

STRUCTURE OF EZOCHASMANINE, EZOCHASMACONITINE, ANISOEZOCHASMACONITINE AND
SYNTHESIS OF VILMORRIANINE A

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Abstract--- The structures of new diterpene alkaloids, ezochasmanine, ezo-
chasmaconitine, and anisozechasmaconitine, have been established as 3-hydroxy-
chasmanine, 14-acetyl-8-benzoylchasmanine, and 14-acetyl-8-anisoylchasmanine
respectively, in correlation with a known alkaloid chasmanine.

Vilmorrianine A (8-acetyl-14-anisoylzechasmanine) was synthesized from
ezochasmanine via benzylation, trichloroethoxycarbonylation, acetylation and
elimination reaction of trichloroethoxycarbonyl group.

Three new minor diterpene alkaloids ezochasmanine 1, ezo-chasmaconitine 2, and
anisozechasmaconitine 3, together with major alkaloids pseudokobusine 4, chasma-
nine 5 and jesaconitine 6 were isolated from Aconitum yesoense Nakai.¹⁾

We describe the structural elucidation of these minor bases 1, 2, 3, and a
synthesis of vilmorrianine A which was isolated from Aconitum vilmorrianum Kom.
and the structure of which was postulated by Yang Tsung-ren et al. in China.²⁾

Ezochasmanine 1 showed following properties; mp 115-118° (ether), $C_{25}H_{41}N O_7 \cdot \frac{1}{3} H_2O$, m/e 467 M^+ , $[\alpha]_D^{21} = +40.3$ (CHCl₃). The 100 MHz 1H -NMR spectrum of 1 in
CDCl₃ exhibited the signals due to one triplet proton on secondary alcoholic car-
bon-14³⁾ (δ 4.10 t. J=5 Hz), four methoxyl groups (3H, s. 3.33, 3.21, 6H, s. 3.31)
and a N-ethyl group (3H, t. 1.08, J=7 Hz, N-CH₂CH₃). Comparison of ^{13}C -NMR spec-
tral data of 1 with that of 5⁴⁾ (Table) clearly revealed the site of additional
hydroxy group in the former compound to chasmanine 5. The presence of a hydroxyl
group at C-3 in 1 was detected by observing the downfield shift of the C-3 (37ppm)
resonance in comparison with 5. The observed upfield shift of the signal due to
C-19 of 1 by 6.6 ppm comparing the corresponding carbon shift of chasmanine 5⁴⁾
can be ascribed to the deletion of 1,3-diaxial hydrogen-hydrogen interaction⁵⁾

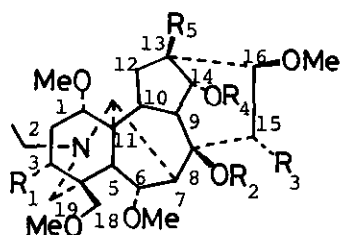
Table ^{13}C -NMR Spectra of Chasmanine 5⁴⁾ and Ezochasmanine 1 (δ_{C} , ppm; CDCl_3)

Carbon atom	<u>5</u>	<u>1</u>	Carbon atom	<u>5</u>	<u>1</u>
C-1	86.1	83.2	C-14	75.5	75.5
C-2	26.0	33.9	C-15	39.2	39.1
C-3	35.2	72.2	C-16	82.2 ^{a)}	82.0 ^{b)}
C-4	39.5	43.5	C-17	62.4	62.2
C-5	48.8	48.5	C-18	80.8	77.4
C-6	82.5 ^{a)}	82.2 ^{b)}	C-19	54.0	47.4
C-7	52.8	52.4	N-CH ₂	49.3	49.1
C-8	72.6	72.5	CH ₃	13.6	13.7
C-9	50.3	48.8	OCH ₃ 1'	56.3	56.4
C-10	38.4	38.1	6'	57.2	57.3
C-11	50.4	50.2	16'	55.9	56.0
C-12	28.6	28.1	18'	59.2	59.2
C-13	45.7	45.3			

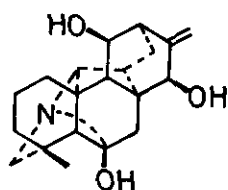
a - b) Assignments bearing the same superscript may be interchanged.

between C-3-H and C-19-H and thus the presence of C-3- α -hydroxyl group in 1 was demonstrated. Acetylation of 1 was carried out in Ac_2O with pyridine at 3° for over night to yield the mono acetate 7, ($\text{C}_{27}\text{H}_{43}\text{N O}_8$ m/e 509 M^+ , mp $58-62^\circ$, hygroscopic) and the diacetate 8, ($\text{C}_{29}\text{H}_{45}\text{N O}_9$ m/e 551 M^+ , amorphous). More vigorous acetylation using Ac_2O , p-TsOH at $80-90^\circ$, however, afforded the triacetate 9, ($\text{C}_{31}\text{H}_{47}\text{N O}_{10}$ m/e 593 M^+ , mp $221-224^\circ$). Additional evidence regarding the stereochemistry of α -hydroxyl group at C-3 can be obtained from ^1H -NMR of mono acetate 7.

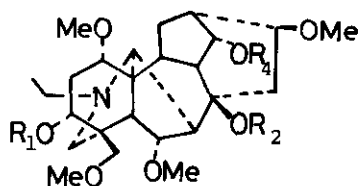
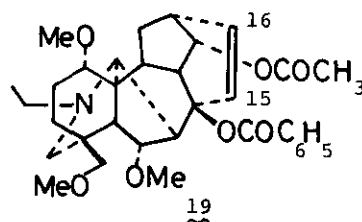
The signals at 4.88ppm (d.d., $J_1 = 6$, $J_2 = 10\text{Hz}$) revealed an axial conformation of β -hydrogen group at C-3. The above observations lend credence to structure 1 for ezochasmanine. Chasmanine 5 can be visually derived from ezochasmanine 1 by elimination of the 3- α -hydroxyl group. The following is the transformation of ezochasmanine 1 to chasmanine 5 for the structural proof of 1. Mono benzylation of 1 using 1.7 equivalents of benzoyl chloride in pyridine at -18° for 2hr resulted in formation of unexpected 14-benzylezochasmanine 10 ($\text{C}_{32}\text{H}_{45}\text{N O}_8$ m/e 571 M^+ , amorphous, δ 5.11, 1H, t, $J = 5\text{Hz}$, C-14-H) in 68% yield. For protecting the 3-hydroxyl group, using a large excess of the β -trichloroethoxycarbonylchloride⁶⁾ in pyridine, 10 could be converted in 83% yield to the derivative 11 ($\text{C}_{35}\text{H}_{46}\text{N O}_{10}\text{Cl}_3$ m/e 745 M^+ , 747 $\text{M}^+ + 2$, amorphous). The remained tertiary hydroxyl group was acetylated with Ac_2O and p-TsOH at $85-92^\circ$ for 2hr. The resulting triacyl derivative 12 was treated with Zn powder in HOAc at room temperature (5hr) to remove the protecting group at 3-position. The final product is 8-acetyl-14-benzylezochasmanine 13 [prism, mp $113-114^\circ$ (AcOEt-hexane), toxic, $\text{C}_{34}\text{H}_{47}\text{N O}_9$ m/e (%) 613 M^+ (3), 582 $\text{M}^+ - \text{OCH}_3$ (62), 553 $\text{M}^+ - \text{HOAc}$ (56), 105 (100), δ 5.02 (1H, t, $J = 5\text{Hz}$, C-14- β -H), 1.36 (3H,



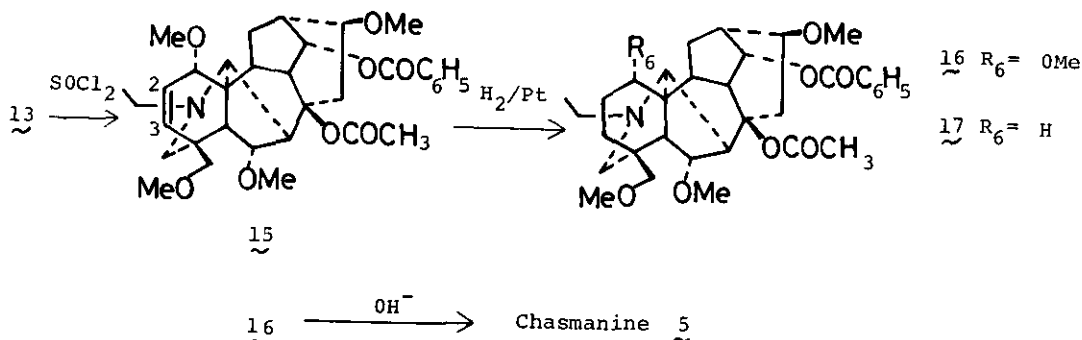
- 1 $R_1 = OH, R_2 = R_3 = R_4 = R_5 = H$ Ezochasmanine
2 $R_1 = H, R_2 = -COC_6H_5, R_3 = R_5 = H, R_4 = -COCH_3$
Ezochasmaconitine
3 $R_1 = H, R_2 = -COC_6H_4OMe(p), R_3 = R_5 = H, R_4 = -COCH_3$
Anisoezochasmaconitine
5 $R_1 = R_2 = R_3 = R_4 = R_5 = H$ Chasmanine
6 $R_1 = R_3 = R_5 = OH, R_2 = -COCH_3, R_4 = -COC_6H_4OMe(p)$
Jesaconitine
18 $R_1 = R_2 = R_3 = R_5 = H, R_4 = -COCH_3$



4 Pseudokobusine



- 7 $R_1 = -COCH_3, R_2 = R_4 = H$
8 $R_1 = R_4 = -COCH_3, R_2 = H$
9 $R_1 = R_2 = R_4 = -COCH_3$
10 $R_1 = R_2 = H, R_4 = -COC_6H_5$
11 $R_1 = -COOCH_2CCl_3, R_2 = H, R_4 = -COC_6H_5$
12 $R_1 = -COOCH_2CCl_3, R_2 = -COCH_3, R_4 = -COC_6H_5$
13 $R_1 = H, R_2 = -COCH_3, R_4 = -COC_6H_5$
14 $R_1 = H, R_2 = -COCH_3, R_4 = -COC_6H_4OMe(p)$
Vilmorrianine A



s. $-OOCCH_3$). 8-Acetyl-14-anisoylchasmaconine 14 [prism, mp 169° (AcOEt-hexane), toxic, CD (MeOH) $\Delta\epsilon$ (nm); $+1.9(256)$, $+3.9(216)$, $[\alpha]_D^{25} = +24.1$ (CHCl₃)] was obtained by the same method. Alkaloid 14 and vilmorrianine A were identified by comparison of mixed melting point, IR and CD spectra. Refluxing of 8-acetyl-14-benzoylchasmaconine 13 (= 13,15-dideoxyaconitine) in excess thionyl chloride⁷⁾ gave the dehydrated product 15 [$\Delta^{2,3}$ -3,13,15-trideoxyaconitine, amorphous, C₃₄H₄₅N O₈ m/e 595 M⁺, δ 6.04 (1H, d.d. J₁ = 10, J₂ = 4Hz, C-2-H), 5.79 (1H, d. J = 10Hz, C-3-H)] in 71% yield after the purification by Al₂O₃ column chromatography. After catalytic reduction using PtO₂ as catalyst, followed by separation using preparative tlc (Et₂O -saturated 25% aq-NH₄OH), 13 gave rise to two reduced products 16 [in 59% yield, mp $148.5-151^\circ$, CD(MeOH) $\Delta\epsilon$ (nm) $+0.9(272)$, $+6.4(228)$] and 17 [in 25% yield, mp $174-178^\circ$, C₃₃H₄₅N O₈ m/e 567.3198 M⁺]. ¹H-NMR spectrum of the latter compound 17 showed signals of three OCH₃ (3,35, 3.28, 3.17 each 3H, s.), one acetyl group (1.41 3H, s.) and C-14-H (5.06 1H, t. J = 4.5Hz). From above observations, the structure 17 (1-demethoxy-3,13,15-trideoxyaconitine⁷⁾) was ascribed to the latter reduced compound. The first reduced compound 16 was found identical with known 8-acetyl-14-benzoylchasmaconine⁸⁾ by comparison of mixture melting point, IR, CD and ¹H-NMR spectra. Finally, 16 was hydrolyzed in alkaline solution to form chasmaconine 5.

Ezochasmaconitine 2 showed following properties; mp $163-165^\circ$ prism (acetone), C₃₄H₄₇N O₈ m/e 597 M⁺, CD(MeOH) $\Delta\epsilon$ (nm) $+1.2(235)$, $+1.1(210)$. The 100 MHz ¹H-NMR spectrum of 2 in CDCl₃ exhibited several signals due to five aromatic protons (7.45-8.00), four methoxyl groups 2.94(3H,s.), 3.24(6H,s.), 3.32(3H,s.) and one acetyl group 1.76(3H,s.) and one proton (4.82 t. J = 4.5Hz) arising on acetylated secondary alcoholic carbon at C-14. On the basis of these data, we assumed a structure of 8-benzoyl-14-acetylchasmaconine 2 for ezochasmaconitine. Then derivation of 5 to 2 was carried out as follows. Acetylation of 5 by use of F₃CCOOH and HOAc provided 14-acetylchasmaconine 18 [amorphous, C₂₇H₄₃N O₇ m/e 493 M⁺, δ 4.79 (1H, t. J = 5Hz, C-14-H), 2.02 (3H,s. C-14-OCOCH₃)] in 63% yield. Treatment of 18 with benzoic acid anhydride (10 eq.) in the presence of p-TsOH·H₂O (1eq.) in boiling toluene for 12hr gave the 8-benzoyl-14-acetylchasmaconine 2 [mp 166° , m/e 597 M⁺, $[\alpha]_D^{19} = +26.1$ (CHCl₃)] in 20% yield and 8-benzoyl-14-acetyl- $\Delta^{15,16}$ -16-demethoxychasmaconine 19 [mp $147.5-149^\circ$, C₃₃H₄₃N O₇ m/e 565 M⁺, C-16-olefinic proton (6.06, 1H, d.d. J₁ = 7, J₂ = 10Hz), C-15-olefinic proton (6.67, 1H, d. J = 10Hz)] in 39% yield

after the purification by preparative tlc. Identity of ezochasmanine and the synthetic alkaloid 2 was established by comparison of mixture melting point, IR, $^1\text{H-NMR}$ and CD spectra.

Anisoezochasmaconitine 3 showed following properties; mp 136-138.5° (ether), $\text{C}_{35}\text{H}_{49}\text{N O}_9$ m/e 627 M^+ , $\text{CD}(\text{MeOH})\Delta\epsilon(\text{nm}) +0.95(256), +3.5(213)$, $\text{UV}\lambda_{\text{max}}^{\text{EtOH}} 259\text{nm}$.

The 100 MHz $^1\text{H-NMR}$ spectrum of 3 in CDCl_3 showed the signals arising from p-anisoyl group [δ 7.93 (2H, d, $J=9\text{Hz}$), 6.86 (2H, d, $J=9\text{Hz}$) aromatic protons, 3.84 (3H, s, OCH_3)] and the signals of C-14-H (4.80, 1H, t, $J=4.5\text{Hz}$), C-14- OCOCCH_3 (1.78, 3H, s.)]. 8-Anisoyl-14-acetylchasmanine {mp 140° (ether), m/e 627 M^+ , $[\alpha]_{\text{D}}^{18} = +14.1$ (CHCl_3), $\text{UV}\lambda_{\text{max}}^{\text{EtOH}} 259\text{nm}$ ($\log\epsilon = 4.29$)} was synthesized from chasmanine 5 (in 33% over all yield) under the same manner described above and identified with the natural anisoezochasmaconitine 3 by comparison of mixture melting point and other physical data of them. Ezochasmaconitine 2 and anisoezochasmaconitine 3 are the first examples of the diterpene alkaloids possessing the aroyl groups at C-8 and acetyl group at C-14. All of the formerly known congeners have the aroyl groups at C-14 and acetyl group at C-8. Mild toxicity was observed for the two new bases, 2 and 3.

Structure of chasmanine 5 was confirmed by X-ray crystallographic study⁹⁾ of the 14-benzoylchasmanine hydrochloride salt and total synthesis¹⁰⁾, and therefore, structures of the titled alkaloids were also established by correlation with 5.

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REFERENCES

1. S.Sakai et al., Presented in part at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980. Abstracts, p 224.
2. Yang Tsung-ren, Hao Xiao-jiang, Chow Jun; Acta Botanica Yunnanica 1 41 (1979).
3. S.W.Pelletier, Z.Djarmati, S.Lajsic, W.H.Decamp; J.Am.Chem.Soc. 98 2617(1976)
4. S.W.Pelletier, Z.Djarmati; J.Am.Chem.Soc., 98 2626 (1976).
5. H.Beierbeck, J.K.Saunders; Can.J.Chem., 54 2985 (1976).
6. T.B.Windholz, D.B.R.Johnston; Tetrahedron Letters; 2555 (1967).
7. R.E.Gilman, L.Marion; Can.J.Chem. 40 1713 (1962).
R.E.Gilman, L.Marion; Tetrahedron Letters; 923 (1962).
Y.Tsuda, L.Marion; Can.J.Chem. 41 3055 (1963).
8. O.Achmatowicz.Jr., Y.Tsuda, L.Marion, T.Okamoto, N.Natsume, H.Chang, K.Kajima; Can.J.Chem. 43 825 (1965).
9. S.W.Pelletier, W.H.DeCamp, Z.Djarmati; J.Chem.Soc., Chem.Comm., 253 (1976).
- 10.T.Y.R.Tsai, C.S.J.Tsai, W.W.Sy, M.N.Shanbhag, W.C.Liu, S.F.Lee, K.Wiesner; Heterocycles, 7 217 (1977).
K.Wiesner, T.Y.R.Tsai, K.P.Nambiar; Can.J.Chem., 56 1451 (1978).

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