A New Approach to Nicotine: Symmetry Consideration for Synthesis Design

by **Tse-Lok Ho*** and **Eugene V. Kuzakov**

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, Republic of China
(e-mail: tlho@cc.nctu.edu.tw)

A synthesis of nicotyrine (**9**), and hence formally racemic nicotine, was carried out by elaboration of the 1:1 adduct **2** of cycloocta-1,5-diene and chlorosulfonyl isocyanate ($ClSO_2-NCO$). Transformation of adduct **2** into carbamate **4** was followed by ozonolysis, tosylation, and NaH treatment, which led to pyrrolidinylpiperidinone **6**. $LiAlH_4$ Reduction, debenzylation, and aromatization yielded **2**.

Nicotine (**1**) is widely occurring in the plant kingdom and a most well-known member of alkaloids [1]. It is the addictive constituent of tobacco and, therefore, its effects are directly related to the socioeconomic issue of tobacco smoking, although scientific evidence has exonerated the carcinogenic role for nicotine[1]). Historically significant is the fact that *Pictet* and *Rotschy* at the University of Geneva described the first synthesis of (±)-nicotine in 1904 *via* nornicotyrine, which arose from pyrolysis of 1-(pyridin-3-yl)-1*H*-pyrrole [2]. This key step is now regarded as involving a [1,5]-sigmatropic rearrangement that achieved the bonding reorganization (N-to-C shift of the pyridin-3-yl group followed by C-to-N move of an H-atom) [3]. Practically all the later syntheses started from pyridine derivatives in which a C-substituent is located at C(3) [4] (an exception is a biomimetic route [5]; for a preparation of nicotyrine from 3-iodopyridine, see [5b]).

Our interest in a synthesis of nicotine stemmed from an analysis of bond connectivity in relation to hidden symmetry elements [6]. It was noted that an intermediate containing a 1,8-diaminooct-4-ene unit or some modifications thereof (see *Fig. 1*) would be viable because simultaneous addition of a single C-chain and one of the N-atoms to the C=C bond would provide all the skeletal atoms of nicotine. Regioselectivity in the addition is not an issue because of the inherent molecular symmetry that is exhibited by the oct-4-ene derivative (see *Fig. 2*).

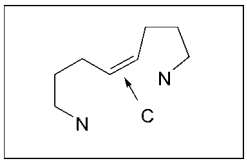


Fig. 1. *Assembly mode of* Nicotiana *alkaloids*

[1]) Nornicotine is a probable carcinogen due to its transformation into an *N*-nitrosamine derivative. Interestingly, it shows promise in alleviating *Alzheimer*'s disease.

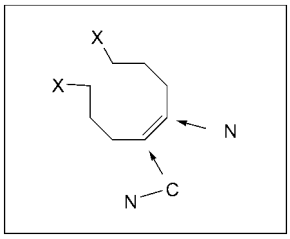
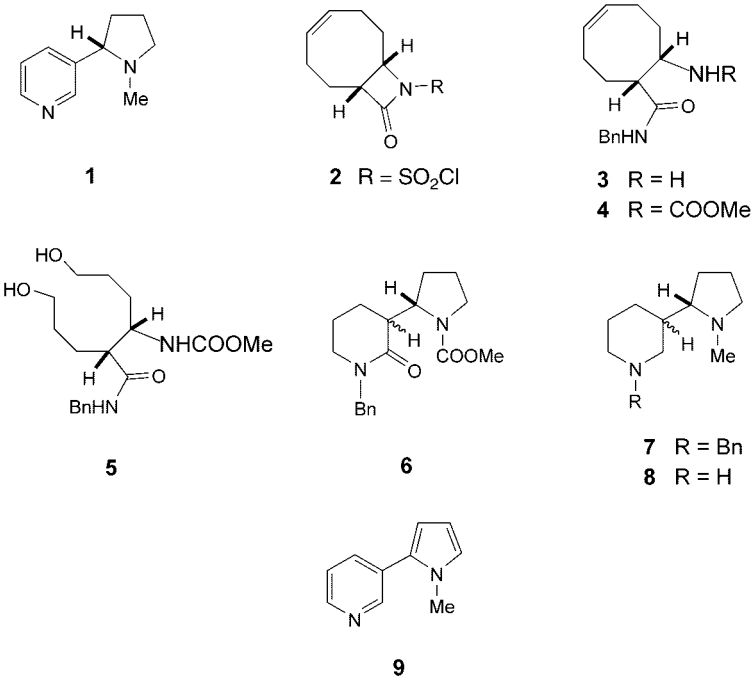


Fig. 2. *Assembly mode evolved from* Fig. 1

Further consideration of the scheme led to a refinement. As a result, we decided to develop a route starting with cycloocta-1,5-diene. Not only the starting material fulfills our symmetry consideration, but the 1:1-adduct **2** (R=SO_2Cl) of cycloocta-1,5-diene and chlorosulfonyl isocyanate ($ClSO_2$–NCO) that we require is a known compound [7]. Accordingly, our work began by aminolysis of **2** (R=H) with benzylamine. The ring opening with benzylamine afforded β-aminoamide **3** that was subsequently protected by reaction with methyl carbonochloridate. Ozonolysis of carbamate **4** followed by a reductive workup with $NaBH_4$ yielded diol **5**. One of the CH_2OH centers is separated from the N-atoms by four and six bonds, while the other CH_2OH center is related to both N-atoms by five bonds. Activation of both OH groups of **5** to induce twofold intramolecular *N*-alkylations may lead to a fused diazabicyclo[5.4.0]undecane or hexahydronicotine derivative **6**. We were quite confident that the second cyclization would proceed rapidly to give a pyrrolidine product hence that our expectation of a



nicotine synthesis would be achievable. Therefore, tosylation of diol **5** was carried out. As partial cyclization of the ditosylate already occurred, we treated the crude product mixture with NaH to complete the formation of **6**. While lactam **6** was obtained as a diastereoisomer mixture due to epimerization of the ditosylate prior to or during cyclization, it should be emphasized that the alternative mode of cyclization was not observed.

At this stage, we attempted to transform the piperidinone moiety of **6** into a pyridin-2(1*H*)-one. Due to unsatisfactory direct dehydrogenation or transformations involving α-halogenation and dehydrohalogenation, we next reduced **6** with $LiAlH_4$ to *N*-benzylhexahydronicotine (**7**) [8]. Hydrogenolysis of **7** furnished hexahydronicotine (**8**) [7] but its partial aromatization was technically tricky. Total dehydrogenation to afford nicotyrine (**9**) was accomplished by heating with Se powder. This represents a formal synthesis of nicotine as the selective reduction of the pyrrole ring is known [1][9].

In summary, we report a new route to the nicotine alkaloids based on symmetry consideration, proceeding *via* the same intermediate as described in the pioneering work of *Pictet* and *Rotschy* [2] on its centenary.

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Experimental Part

General. Column chromatography (CC): *Merck* silica-gel (63–200 mesh). TLC: *Merck* silica-gel *60 F254* plates. M.p.: uncorrected; *Laboratory Devices*. IR Spectra: *Bio-Rad FTS 165*; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian Unity-300*; $CDCl_3$ as solvent unless otherwise indicated; δ in ppm, *J* in Hz. EI-MS: *Trio-2000* and *Jeol SX-102A*; ionization potential 70 eV.

8-Amino-N-*benzylcyclooct-4-ene-1-carboxamide* (**3**). Benzylamine (9.0 g, 84 mmol) was mixed with a soln. of lactam **2** (10.6 g, 70 mmol) in dry toluene (60 ml), and the mixture was refluxed under N_2 for 36 h. The cooled mixture was evaporated, and the residue was subjected to distillation at $<140°$/1 Torr to remove excess benzylamine. The remaining viscous oil (15.5 g) was directly used for derivatizing into the carbamate. For characterization, a portion of this oil was shaken with a sufficient amount of 6N HCl, and the aq. phase was washed twice with CH_2Cl_2, basified with 10% NaOH soln. to pH 10 and extracted with CH_2Cl_2. The combined org. extract was dried (Na_2SO_4) and evaporated: **3**. Yellow oil. IR: 3416 (N–H), 2932 (C–H), 1644 (C=O). ^{1}H-NMR: 1.65–2.27 (*m*, 8 H); 2.49 (*m*, 1 H); 3.29 (*m*, 1 H); 4.33 (*d*, *J* = 5.4, 2 H); 5.53 (*dm*, *J* = 10.5, 1 H); 5.66 (*dm*, *J* = 10.5, 1 H); 7.17–7.27 (*m*, 5 H); 8.01 (br., NH). ^{13}C-NMR: 23.27 (*t*); 24.65 (*t*); 28.14 (*t*); 36.14 (*t*); 42.68 (*t*); 47.23 (*d*); 51.57 (*d*); 126.88 (*d*); 127.23 (2C, *d*); 128.30 (2C, *d*); 128.86 (*d*); 130.98 (*d*); 138.74 (*s*); 176.47 (*s*). EI-MS: 258 (12, $M^{+\bullet}$), 162 (13), 162 (17), 124 (19), 123 (25), 107 (12), 106 (38), 97 (18), 96 (18), 91 (100). HR-MS: 258.1727 ($C_{16}H_{22}N_2O^{+\bullet}$; calc. 258.1733).

{8-[(Benzylamino)carbonyl]cyclooct-4-en-1-yl}carbamic Acid Methyl Ester (**4**). A stirred soln. of crude **3** (15.0 g), pyridine (5.1 g), and *N*,*N*-dimethylpyridin-4-amine (DMAP; 0.05 g) in dry CH_2Cl_2 (50 ml) was cooled to 0° and treated with a soln. of methyl carbonochloridate (6.04 g in 15 ml of dry CH_2Cl_2) *via* dropwise addition during 20 min. Stirring was continued for 2 h at 0° and 3 h at r. t. Then the mixture was poured into cold H_2O (100 ml). The aq. phase was washed with CH_2Cl_2 (20 ml), the combined org. soln. washed twice with cold H_2O, dried (Na_2SO_4), and evaporated, and the crude product chromatographed (SiO_2, AcOEt/hexane 4:6): **4** (10.6 g, 48% over 2 steps). IR: 3315 (N–H), 2945 (C–H), 1698, 1657 (C=O). ^{1}H-NMR: 1.66–2.34 (*m*, 8 H); 2.68 (*m*, 1 H); 3.52 (*s*, 3 H); 4.16 (*m*, 1 H); 4.31 (*d*, *J* = 5.4, 2 H); 5.45 (*d*, *J* = 8.1); 5.58 (*m*, 2 H); 5.65 (*m*, 2 H); 7.15–7.25 (*m*, 5 H). ^{13}C-NMR: 22.69 (*t*); 25.59 (*t*); 27.83 (*t*); 33.15 (*t*); 43.01 (*t*); 48.50 (*d*); 50.57 (*d*); 51.88 (*q*); 126.90 (*d*); 127.21 (2C, *d*); 128.24 (2C, *d*); 129.83 (*d*); 130.06 (*d*); 138.33 (*s*); 156.54 (*s*); 174.45 (*s*). EI-MS: 316 (16, $M^{+\bullet}$), 288 (11), 162 (46), 149 (14), 128 (16), 108 (15), 107 (18), 106 (100), 91 (90), 79 (17). HR-MS: 316.1791 ($C_{18}H_{24}N_2O_3^{+\bullet}$; calc. 316.1787).

{2-[(Benzylamino)carbonyl]-5-hydroxy-1-(3-hydroxypropyl)pentyl}carbamic Acid Methyl Ester (**5**). A stream of O_3/O_2 was bubbled through a soln. of **3** (7.5 g, 24 mmol) in MeOH/CH_2Cl_2 1:1 (40 ml) at $-80°$ until a

blue color appeared and a crystalline precipitate formed (after *ca.* 1.25 h). The soln. was purged with N_2 while maintaining the low temp. until the blue color disappeared. Dimethyl sulfide (11 ml) and then $NaBH_4$ (4.5 g, 0.12 mol) were added in portions under N_2. After the addition, the cooling bath was removed, and the mixture was stirred for 1 h. Solvents were evaporated, and the residue was washed with H_2O and CH_2Cl_2, collected, and dried to constant weight. Recrystallization of the solid gave **5** (6.82 g, 82%). M.p. 158–161°. (MeOH/AcOEt 1:2). IR: 3305, 3280 (N–H, O–H), 2951 (C–H), 1695, 1630 (C=O). ^{1}H-NMR ((D$_5$)pyridine): 1.87–2.40 (*m*, 8 H); 3.02 (*m*, 1 H); 3.67 (*s*, 3 H); 3.88 (*m*, 4 H); 4.59 (*m*, 1 H); 4.71 (*d*, *J* = 5.4, 2 H); 5.21 (*s*, OH); 7.18–7.33 (*m*, 3 H); 7.52 (*d*, *J* = 7.5, 2 H); 8.22 (*d*, *J* = 9.0, 1 H); 9.53 (*t*, *J* = 6.0, 1 H). ^{13}C-NMR: 27.02 (*t*); 30.06 (*t*); 30.26 (*t*); 31.62 (*t*); 43.12 (*t*); 51.43 (*q*); 52.66 (*d*); 54.00 (*d*); 61.73 (*t*); 61.80 (*t*); 126.94 (*d*); 127.89 (2C, *d*); 128.50 (2C, *d*); 140.05 (*s*); 157.83 (*s*); 174.25 (*s*). EI-MS: 352 (3, $M^{+\bullet}$), 207 (44), 162 (112), 132 (110), 106 (82), 105 (88), 91 (99), 90 (77), 76 (54). HR-MS: 352.1995 ($C_{18}H_{28}N_2O_5^{+\bullet}$; calc. 352.1997).

2-(1-Benzyl-2-oxopiperidin-3-yl)pyrrolidine-1-carboxylic Acid Methyl Ester (**6**). To a soln. of **5** (3.05 g, 8.7 mmol) and Et_3N (1.93 g, 19 mmol) in anh. THF (80 ml), a soln. of TsCl (4.12 g, 22 mmol) in THF (20 ml) was added dropwise within 15 min at 0°. The mixture was warmed to r. t. while stirring for 3 h, and then brought to reflux for 6 h. After cooling, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (70 ml). The soln. was washed twice with sat. $NaHCO_3$ soln. and brine, dried (Na_2SO_4) and evaporated: mixture of ditosylate and partially cyclized product (3.82 g) (by NMR). This residue was dissolved in anh. THF (70 ml), the soln. cooled to 0°, and NaH (1.73 g, 60% dispersion in mineral oil, 43.5 mmol) added under N_2. After 20 min, the cooling bath was removed and the mixture refluxed for 7 h. After cooling, the mixture was partitioned between CH_2Cl_2 (70 ml) and H_2O (100 ml), the aq. phase extracted with more CH_2Cl_2 (2 × 30 ml), the combined org. phase washed with brine, dried (Na_2SO_4) and evaporated, and the the residue subjected to CC (silica gel, 30% AcOEt/hexane): **6** (1.46 g, 53% over 2 steps), 1:1 mixture of the *erythro*- and *threo*-isomers. IR: 2948, 2871 (C–H), 1694, 1627 (C=O). ^{1}H-NMR: 1.50–1.78 (*m*, 8 H); 2.06 (*m*, 1 H); 3.09 (*m*, 2 H); 3.20 (*m*, 1 H); 3.31 (*m*, 1 H); 3.59 (*s*, 3 H); 4.49 (br., 2 H); 4.57 (*m*, 1 H); 7.13–7.24 (*m*, 5 H). ^{13}C-NMR: 21.76 (*t*); 21.88 (*t*); 23.55, 23.97 (2*t*, 2 isomers); 27.41, 28.07 (2*t*, 2 isomers); 42.98, 44.36 (2*d*, 2 isomers); 46.97 (*t*); 49.75 (*t*); 51.80, 52.07 (2*q*, 2 isomers); 57.46, 58.06 (2*d*, 2 isomers); 126.94 (*d*); 127.68 (2C, *d*); 128.24 (2C, *d*); 137.17 (*s*); 155.50 (*s*); 170.36, 170.65 (2*s*, 2 isomers). EI-MS: 316 (47, $M^{+\bullet}$), 257 (68), 189 (100), 160 (13), 159 (16), 128 (76), 128 (75), 91 (90), 82 (15). HR-MS: 316.1787 ($C_{18}H_{24}N_2O_3^{+\bullet}$; calc. 316.1787).

N-*Benzylhexahydronicotine* (= *1-Benzyl-3-(1-methylpyrrolidin-2-yl)piperidine*; **7**). A soln. of **6** (0.3 g, 0.95 mmol) in anh. THF (3 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.18 g, 4.72 mmol) in THF (7 ml) under N_2. The mixture was refluxed for 12 h, cooled, and quenched with wet THF, then with H_2O. Addition of 1N NaOH (5 ml) led to a precipitate that was filtered. The filter cake was washed with THF and MeOH (10 ml each), and the org. solns were combined and evaporated. The residue was partitioned between H_2O (15 ml) and CH_2Cl_2 (3 × 10 ml), and usual workup led to **7** (0.24 g).

Hexahydronicotine (= *3-(1-Methylpyrrolidin-2-yl)piperidine;* **8**). Compound **7** (0.24 g) was debenzylated under hydrogenolysis conditions. The crude product was percolated through a SiO_2 column with 40% AcOEt/hexane: **8** (0.14 g).

Nicotyrine (= *3-(1-Methyl-1*H*-pyrrol-2-yl)pyridine;* **9**). A soln. of **7** (0.11 g, 0.33 mmol) in CH_2Cl_2 (2 ml) was added dropwise to Se powder (0.47 g, 5.9 mmol). The solvent was carefully evaporated and the mixture was heated at 250–260° for 30 h under N_2. The mixture was cooled and the residue scratched off from the flask, smashed to a fine powder in a mortar, and extracted with boiling CH_2Cl_2 (20 ml). Filtration and evaporation left a black mass which was chromatographed (SiO_2, 15–30% AcOEt/hexane: **9** (0.02 g , 18%). ^{1}H-NMR: 3.65 (*s*, 3 H); 6.21, 6.27, 6.75 (br., 1 H each); 7.30 (*dm*, *J* = 7.8, 1 H); 7.68 (*dm*, *J* = 7.8, 1 H); 8.50 (*d*, *J* = 3.9, 1 H); 8.66 (br., 1 H). ^{13}C-NMR: 35.02 (*q*); 108.16 (*d*); 109.72 (*d*); 123.18 (*d*); 124.68 (*d*); 129.21 (*s*); 130.72 (*s*); 135.44 (*d*); 147.58 (*d*); 149.12 (*d*). EI-MS: 158 (100, $M^{+\bullet}$), 157 (39), 130 (11).

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