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Structure Elucidation of a New Aconite Alkaloid, 15-α-Hydroxyneoline

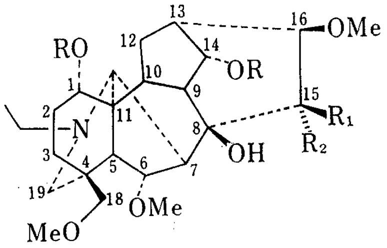
A new diterpene alkaloid was isolated from the root of an aconitum species collected at Mt. Mineoka (Chiba Pref.). The structure of this new base was deduced to be 15-α-hydroxyneoline from the spectroscopic studies and was established by the chemical modification of neoline.

Keywords——Aconitum sp.; diterpenoid alkaloids; noline; 15-α-hydroxyneoline; 15-β-hydroxyneoline; isolation; structure elucidation; ^{13}C-NMR

We have investigated the alkaloidal constituents of the root of an Aconitum species collected at Mt. Mineoka in the southern part of the Boso Peninsula (Chiba Pref.) in May, 1977.

In this communication, we report the structural elucidation of a new diterpene alkaloid, 15-α-hydroxyneoline (1),[1] isolated along with eight known alkaloids: mesoaconitine, hypaconitine, deoxyaconitine, 14-acetyltalatizamine,[2] isotalatizidine, neoline, takaosamine[2] and ignavine from the above plant.

The new base (1) (prisms, $C_{24}H_{39}NO_7$) showed following properties: mp 206.5—207°C (from AcOEt); MS *m/z* (%): 453 (M^+, 24), 436 (M^+–OH, 100); $[\alpha]_D^{22.5}$ +19.3° ($CHCl_3$). The 100 MHz ^{1}H-NMR spectrum of (1) in $CDCl_3$ exhibited signals at δ: 1.11 (3H, t, J=7 Hz, N–$CH_2C\underline{H}_3$), 3.33, 3.36 and 3.45 (each 3H, s, OCH_3), 4.12 (2H, m, C-6-H, C-14-H), 4.40 (1H, d, J=7 Hz, C-15-β-H), and 7.60 (1H, broad, disappeared on addition of D_2O, C-1-α-OH). Acetylation of (1) with Ac_2O–pyridine afforded triacetate (3) [amorphous, M^+ *m/z*; 579, ^{1}H-NMR δ: 203, 205, 2.20 (each 3H, s, $OCOCH_3$), 4.70 (1H, t, J=4.5 Hz, C-14-β-H), 4.83 (1H, dd, J_1=6 Hz, J_2=10 Hz, C-1-β-H) and 5.11 (1H, d, J=6 Hz, C-15-β-H)].



1: R=H, R₁=H, R₂=OH 15-α-hydroxyneoline
3: R=Ac, R₁=H, R₂=OAc
6: R=Ac, R₁=OH, R₂=H
8: R=H, R₁=OH, R₂=H 15-β-hydroxyneoline

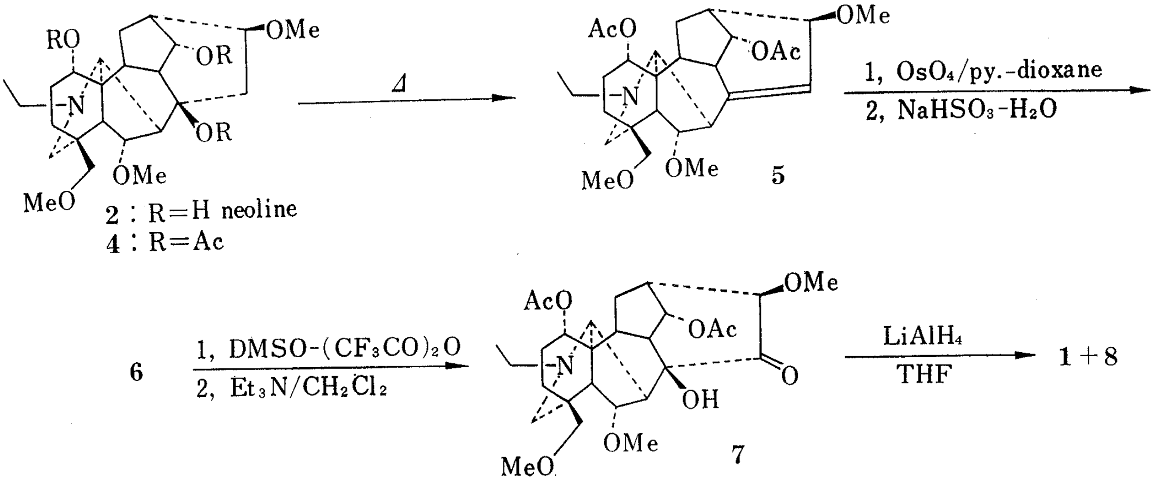


Chart 1

Table I. ^{13}C-NMR Spectra of Neoline (**2**), 15-α-Hydroxyneoline (**1**) and 15-β-Hydroxyneoline (**8**)[a]

Carbon	**2**	**1**	**8**
C-1	72.3	72.1	72.1
C-2	29.5[b]	29.5[b]	29.3[b]
C-3	29.9[b]	30.1[b]	29.9[b]
C-4	38.2	38.1	38.1
C-5	44.9	44.1	44.1
C-6	83.3	84.3	83.4
C-7	52.3	46.6	52.9
C-8	74.3	79.0	74.6
C-9	48.3	48.5	48.0
C-10	40.7	40.7	42.4
C-11	49.6	49.4	49.5
C-12	29.8[b]	30.7[b]	30.7[b]
C-13	44.3	43.6	44.1
C-14	75.9	75.7	74.7
C-15	42.7	79.0	68.1
C-16	82.3	90.4	84.0
C-17	63.6	62.6	61.9
C-18	80.3	80.1	80.1
C-19	57.2	56.7	56.9
N-CH_2	48.2	48.5	48.2
CH_3	13.0	13.1	13.0
OCH_3 6′	57.8	57.5	57.9
OCH_3 16′	56.3	58.0	58.0
OCH_3 18′	59.1	59.1	59.2

a) In ppm downfield to TMS; in $CDCl_3$.
b) Assignments bearing the same superscript may be interchanged.

The presence of the hydroxy group at C-15 in (**1**) was deduced from the observed significant downfield shift of the C-15 (36.3 ppm) signal relative to the corresponding resonance of neoline (**2**)[3] in the ^{13}C-NMR spectra (Table I). Thus 5.7 ppm upfield shift of the C-7 signal compared with the corresponding frequency of (**2**) can be explained in terms of the release from 1,3-diaxial hydrogen-hydrogen interaction[4] between C-7-H and C-15-α-H.

The following is the conversion of a known alkaloid, neoline (**2**)[5] to the new base for the structural proof of (**1**). Triacetylneoline (**4**), obtainable from (**2**), was converted, through pyrolysis under reduced pressure (200°/2 mmHg, 10 min), to C_8–C_{15} olefinic compound (**5**)[6] [mp 170—172°, M^+ m/z; 503, NMR δ 5.46 (1H, d, $J=7$ Hz, C-15-H)] in 95% yield. Compound (**5**) was treated successively with OsO_4 in pyridine-dioxane and with $NaHSO_3$–H_2O affording cis diol (**6**) [amorphous, M^+ m/z; 537, NMR δ 4.00 (1H, d, $J=8$ Hz)] in 62% yield (after purification by Al_2O_3 column chromatography).

Inversion of the C-15 configuration of cis diol (**6**) was accomplished by carrying out oxidation according to the Swern's method[7] [DMSO-$(CF_3CO)_2O/CH_2Cl_2$ and then Et_3N] and reduction of the resultant ketone (**7**) with $LiAlH_4$ in THF at 0°C, giving rise to the desired triol (**1**) and its isomer (**8**) [mp 175—177°C, $[\alpha]_D^{19}$ $+24.7°$] in 64% and 26% yields, respectively. Direct comparison of synthetic 15-α-hydroxyneoline with the new base (**1**) established the identity in all respects.

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References and Notes

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Synthesis of a Heptacosapeptide Amide corresponding to the Entire Amino Acid Sequence of Chicken Gastrin Releasing Peptide (GRP)[1]

The heptacosapeptide amide corresponding to the entire amino acid sequence of chicken gastrin releasing peptide was synthesized using a new amide forming reagent, 3-acyl-thiazolidine-2-thione, and a new deprotecting system, 1 M trifluoromethanesulfonic acid (TFMSA)-thioanisole in TFA.

Keywords——total synthesis of chicken gastrin releasing peptide; trifluoromethanesulfonic acid-thioanisole deprotection; a new amide forming reagent; 3-acyl-thiazolidine-2-thione; side reaction at the Trp residue; Curtius rearrangement in an azide condensation reaction

Succeeding to the structural elucidation of porcine GRP,[2] McDonald *et al.*, characterized the similar heptacosapeptide with similar bombesin-like activity from chicken intestine.[3] Within this molecule, nine amino acids differ from those of porcine GRP. However its C-terminal tridecapeptide portion is identical with that of porcine origin except for one amino acid residue at position 19 (Figure).

Following to the synthesis of porcine GRP,[4] we wish to report the synthesis of this newly found GRP from chicken origin. The method we employed for the present synthesis is essentially the same as employed for the former synthesis of porcine GRP. Amino acid derivatives bearing protecting groups removable by 1 M TFMSA-thioanisole[5] was employed; *i.e.*, Lys(Z), Arg(Mts)[6] and Ser(Bzl). The Met residue was protected as its sulfoxide.[7]

Of seven peptide fragments, three fragments, (1), (2) and (4), are identical with those employed for our previous synthesis of porcine GRP. The other four fragments were newly