillation of the residue afforded 1-methylpyrrolizidine (3.375 g, 67% yield), bp 100–103 °C (108–112 torr), the IR spectrum of which was identical with that of the authentic (±)-heliotridane.[3c] Gas chromatographic analyses of this base indicated the presence of a small amount (7%) of (±)-pseudoheliotridane (**2**), possessing a retention time of 3.1 min. The picrate of this base melted at 244–247.5 °C dec.

Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.53; H, 5.05; N, 15.90.

Reduction of 4 with Formic Acid. Preparation of (±)-Pseudoheliotridane (2). To the enamine **4** (37.102 g, 0.302 mol) was added formic acid (27.8 g, 0.604 mol) with stirring under ice cooling. After being stirred for 1 h at room temperature, the mixture was kept at 60–70 °C for 3 h with stirring. To the mixture was added 40% aqueous sodium hydroxide (40 mL), and the resulting mixture was extracted with ether (150 mL). The ether extract was washed with saturated sodium chloride (10 mL) and dried over magnesium sulfate. After evaporation of the solvent,[9] the residue was distilled to give 1-methylpyrrolizidine (25.76 g, 68% yield) as a colorless oil, bp 80–82 °C (45 torr). The product could be resolved for satisfactory identification as authentic (±)-pseudoheliotridane.[3c] Gas chromatographic analyses of the product, however, indicated that the product contains the stereoisomer **1**, possessing a long retention time (4.1 min), in the amount of 25%. Redistillation of this sample with a microspinning-band column afforded a more purified sample of **2**, with 93.5% isomeric purity (fraction boiling at 148–150 °C). The picrate of this fraction melted at 236–238 °C dec.

Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.55; H, 5.20; N, 15.54.

(9) Isomeric ratio of the crude product (1:2) was 34:66 by gas chromatography.

Registry No. **1**, 17463-81-9; 1 picrate, 17463-80-8; **2**, 76548-10-2; **2** picrate, 76548-11-3; **3**, 76466-47-2; **4a**, 76466-48-3; **4b**, 76466-49-4; **5**, 76466-51-8; 2-pyrrolidinone, 616-45-5; α-methyl-γ-butyrolactone, 1679-47-6.

Improved Synthesis and Characterization of Pictet-Spengler Adducts of Phenylpyruvic Acid and Biogenic Amines

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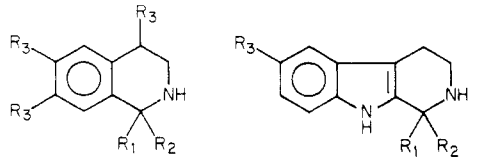
Introduction

Tetrahydroisoquinolines and β-carbolines derived from biogenic amines and from appropriate carbonyl substrates have recently attracted attention in addressing such problems as aberrant metabolism in alcoholism,[1] phenylketonuria,[2] L-dopa chemotherapy of Parkinson's disease,[3] and mental diseases such as schizophrenia.[4] A number of reports have appeared[5] describing the various physiological effects of compounds having the general features of **1** and **2**.



1 **2**

R_1 = H, CH_3, $CH_2C_6H_5$; R_2 = H, CO_2H; R_3 = H, OH, OCH_3

The Pictet-Spengler condensation of aromatic amines with aldehydes and ketones has been used extensively for the preparation of tetrahydroisoquinolines and β-carbolines.[6] We were interested in the synthesis of tetrahydroisoquinolines and β-carbolines possessing as a common feature 1,1-disubstitution by a benzyl and carboxylic acid group (**5a,b** and **7a–c**). Some of the adducts, namely, **5a** and **7a**, were described as early as 60 years ago.[7,8] Although a few 4-hydroxy-substituted tetrahydroisoquinolines have been synthesized,[6-11] the literature offers

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