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THE STRUCTURE OF THE NEW DITERPENE ALKALOID NOMININE AND THE ABSOLUTE CONFIGURATION OF KOBUSINE

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The structure of nominine (II), a minor diterpene alkaloid isolated from *Aconitum sanyoense* Nakai (native of Nomi, Kyoto prefecture) was established as 11-deoxykobusine by chemical transformation of kobusine (Ia); their absolute configurations have been established from CD spectral studies.

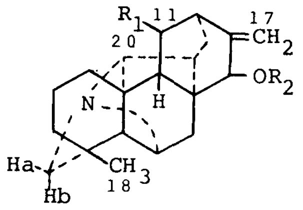
KEYWORDS —— diterpene alkaloid; *Aconitum sanyoense* Nakai; *Ranunculaceae*; nominine; kobusine; spiradine A; Wolff-Kishner reduction; unusual rearrangement; X-ray analysis; CD spectrum; chemical transformation; absolute configuration

Nomi-base I, $C_{20}H_{27}NO$, was isolated as a minor base of *Aconitum sanyoense* Nakai collected at Nomi, Sakyo-ku, Kyoto prefecture.1) This base is the most simple heptacyclic diterpene alkaloid, which we have named nominine.

Nominine has the following spectral data : IR 3130 cm^{-1} (OH, in KBr), NMR ($CDCl_3$) δ^{400MHz}_{ppm} 4.93, 4.95 (each, 1H, s, $=CH_2$), 3.99 (1H, s, C_{15}-H), 3.21 (1H, br s, C_6-H), 2.50 (1H, d, J= 12Hz, C_{19}-Hb), 2.49 (1H, s, C_{20}-H), 2.37 (1H, d, J= 12Hz, C_{19}-Ha), 0.97 (3H, s, C_{18}-H_3), Mass m/z (%), 297 (M^+, 100), 282 (11), 146 (21). We can easily postulate the structure (II) (11-deoxykobusine) to nominine from the above spectral data. Now, we report the conversion of kobusine (Ia) to nominine (II), the structure of the former being already established from the X-ray analysis of its methiodide.2) However, the absolute configuration indicated for (Ia) is based on analogy with the other atisine type diterpene alkaloids. We have revealed the correct absolute configuration of kobusine as in (Ia) on the basis of the CD spectra of 11-dehydrokobusine (If).

Kobusine (Ia) has two secondary hydroxy groups at C-11 and C-15. It can be assumed that there is a larger steric hindrance at the β-OH group on C-15 than the β-OH group on C-11, since 1,3 diaxial nonbonding interactions exist between the H and OH groups on C-9 and C-15.

Benzoylation (1.2 eq mol. PhCOCl and pyridine, -40°C – r.t.) gave three benzoylkobusine derivatives: 11,15-dibenzoylkobusine [amorphous, m/z; 521 (M^+), δ 5.77 (1H, s, C_{15}-H), 5.44 (1H, d, J= 5Hz, C_{11}-H), in 12% yield], 11-benzoylkobusine [mp 214-215°C, $C_{27}H_{31}NO_3 \cdot \frac{1}{2} H_2O$, δ 5.36 (1H, d, J= 5Hz, C_{11}-H), 3.97 (1H, s, C_{15}-H), in 36% yield] and 15-benzoylkobusine (Id) [mp 125-134°C, $C_{27}H_{31}NO_3 \cdot$



(I)

a: R_1= OH R_2= H kobusine
b: R_1= OSi$(CH_3)_3$ R_2= H
c: R_1= OSi$(CH_3)_3$ R_2= COPh
d: R_1= OH R_2= COPh
e: R_1= =O R_2= COPh
f: R_1= =O R_2= H

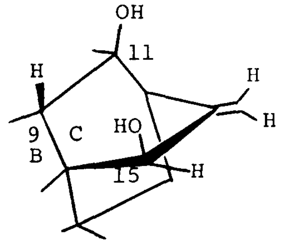
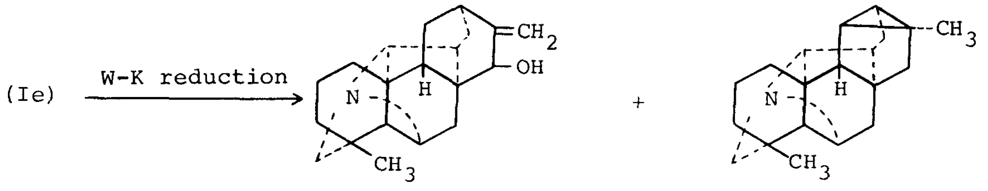


Fig. 1

$\frac{1}{2}$ $CH_3CO_2C_2H_5$, $\nu_{c=o}^{KBr}$ 1705, 1732, δ 5.70 (1H, s, C_{15}-H), 4.07 (1H, d, J= 5Hz, C_{11}-H), in 35% yield]. However, trimethylsilylation (TMS-Cl 1.02 eq /Py. at -42 - -35°C) of (Ia) stereospecifically produced 11-trimethylsilylkobusine (Ib), mp 98.5 - 99°C, $C_{23}H_{35}NO_2Si$, in 60% yield after purification by Al_2O_3 column chromatography. 15-Benzoylkobusine (Id) was obtained in a quantitative yield after desilylation of the reaction product (Ic) which resulted from treating (Ib) with benzoyl chloride (1.02 eq) and pyridine. Oxidation of (Id) with pyridinium chlorochromate (PCC 3 eq and NaOAc 0.26 eq in CH_2Cl_2) afforded 11-dehydro-15-benzoylkobusine (Ie) [amorphous, m/z 415 (M^+), δ 5.86 (1H, s, C_{15}-H)] in 80% yield.



(II) (III)

The Wolff-Kishner reduction of (Ie) using Nagata's procedure[3)] gave rise to two 11-deoxykobusine derivatives : (II) [mp 251 - 254°C, $C_{20}H_{27}NO$, $[\alpha]_D^{24}$ + 53.4°, δ 3.99 (1H, s, C_{15}-H) in 22% yield] and (III) [mp 187 - 188°C, $C_{20}H_{27}NO$, δ 3.77 (1H, s, C_{15}-H), 3.19 (1H, br s, C_6-H), 1.20 (3H, s, C_{17}-H_3), 1.16 (1H, q, C_{11}-H), 0.94 (3H, s, C_{18}-H_3), 0.76 (1H, m, C_{12}-H), m/z 297 (M^+) in 46% yield]. The IR spectrum and melting point of (II) were found to be identical with those of nominine, and mixed the two caused no depression in the m.p. The NMR spectrum (400 MHz) of another 11-deoxyderivative (III) indicated that two tertiary methyl groups are present and that vinyl protons have disappeared. The appearance of a deshielded methyl signal at δ 1.16 and a shielded methine signal at δ 0.76 was assumed to indicate that a new cyclopropane ring was formed in the molecule.

The structure (III) was determined by single crystal X-ray diffraction analysis. Crystals of (III) belong to an orthorhombic space group $P2_12_12_1$ with the cell parameters of a= 10.955(4), b= 15.731(6), c= 9.523(3)Å, Z= 4 and Dc= 1.20g/cm^3. The structure was solved by the multisolution direct method and refined with a block diagonal least squares procedure to R= 0.084 for 1635 unique reflections with Fo > 2σ(Fo) measured on a Rigaku AFC-5 diffractometer with CuKα radiation.

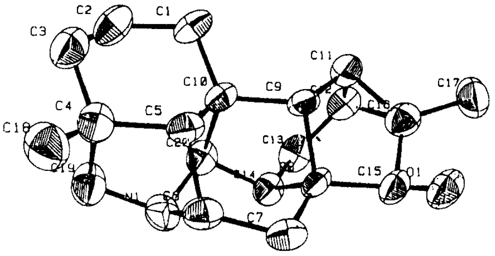


Fig. 2 An ORTEP drawing of the structure of (III)

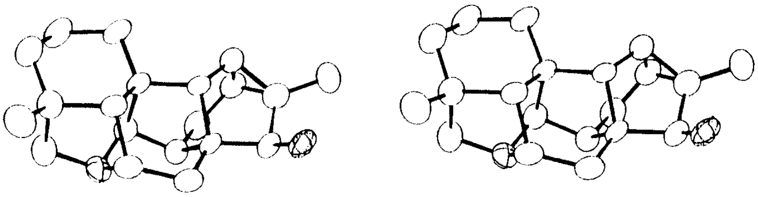
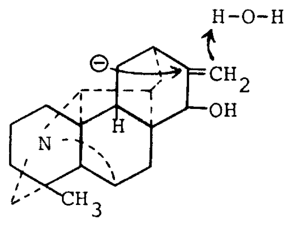
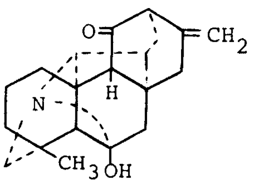


Fig. 3 Stereoscopic view of the structure of (III)



(IV)

The structure of the unexpected reaction product is thus established as the cyclopropyl derivative (III). Its formation can be explained as the result of a sequence of reactions through an intermediate such as (IV), produced under the conditions of Wolff-Kishner reaction using $NH_2NH_2\cdot H_2O$ and $NH_2NH_2\cdot HCl$. Formation of carbanion on C-11 could then lead to protonation at C-17 to afford the cyclopropyl ring. In fact, we could not obtain clear reduction products when using the usual Wolff-Kishner reduction conditions without addition of $NH_2NH_2\cdot HCl$. Carbon-carbon bond formation under Wolff-Kishner reduction conditions is rare.[4)]



(V) Spiradine A

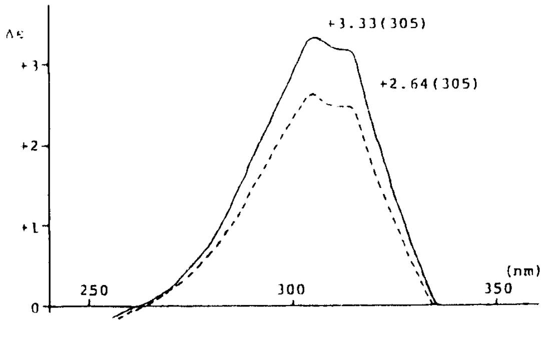


Fig. 4. CD spectra of (If) ——— and (V) - - - - -

The structure of spiradine A including the absolute configuration has already been determined satisfactorily as shown by formula (V).[5] The CD spectrum of 11-dehydrokobusine (If), [$C_{20}H_{25}NO_2$, mp 283.5 - 285.5°C, $\nu_{c=o}^{KBr}$ 1720 cm^{-1}, λ_{max}^{EtOH} 304.5 nm (log ε: 2.27), m/z(%): 311 (M^+, 64), 283 (100), CD (MeOH) $\Delta\varepsilon$(nm): 0 (262), 3.33 (305), 2.64 (313), 0 (335)], obtained by the hydrolysis of 11-dehydro-15-benzoylkobusine (Ie), gave a curve very similar to that of spiradine A (V) as shown in Fig. 4. This positive Cotton effect is consistent with the rule[6] relating the sign of the Cotton effect to the molecular geometry of β,γ-unsaturated ketones. Recently, Harada *et al.* have reported a chiroptical method for determining the absolute configuration of allylic alcohols and we have applied this rule to the present study.[7] The CD spectrum of compound (Id) exhibited a positive benzoate Cotton effect [$\lambda_{ext.}^{MeOH}$ nm($\Delta\varepsilon$): 225.5 (+4.96)] as expected for the structure (Id).

The absolute configurations of kobusine (Ia) and nominine (II) are thus established to be of the (−)-kaurene type as with other aconite diterpene alkaloids.

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