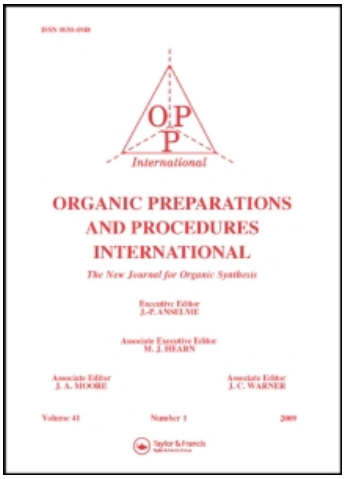

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A CONVENIENT SYNTHESIS OF δ-CONICEINE

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^{13}C NMR: δ 18.7 (CH_3), 26.0 (CH_3-Ar), 65.5 (CH_2), 68.2 (CH_2), 121.9, 125.6, 127.6, 136.4, 137.7.
M.S. (m/e): 148.0 (85.7), 149.0 (10.6, 118.0 (100).
Anal. Calcd for $C_{10}H_{12}$: C, 81.08; H, 8.11. Found: C, 81.05; H, 8.13

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A CONVENIENT SYNTHESIS OF δ-CONICEINE

Submitted by (02/09/95)

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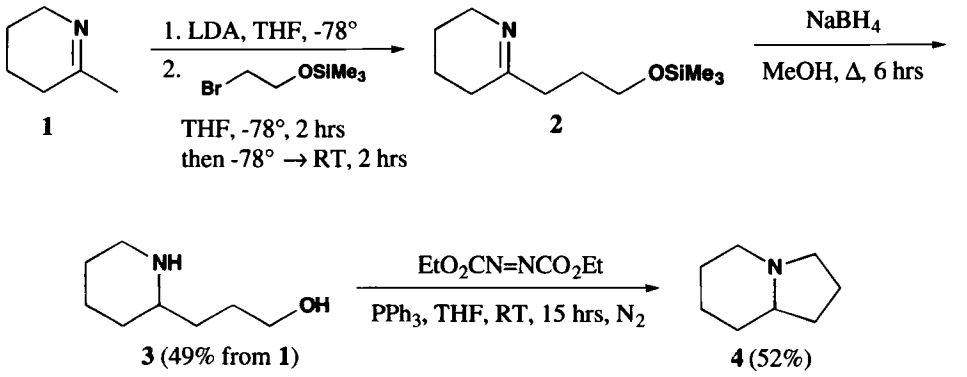
The indolizidine alkaloids have elicited an enormous interest on account of their exotic provenance and appealing biological activity.[1,2] They have been isolated from diverse classes of organisms, including ants, neotropical arrow poison frogs and plants. Many methods have been devised for their synthesis. Indolizidine (or δ-coniceine **4**), although not naturally occurring, has been considered as a typical synthetic target molecule.[3] As a consequence, a whole range of synthetic methodologies have been applied to the synthesis of 1-azabicyclo[4.3.0]nonane (**4**). Most

procedures for the synthesis of δ-coniceine comprise many steps, in several cases resulting in methods of only an academic interest. For practical purposes, such syntheses are not attractive for obtaining substantial quantities of δ-coniceine. In sharp contrast with many of these lengthy syntheses, we now report a very short and reliable synthesis of 1-azabicyclo[4.3.0]nonane.

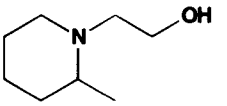
6-Methyl-2,3,4,5-tetrahydropyridine (**1**), easily prepared from 2-methylpiperidine by N-chlorination and subsequent base-induced 1,2-dehydrochlorination,[4] was regioselectively deprotonated[5] by lithium diisopropylamide in THF at -78° and subsequently reacted with 2-bromoethyl



1 **2**

3 (49% from **1**) **4** (52%)

trimethylsilyl ether to afford 6-(3-trimethylsilyloxypropyl)-2,3,4,5-tetrahydropyridine (**2**). Removal of the protecting trimethylsilyl group and reduction of the carbon-nitrogen double bond of the piperideine **2** was achieved in one step with sodium borohydride in methanol for 6 hrs to afford 2-(3-hydroxypropyl)piperidine (**3**) and the isomeric 1-(2-hydroxyethyl)-2-methylpiperidine (**5**) in a 97:3 ratio, respectively. 2-(3-Hydroxypropyl)piperidine (**3**) was isolated in 49% yield after purification by vacuum distillation. The N-alkylation product **5** was formed in increasing amount with increasing temperatures of the alkylation procedure. When the alkylation of the 1-azaenolate derived from **1**, was performed with 2-bromoethyl trimethylsilyl ether at 0°, the ratio of **3**:**5** was about 1:1. 2-(3-Hydroxypropyl)piperidine **3** had already been prepared previously by catalytic hydrogenation of 2-(3-hydroxypropyl)pyridine,[6] by free-radical coupling of piperidine with allyl alcohol in the presence of di-*t*-butylperoxide,[7] by hydride reduction of 6-(2-carboxyethyl)-2-piperidone,[8] and by reduction and deprotection of 1-(methoxycarbonyl)-2-[3-hydroxy-1-propynyl]-1,2-dihydropyridine THP ether.[3m]



5

The cyclocondensation of 2-(3-hydroxypropyl)piperidine **3** into δ-coniceine **4** has been reported several times in the literature, utilizing phosphorus pentoxide or sulfuric acid,[9,10] hydrogen bromide, followed by sodium hydroxide,[7] Raney nickel,[11] and triphenylphosphine/ carbon tetrachloride or carbon tetrabromide.[3m,3l] Attempts to convert 2-(3-hydroxypropyl)piperidine (**3**) to δ-coniceine (**4**) *via* O-mesylation and subsequent base-induced cyclization failed. The conversion of **3** into **4** was accomplished using diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran

at room temperature in an inert atmosphere, according to a procedure for the Mitsunobu cyclization of 1,4- and 1,5-amino alcohols.[12] The indolizidine **4** was isolated in 52% yield after distillation. This 1-azabicyclo[4.3.0]nonane was identical in all aspects (^{1}H NMR, ^{13}C NMR, IR, MS) with reported spectroscopic data.[3m]

EXPERIMENTAL SECTION

^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (67 MHz) were recorded with a Jeol JNM EX270 NMR spectrometer. IR spectra were measured with a Perkin Elmer model 1310 spectrophotometer. Mass spectra were obtained from a Varian MAT 112 mass spectrometer (70 eV) using GC-MS coupling. 2-Methyl-1-piperideine (**1**, bp. 37-40°/9 mmHg) was prepared by N-chlorination with N-chlorosuccinimide and subsequent base-induced dehydrochlorination with potassium hydroxide in methanol.[4]

Preparation of 2-(3-Hydroxypropyl)piperidine (3).- A solution of 6.8 g (0.07 mol) of 2-methylpiperideine (**1**) in 5 mL of dry tetrahydrofuran was added dropwise *via* a syringe to a freshly prepared solution of 0.084 mol of lithium diisopropylamide in 70 mL of tetrahydrofuran (LDA was generated at 0° from diisopropylamine in THF and *n*-butyllithium in hexane) at -78° (nitrogen atmosphere) with stirring. After 1 hr at this temperature, a solution of 16.46 g (0.084 mol) of 2-bromoethyl trimethylsilyl ether in 3 mL of tetrahydrofuran was added dropwise *via* a syringe. This solution was stirred for 2 hrs at -78°, after which the cooling bath was removed and stirring was continued for 2 hrs. The reaction mixture was poured in 100 mL of 1N sodium hydroxide and extracted three times with 30 mL of diethyl ether. The combined extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residual oil was dissolved in 105 mL of dry methanol. This solution was cooled to 0° and 5.32 g (0.14 mol) of sodium borohydride was added portionwise. The solution was then refluxed under stirring for 6 hrs, after which the reaction mixture was poured in brine. It was then extracted twice with 50 mL of diethyl ether and twice with 50 mL of dichloromethane and the combined extracts were dried ($MgSO_4$). After evaporation of the solvents *in vacuo*, the resulting colorless oil was distilled to afford 0.17 g (1.7%) of 1-(2-hydroxyethyl)-2-methylpiperidine (**5**), bp. 60-65°/0.01 mmHg and 4.88 g (49%) of 2-(3-hydroxypropyl)piperidine (**3**), bp. 78-80°/0.01 mmHg, lit.[8] bp. 248-249°/ 760 mmHg.

IR (NaCl) : 3250 cm^{-1} (broad, OH). ^{1}H NMR ($CDCl_3$): δ 1.0-2.0 (10H, m, 5 CH_2); 2.3-2.7 (2H, m, CH_2); 2.9-3.2 (1H, m, NCH); 3.4-3.9 (4H, m, NCH_2 and OCH_2). ^{13}C NMR ($CDCl_3$): δ 24.76 (CH_2); 26.50 (CH_2); 30.35 (CH_2); 33.06 (CH_2); 35.94 (CH_2); 46.47 (NCH_2); 56.75 (NCH); 62.49 (OCH_2). Mass spectrum *m/z* (%) : 143 (M^+; 5); 142(3); 112(67); 84(100); 58(16); 56(20); 55(18); 44(22); 43(22); 42(10); 41(10).

When the alkylation of **1** (1.94 g; 0.02 mol) with 2-bromoethyl trimethylsilyl ether was performed at 0° for 5 hrs, the subsequent reductive methanolysis gave a reaction mixture from which 0.60 g (21%) of **5** and 0.72 g (25%) of **3** were obtained by vacuum distillation.

1-(2-Hydroxyethyl)-2-methylpiperidine (5): IR (NaCl) : 3300 cm^{-1} (broad, OH). ^{1}H NMR ($CDCl_3$):

δ 1.05 (3H, d, J = 6.2 Hz, CH_3); 1.2-1.4 (2H, m, CH_2); 1.4-1.7 (4H, m, CH_2); 2.1-2.3 (2H, m, CH_2); 2.3-2.4 (1H, m, C*H*Me); 2.8-3.0 (2H, m, NCH_2); 3.1 (1H, broad s, OH); 3.4-3.7 (2H, m, OCH_2). ^{13}C NMR ($CDCl_3$): δ 18.42 (CH_3); 23.22 (CH_2); 26.00 (CH_2); 34.28 (CH_2); 51.14 (CH_2); 54.59 (NCH_2); 56.26 (CH); 58.04 (OCH_2). Mass spectrum *m/z* (%) : 143 (M^+; 5); 128(14); 113(11); 112(100); 100(5); 98(5); 84(8); 83(5); 70(7); 69(7); 56(16); 55(22); 44(38); 42(19); 41(19).

Synthesis of 1-Azabicyclo[4.3.0]nonane (4).- A solution of 2.86 g (0.02 mol) of 2-(3-hydroxypropyl)piperidine **3** in 100 mL of dry THF was treated with 5.76 g (0.022 mol) of triphenylphosphine and 3.83 g (0.022 mol) of diethyl azodicarboxylate. The mixture was stirred at room temperature for 15 hrs under a nitrogen atmosphere.[12] The reaction mixture was poured in water, extracted twice with ether, and the combined extracts dried ($MgSO_4$). Evaporation of the solvent gave a crude oil which was distilled to afford 1.3 g (52%) of 1-azabicyclo[4.3.0]nonane **4**, bp. 45-46°/9 mmHg, lit.[31] bp. 59-62°/28 mmHg, lit.[7] bp. 86°/32 mmHg. ^1H NMR ($CDCl_3$): δ 1.03-2.05 (13H, m, 6 CH_2 and NCH); 3.0-3.1 (2H, m, NCH_2). ^{13}C NMR ($CDCl_3$): δ 20.7 (CH_2); 24.7 (CH_2); 25.6 (CH_2); 30.6 (CH_2); 31.1 (CH_2); 53.2 (NCH_2); 54.3 (NCH_2); 64.4 (NCH).

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SYNTHESIS OF PYRAZINO(3,2,1-J,K)CARBAZOLE DERIVATIVES

Submitted by (04/07/95)

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In connection with another project, we required an efficient synthetic route to pharmacologically active pyrazinocarbazoles. The syntheses reported[1] so far suffer from some limitations such as complex procedures, low yield or difficulty assessible starting material. In these procedures, the pyrazino ring was constructed from the 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1**)[2,3] by alkylation followed by cyclization under forcing reaction conditions in low yields. The alkylation of 1-oxo-1,2,3,4-tetrahy-