Synthesis of Na-Demethyl-20-Deethylsuaveoline, The Structure Proposed for Sellowiine

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SYNTHESIS OF N_a-DEMETHYL-20-DEETHYLSUAVEOLINE, THE STRUCTURE PROPOSED FOR SELLOWIINE

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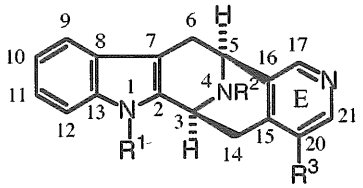
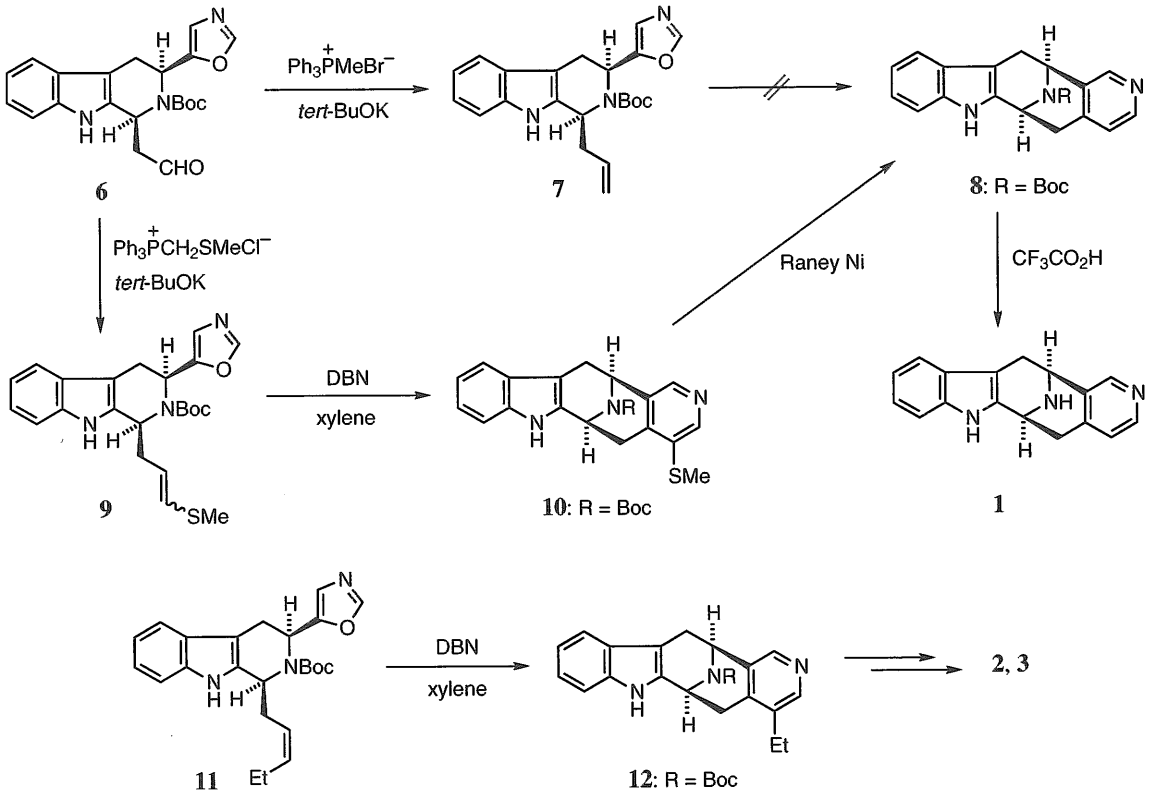
Abstract – A synthesis of N_a-demethyl-20-deethylsuaveoline (**1**), the structure assigned to the *Rauwolfia* alkaloid sellowiine, has been accomplished for the first time through a route using intramolecular oxazole–olefin Diels–Alder reaction. The ^{1}H- and ^{13}C-NMR spectral data and the specific rotation of the synthetic **1** were in disagreement with those reported for a natural sample, leaving the chemistry of this alkaloid incomplete.

In 1996, Batista *et al.* reported the isolation of sellowiine, a macroline-related alkaloid containing a 9-azabicyclo[3.3.1]nonane skeleton fused by two aromatic heterocycles, indole and pyridine rings, from leaves of *Rauwolfia sellowii*.[1] Four additional alkaloids [*i.e.*, suaveoline (**2**),[2] norsuaveoline (**3**),[2g] macrophylline (**4**),[2g,i,3] and macrocaffrine (**5**)[2g,3b]] possessing the skeleton similar to that of sellowiine have been known to occur in various *Rauwolfia* species. The structure of sellowiine was deduced to be N_a-demethyl-20-deethylsuaveoline (**1**) on the basis of comparison of spectral data with those reported for suaveoline (**2**).[1a] Recently, we have achieved the total synthesis of suaveoline (**2**) and norsuaveoline (**3**) *via* a highly stereoselective route starting from L-tryptophan methyl ester and exploiting intramolecular oxazole–olefin Diels–Alder reaction.[4,5] Central feature of the synthetic strategy is that all the suaveoline-related alkaloids (**1**–**5**) containing different substituents at the 20-position would be readily accessible from the oxazole–aldehyde (**6**) postulated as a key intermediate through the introduction of an appropriate olefinic dienophile. In the present paper, we wish to record the first synthesis of N_a-demethyl-20-deethylsuaveoline (**1**), whose structure was proposed for sellowiine, from the aldehyde (**6**).



1: $R^1 = R^2 = R^3 = H$
2: $R^1 = Me$, $R^2 = H$, $R^3 = Et$
3: $R^1 = R^2 = H$, $R^3 = Et$
4: $R^1 = H$, $R^2 = Me$, $R^3 = CH_2CH_2OH$
5: $R^1 = H$, $R^2 = Me$, $R^3 = CH_2OH$

In connection with our previous synthetic studies of **2** and **3**,[4] the oxazole–olefin (**7**) seemed most attractive as a precursor for the synthesis of **1** using intramolecular Diels–Alder reaction. The olefin (**7**) was obtained by the Wittig reaction of the aldehyde (**6**), easily available from L-tryptophan methyl ester,[4] with the ylide derived from methyltriphenylphosphonium bromide and *tert*-BuOK. We have already reported that the intramolecular Diels–Alder reaction of **11** proceeded smoothly in boiling xylene in the presence of DBN, affording the pyridine (**12**) in a good yield.[4] However, we found no evidence for the formation of the pyridine (**8**) on treatment of **7** under these conditions. Thus, the terminal olefin (**7**) proved to be undesirable as a substrate of intramolecular oxazole–olefin Diels–Alder reaction, probably due to rapid decomposition of **7** at elevated temperature.



Therefore, we next selected the oxazole–olefin (**9**) possessing a methylthio group, a readily removable substituent, at the terminal position of the olefinic dienophile as the second candidate. The requisite olefin (**9**) was obtained in 68% yield as a separable 7 : 3 mixture of the (*E*)- and (*Z*)-isomers *via* the Wittig reaction of the aldehyde (**6**) with the ylide generated from methylthiomethyltriphenylphosphonium chloride[6] and *tert*-BuOK. Since (*E*)-**9** and (*Z*)-**9** exhibited a similar behavior with each other on the following intramolecular Diels–Alder reaction in preliminary experiments, the mixture of **9** was used directly in the next reaction. Thus, treatment of **9** in boiling xylene was carried out in the presence of DBN (5 equiv.) for 30 h according to our previous procedure,[4] giving the pentacyclic pyridine (**10**) in 66% yield. The desired pyridine (**8**) unsubstituted at the 20-position was then obtained from **10** in 65% yield by desulfurization of

the methylthio group with Raney Ni in boiling EtOH. Finally, removal of the Boc group in **8** with CF_3CO_2H provided **1** in 98% yield.

Although the UV (MeOH) spectral data for the synthetic **1** were closely similar to those reported[1a] for natural sellowiine, the ^1H- and ^{13}C-NMR ($CDCl_3$) spectral properties and the specific rotations of both samples were not identical. However, it may be seen from Table I that the ^{13}C-NMR spectral data of **1** were mostly analogous to those of suaveoline (**2**)[2h] and norsuaveoline (**3**)[7] except for the carbons on the E ring and the C(14) carbon which resonates at lower field than do the corresponding carbons of **2** and **3** by 3.7 ppm owing to release from the steric shift based on the ethyl group at the 20-position. Therefore, it seems likely that our synthetic sample (**1**) possesses N_a-demethyl-20-deethylsuaveoline structure.

TABLE I. ^{13}C Chemical Shifts of Sellowiine, **1**, Suaveoline (**2**), and Norsuaveoline (**3**) in $CDCl_3$

Carbon	Chemical shift			
	Sellowiine[a)]	**1**	**2**[b)]	**3**[c)]
C(2)	133.3	135.3[d)]	136.3	135.11
C(3)	52.7	45.6[e)]	44.5	45.78
C(5)	47.7	48.2[e)]	48.3	48.40
C(6)	34.7	31.2	31.4	31.92
C(7)	105.3	106.1	105.2	105.99
C(8)	127.1	127.3	126.9	127.32
C(9)	118.1	118.2	118.1	118.21
C(10)	121.9	121.9	119.2	121.99
C(11)	119.7	119.6	121.4	119.67
C(12)	110.9	110.9	108.8	111.02
C(13)	135.9	135.9	137.0	136.06
C(14)	26.6	34.9	31.2	31.15
C(15)	142.6	142.2	139.6	139.91
C(16)	136.0	135.1[d)]	134.5	134.25
C(17)	148.2	148.2	146.2	146.17
C(18)	—	—	13.8	13.90
C(19)	—	—	22.9	22.84
C(20)	124.1	124.2	136.9	137.11
C(21)	147.3	147.3	147.0	147.03
$N(1)CH_3$	—	—	29.4	—

a) Taken from ref. 1a. *b*) Taken from ref. 2h.
c) Taken from ref. 7. Tentative assignments were made for ready comparison with **1**.
d,e) Assignments indicated by a given superscript may be interchanged.

In conclusion, the first synthesis of N_a-demethyl-20-deethylsuaveoline (**1**), proposed for the *Rauwolfia* alkaloid sellowiine, has been achieved *via* the intramolecular Diels–Alder reaction of the oxazole–olefin derivative (**9**). Unfortunately, no sample of the alkaloid, to which structure (**1**) was assigned, was available for detailed and direct comparison with the synthetic **1**, and thus its chemistry is incompletely understood.

EXPERIMENTAL

General Notes. All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Flash chromatography[8] was carried out by using Merck silica gel 60 (No. 9385). Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Shimadzu FTIR-8400 IR spectrophotometer, a Hitachi U-3010 UV spectrophotometer, a JEOL JNM-GSX-500 (^{1}H 500 MHz, ^{13}C 125 MHz) NMR spectrometer, or a JASCO J-820 spectropolarimeter. Chemical shifts are reported in δ values relative to internal Me_4Si. Optical rotations were measured with a Horiba SEPA-300 polarimeter using a 1-dm sample tube.

(1*S*,3*S*)-2-*tert*-Butoxycarbonyl-3-(5-oxazolyl)-1-(2-propenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (7). A stirred mixture of methyltriphenylphosphonium bromide (646 mg, 1.8 mmol), *tert*-BuOK (226 mg, 2.0 mmol), and benzene (4 mL) was heated under reflux in an atmosphere of N_2 for 1 h. After cooling, a solution of the aldehyde (**6**) (137 mg, 0.36 mmol) in benzene (2 mL) was added. The mixture was then stirred at rt for 30 min and partitioned between ether and H_2O. The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellow oil. Purification by flash chromatography [AcOEt–hexane (1 : 3, v/v)] provided **7** (70 mg, 51%) as a slightly yellowish foam, MS *m/z*: 379 (M^+); ^{1}H-NMR ($CDCl_3$) δ: 1.57 (9H, s, CMe_3), 1.66 and 2.32 [1H each, br, C(1)CH_2], 3.25 (1H, ddd, *J* = 15, 6.5, 2 Hz) and 3.29 [1H, d, *J* = 15 Hz, C(4)H_2], 5.09 (1H, d, *J* = 17 Hz) and 5.19 (1H, d, *J* = 10 Hz, CH=C$\underline{H}_2$), 5.18, 5.97, and 6.10 [3H, br each, C(1)H, C(3)H, and C$\underline{H}$=CH_2], 6.60 [1H, s, C(4')H], 7.14 and 7.19 [1H each, dd, *J* = 8, 7.5 Hz, C(6)H and C(7)H], 7.30 and 7.55 [1H each, d, *J* = 8 Hz, C(5)H and C(8)H], 7.76 [1H, s, C(2')H], 7.97 (1H, br, NH).[9]

(1*S*,3*S*)-2-*tert*-Butoxycarbonyl-1-(3-methylthio-2-propenyl)-3-(5-oxazolyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (9). A mixture of methylthiomethyltriphenylphosphonium chloride[6] (636 mg, 1.8 mmol) and *tert*-BuOK (183 mg, 1.6 mmol) was stirred in benzene (5 mL) at rt in an atmosphere of N_2 for 20 min. After a solution of the aldehyde (**6**) (123 mg, 0.32 mmol) in benzene (2 mL) was added, stirring was continued for a further 20 min. The reaction mixture was then partitioned between ether and H_2O. The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellowish oil, which was purified by flash chromatography [AcOEt–hexane (1 : 2, v/v)] to give **9** (93 mg, 68%) as a yellow foam, MS *m/z*: 425 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 1686 (carbamate CO); ^{1}H-NMR ($CDCl_3$) δ: 1.57 (9H, s, CMe_3), 1.78 and 2.27 [1H each, br, C(1)CH_2], 2.22 (9/10H) and 2.27 (21/10H) (s each, SMe), 3.24 (1H, dd, *J* = 15, 6 Hz) and 3.28 [1H, d, *J* = 15 Hz, C(4)H_2], 5.11 (br), 5.20 (br), 5.52 (m), 5.55 (br), 5.95 (br), and 6.11 (br) [3H, C(1)H, C(3)H, and C$\underline{H}$=CHSMe], 5.97 (7/10H, d, *J* = 14.5 Hz) and 6.06 (3/10H, d, *J* = 9.5 Hz, CH=C$\underline{H}$SMe), 6.61 [1H, s, C(4')H], 7.14 and 7.19 [1H each, dd, *J* = 8, 7.5 Hz, C(6)H and C(7)H], 7.31 (3/10H), 7.32 (7/10H), and 7.55 (1H) [d each, *J* = 8 Hz, C(5)H and C(8)H], 7.756 (3/10H) and 7.760 (7/10H) [s each, C(2')H], 7.91 (7/10H) and 8.04 (3/10H) (br each, NH);[9] HRMS *m/z* calcd for $C_{23}H_{27}N_3O_3S$: 425.1773, found: 425.1763. The ^{1}H-NMR spectrum of this sample indicated that it was a

7 : 3 mixture of (*E*)-**9** and (*Z*)-**9**.

***N*$_b$-*tert*-Butoxycarbonyl-20-methylthio-*N*$_a$-demethyl-20-deethylsuaveoline (10).** A stirred mixture of **9** (203 mg, 0.48 mmol), DBN (306 mg, 2.5 mmol), and xylene (10 mL) was heated under reflux in an atmosphere of Ar for 30 h. After cooling, the reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography [AcOEt–hexane (1 : 2, then 2 : 1, v/v)] to afford **10** (129 mg, 66%) as a slightly yellow solid, mp 226–227 °C (decomp); $[\alpha]_D^{25}$ +58.9° (*c* 0.50, $CHCl_3$); MS *m/z*: 407 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1690 (carbamate CO); ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H) and 1.50 (6H) (s each, CMe_3), 2.44 (3H, s, SMe), 2.86 [1H, d, *J* = 15.5 Hz, C(6)H], 2.96 (1/3H) and 2.99 (2/3H) [d each, *J* = 17.5 Hz, C(14)H], 3.10 (1/3H) and 3.16 (2/3H) [dd each, *J* = 17.5, 5.5 Hz, C(14)H], 3.44 (2/3H) and 3.48 (1/3H) [dd each, *J* = 15.5, 5.5 Hz, C(6)H], 5.58 (2/3H) and 5.60 (1/3H) [d each, *J* = 5.5 Hz, C(3)H], 5.76 (1/3H) and 5.79 (2/3H) [d each, *J* = 5.5 Hz, C(5)H], 7.05 (2/3H), 7.06 (1/3H), 7.12 (2/3H), and 7.13 (1/3H) [dd each, *J* = 8, 7.5 Hz, C(10)H and C(11)H], 7.28 (1H), 7.37 (2/3H), and 7.39 (1/3H) [d each, *J* = 8 Hz, C(9)H and C(12)H], 7.98 (1/3H) and 8.13 (2/3H) [br each, N(1)H], 8.15 (1/3H) and 8.16 (2/3H) [s each, C(21)H], 8.33 [1H, s, C(17)H]; HRMS *m/z* calcd for $C_{23}H_{25}N_3O_2S$: 407.1667, found: 407.1672.

***N*$_b$-*tert*-Butoxycarbonyl-*N*$_a$-demethyl-20-deethylsuaveoline (8).** A mixture of **10** (129 mg, 0.32 mmol), Raney Ni (1.2 g), and EtOH (5 mL) was heated under reflux for 8 h. The catalyst was filtered off and washed with EtOH. The filtrate and washings were combined and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by flash chromatography [AcOEt–hexane (2 : 1, v/v)] provided **8** (74 mg, 65%) as a colorless foam, $[\alpha]_D^{26}$ –46.0° (*c* 0.30, $CHCl_3$); MS *m/z*: 361 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1686 (carbamate CO); ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H) and 1.51 (6H) (s each, CMe_3), 2.85 [1H, d, *J* = 15.5 Hz, C(6)H], 2.88 (1/3H) and 2.92 (2/3H) [d each, *J* = 17 Hz, C(14)H], 3.35–3.50 [2H, m, C(6)H and C(14)H], 5.56 (1/3H) and 5.60 (2/3H) [d each, *J* = 5 Hz, C(3)H], 5.75 (2/3H) and 5.78 (1/3H) [d each, *J* = 5.5 Hz, C(5)H], 6.89 (1/3H) and 6.93 (2/3H) [d each, *J* = 5 Hz, C(20)H], 7.04 (2/3H), 7.06 (1/3H), 7.11 (2/3H), and 7.13 (1/3H) [dd each, *J* = 8, 7.5 Hz, C(10)H and C(11)H], 7.27 (1H), 7.36 (2/3H), and 7.39 (1/3H) [d each, *J* = 8 Hz, C(9)H and C(12)H], 7.99 (1/3H) and 8.19 (2/3H) [br each, N(1)H], 8.25 (1/3H) and 8.26 (2/3H) [d each, *J* = 5 Hz, C(21)H], 8.51 [1H, s, C(17)H]; HRMS *m/z* calcd for $C_{22}H_{23}N_3O_2$: 361.1790, found: 361.1789.

***N*$_a$-Demethyl-20-deethylsuaveoline (1).** A mixture of **8** (23 mg, 0.064 mmol) and CF_3CO_2H (0.3 mL) in CH_2Cl_2 (1 mL) was stirred at 0 °C for 5 h. The reaction mixture was then poured into cold 10% aqueous Na_2CO_3 (5 mL) and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated *in vacuo*. Purification of the residue by flash chromatography [$CHCl_3$–MeOH (10 : 1, then 5 : 1, v/v)] gave **1** (16.3 mg, 98%) as a colorless solid, mp *ca.* 200 °C; $[\alpha]_D^{22}$ –63.9° (*c* 0.87, $CHCl_3$); MS *m/z* (relative intensity): 262 (25), 261 (M^+, 100), 260 (46), 245 (19), 244 (44), 243 (33), 233 (21), 232 (20), 169 (56), 131 (19), 130 (24); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470, 3170 (NH); UV λ_{max}^{MeOH} nm (ε): 221 (26000), 267.5

(7100), 281.5 (6900), 290 (5300); CD (c 1.40×10^{-4} M, MeOH) $[\theta]^{25}$ (nm): +13600 (295) (pos. max.), +11000 (291) (neg. max.), +14500 (288) (pos. max.), –7500 (269) (neg. max.), –1500 (258) (pos. max.), –5300 (247) (neg. max.), –3500 (240) (pos. max.), –88400 (224) (neg. max.); ^{1}H-NMR ($CDCl_3$) δ: 2.856 [1H, d, J = 17 Hz, C(14)H], 2.862 [1H, d, J = 15.5 Hz, C(6)H], 3.35 [1H, dd, J = 15.5, 5.5 Hz, C(6)H], 3.40 [1H, dd, J = 17, 5.5 Hz, C(14)H], 4.55 [1H, d, J = 5.5 Hz, C(3)H], 4.69 [1H, d, J = 5.5 Hz, C(5)H], 6.89 [1H, d, J = 5 Hz, C(20)H], 7.05 and 7.12 [1H each, dd, J = 8, 7.5 Hz, C(10)H and C(11)H], 7.28 and 7.39 [1H each, d, J = 8 Hz, C(9)H and C(12)H], 7.95 [1H, br, N(1)H], 8.24 [1H, d, J = 5 Hz, C(21)H], 8.46 [1H, s, C(17)H]; ^{13}C-NMR (Table I); HRMS m/z calcd for $C_{17}H_{15}N_3$: 261.1266, found: 261.1261.

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