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# Studies on the Constituents of Aconitum Species. IV.[1] On the Components of *Aconitum japonicum* THUNB.[2]

HIDEO BANDO, KOJI WADA, MASAKI WATANABE, TAKAO MORI, and TAKASHI AMIYA*

*Hokkaido Institute of Pharmaceutical Sciences, 7–1, Katsuraoka-cho, Otaru 047–02, Japan*

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Two new alkaloids, aljesaconitine A and aljesaconitine B, and six known alkaloids, aconitine, jesaconitine, mesaconitine, neoline, hokbusine A, and delcosine, were isolated from the roots of *Aconitum japonicum* THUNB. (formerly known as *Aconitum subcuneatum* NAKAI). The structures of aljesaconitines A and B were determined on the basis of spectral data and derivation from jesaconitine. An acetoxy group at C-8 of an aconitine-type alkaloid was found to be easily changed to an alkoxy group by the use of alcohols such as methanol and ethanol in the extraction procedure. Quantitative determination and the $LD_{50}$ values of these 8-*O*-alkyl derivatives are also described.

**Keywords**——aljesaconitine A; aljesaconitine B; hokbusine A; delcosine; *Aconitum japonicum*; quantitative determination; acute toxicity

The isolation and structural elucidation of ten alkaloids from *Aconitum japonicum* THUNB. (earlier reported as *Aconitum subcuneatum* NAKAI) were reported in our previous paper.[1,2] In that paper, we dealt with fraction A among the chromatographic fractions A through E. In this work, fraction B was chromatographed over alumina and on silica gel to give two new alkaloids named aljesaconitine A (**7**) and aljesaconitine B (**8**), together with six known alkaloids, aconitine (**1**), jesaconitine (**2**), mesaconitine (**3**), neoline (**4**), hokbusine A (**5**),[3] and delcosine (**6**).[4] Compounds **1**—**4** have been reported[1,5] but **5** and **6** have not previously been found in this plant.

In this paper, we wish to report the structural elucidation of **7** and **8** separated from fraction B, as well as the quantitative determination of the main components (**1**, **2**, and **3**) and 8-*O*-methyl derivatives (**5** and **7**), and the acute toxicity of the 8-*O*-alkyl derivatives.

## Structure Determination

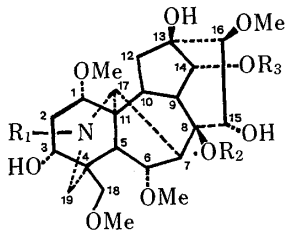
Compound **7** showed the following properties; amorphous powder, $[\alpha]_D^{20} = +7.5°$ ($c = 0.93$, EtOH), $C_{34}H_{49}NO_{11}$. The proton nuclear magnetic resonance ($^1$H-NMR) spectrum of **7** was very similar to that of **2** having an anisoyloxy group at C-14, but did not show the signal of a shielded acetoxy group at C-8 which appeared near $\delta$ 1.36 in the case of **2** as well as **1**.[6] Six methoxy groups were apparent from the spectrum and one of them was at $\delta$ 3.15, suggesting a shielded methoxy group. The methoxy group was assigned to be at C-8 in place of an acetoxy group, because a methoxy group was seen at $\delta$ 3.13 in the spectrum of hokbusine A (**5**), which was the first 8-*O*-alkyl aconitine-type alkaloid isolated from *A. carmicaeli*.[3] The spectrum of **7** suggested that its structure was 8-*O*-methyl-14-anisoylaconine. This structure was supported by the carbon-13 ($^{13}$C-) NMR spectrum (Table I). Compound **7** was readily formed when **2** was stirred in methanol.

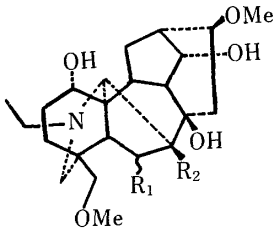
Compound **8** showed the following properties; amorphous powder, $[\alpha]_D^{20} = +5.8°$ ($c = 1.18$, EtOH), $C_{35}H_{51}NO_{11}$. The $^1$H-NMR spectrum of **8** was very similar to that of **7** except for the shielded methoxy group. A methyl group was seen at $\delta$ 0.64 (3H, t, $J = 6.0$ Hz)

and was assigned as the methyl group of an ethoxy group located at C-8 in place of the methoxy group of **7**. The structure of **8**, therefore, was assigned as 8-*O*-ethyl-14-anisoylaconine. This was confirmed by the $^{13}$C-NMR spectrum and the transformation of **2** into **8** by the use of ethanol.

The structure of **5** was determined by comparison of the spectral data with the literature values[3] and transformation of **3** into **5** by methanol treatment. The identification of **6** was carried out by direct comparison with an authentic sample.[4]

Compounds **5**, **7**, and **8**, the aconitine-type alkaloids having an alkoxy group at C-8, were probably artifacts formed in the extraction procedure with methanol or ethanol. Recently, 8-*O*-ethyl-14-benzoylmesaconine (**9**) was isolated from *A. ibukiense* and derived from mesaconitine (**3**) by Sakai *et al.*[7] and 8-*O*-methyl-14-benzoylaconine (**10**) was derived from **1** by Kitagawa *et al.*[8] These two groups suggested that the 8-*O*-alkyl derivatives were formed during extraction with alcohols.[7,8] Furthermore, the two groups suggested their respective mechanisms that an acetoxy group at C-8 was transformed into the alkoxy group. We concluded that **5** and **7** were natural products, since **5** and **7** were found in both the chloroform and the ether extracts by means of high-performance liquid chromatography (HPLC), as described below. With respect to the mechanism, we support the proposal of Sakai *et al.*,[7] because when mesaconitine *N*-oxide was allowed to stand in methanol at 60 °C for 7 d, no transformation into the 8-*O*-methyl derivative occurred. The above result favors the mechanism involving the lone-pair electrons on the nitrogen atom.




| | | | |
|---|---|---|---|
| **1**: | $R_1$=Et, | $R_2$=Ac, | $R_3$=Bz |
| **2**: | $R_1$=Et, | $R_2$=Ac, | $R_3$=An |
| **3**: | $R_1$=Me, | $R_2$=Ac, | $R_3$=Bz |
| **5**: | $R_1$=Me, | $R_2$=Me, | $R_3$=Bz |
| **7**: | $R_1$=Et, | $R_2$=Me, | $R_3$=An |
| **8**: | $R_1$=Et, | $R_2$=Et, | $R_3$=An |
| **9**: | $R_1$=Me, | $R_2$=Et, | $R_3$=Bz |
| **10**: | $R_1$=Et, | $R_2$=Me, | $R_3$=Bz |

Bz=CO–$C_6H_5$
An=CO–$C_6H_4$–OMe(*p*)

**4**: $R_1$=α-OMe, $R_2$=H
**6**: $R_1$=β-OMe, $R_2$=OH

Chart 1

**Quantitative Determination**

Highly toxic compounds **1**—**3** were the main components in the extract of this plant. To determine whether **5** and **7** were natural products or artifacts, we evaluated the contents of the three main components and two C-8 methoxy derivatives **5** and **7** by means of HPLC, since HPLC is an important tool in the quantitative determination of diterpene alkaloids.[9]

Three kinds of extracts, methanol, chloroform, and ether extracts, were prepared according to Hikino *et al.* (Chart 2).[10] The chromatogram of the chloroform extract is shown in Fig. 1. Aljesaconitine A (**7**) appeared as a shoulder peak (20 min) and its content was too small to determine. However, it was found that **7** was not an artifact since the peak appeared in the chromatograms of the methanol, chloroform, and ether extracts. Hokbusine A (**5**) was also concluded to be a natural product on the same basis. The absence of methanol in the

TABLE I. $^{13}C$-Chemical Shifts and Assignments for Jesaconitine (**2**),[5] Aljesaconitine A (**7**) and Aljesaconitine B (**8**)

| Carbon | 2 | 7 | 8 | Carbon | 2 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| 1 | 83.3 | 82.2 | 82.5 | N–$CH_2$ | 48.9 | 48.8 | 48.9 |
| 2 | 33.6 | 32.8 | 33.2 | $CH_3$ | 13.3 | 13.0 | 13.2 |
| 3 | 70.9 | 71.5 | 71.6 | 1′ | 55.8 | 55.6 | 55.8 |
| 4 | 43.1 | 43.0 | 42.9 | 6′ | 57.9 | 58.4 | 58.5 |
| 5 | 46.6 | 45.4 | 45.5 | 16′ | 61.1 | 62.3 | 62.3 |
| 6 | 82.3 | 83.1 | 83.4 | 18′ | 59.0 | 59.0 | 59.0 |
| 7 | 44.6[a] | 45.0 | 45.2 | O=C | 165.7 | 165.7 | 165.8 |
| 8 | 91.9 | 82.2 | 82.1 | $C_6H_5$ | 122.1 | 122.4 | 122.7 |
| 9 | 44.2[a] | 42.4 | 42.9 | | 131.6 | 131.6 | 131.6 |
| 10 | 40.8 | 41.4 | 41.3 | | 113.8 | 113.5 | 113.6 |
| 11 | 49.9 | 50.3 | 50.5 | | 163.5 | 163.2 | 163.1 |
| 12 | 35.8 | 36.1 | 36.2 | $OCH_3(p)$ | 55.4 | 55.3 | 55.3 |
| 13 | 74.0 | 74.7 | 74.2 | O=C | 172.4 | — | — |
| 14 | 78.6[b] | 79.4 | 79.2 | $CH_3$ | 21.5 | — | — |
| 15 | 78.8[b] | 76.9 | 77.3 | 8-*O*-$CH_3$ | — | 49.8 | — |
| 16 | 90.0 | 93.3 | 93.3 | 8-*O*-$CH_2$ | — | — | 57.1 |
| 17 | 60.9 | 61.3 | 61.1 | $CH_3$ | — | — | 15.3 |
| 18 | 75.8 | 77.4 | 76.8 | | | | |
| 19 | 46.9 | 47.6 | 47.3 | | | | |

$\delta$ (ppm) downfield from TMS in $CDCl_3$. Assignments marked *a*) or *b*) may be interchanged in each column.

TABLE II. Quantitative Determination of Diterpene Alkaloids in Dried Powder (mg/kg)

| Alkaloid | MeOH | Ether | $CHCl_3$ |
|---|---|---|---|
| Aconitine (**1**) | $1.61 \times 10^3$ | $2.02 \times 10^3$ | $1.71 \times 10^3$ |
| Jesaconitine (**2**) | $2.66 \times 10^3$ | $3.21 \times 10^3$ | $2.55 \times 10^3$ |
| Mesaconitine (**3**) | $9.45 \times 10^2$ | $1.31 \times 10^3$ | $1.04 \times 10^3$ |
| Hokbusine A (**5**) | $1.37 \times 10^2$ | $1.23 \times 10^2$ | $1.39 \times 10^2$ |

dried powder (6 g)
↓ solvent (60 ml), 28% $NH_4OH$ (2.5 ml)
stirred for 30 min
↓ $H_2O$ (2.5 ml), filtered, evaporated
extract

Chart 2. Extraction Procedure for the Quantitative Determination of Diterpene Alkaloids in Dried Powder of *Aconitum japonicum* THUNB.

TABLE III. Acute Toxicities of 8-*O*-Alkyl Derivatives in Mice

| Alkaloid | $LD_{50}$ (mg/kg) *s.c.* | *p.o.* |
|---|---|---|
| Hokbusine A (**5**) | 21 | 207 |
| Aljesaconitine A (**7**) | 5.2 | 56.5 |
| Aljesaconitine B (**8**) | 1.9 | 43.8 |
| 8-*O*-Ethyl-14-benzoylmesaconine (**9**) | 3.6 | 45.9 |
| *A. japonicum* | | |
| MeOH extr. | 9.1 | 48.6 |
| $H_2O$ extr. | 20.5 | 101.4 |

chloroform and ether used for extraction was confirmed by gas chromatography.

Quantitative determination of **1**, **2**, **3**, and **5** was based on calibration curves, and the results are shown in Table II. The content of jesaconitine (**2**) was the highest.

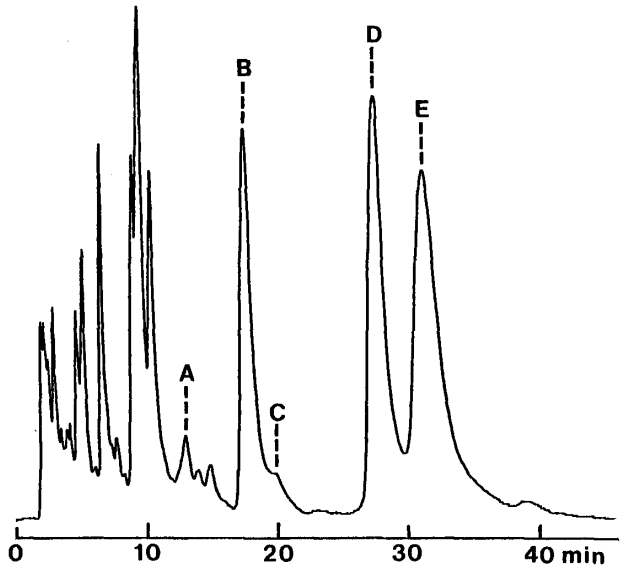



Fig. 1. High-Performance Liquid Chromatogram of Chloroform Extract

Column, Nucleosil 5-$C_{18}$ (300 × 5 mm, i.d.); mobile phase, 0.05 M phosphate buffer–acetonitrile (71 : 29) pH 2.5; flow rate, 1.1 ml/min; detector, UV (254 nm); sensitivity, 0.08 absorbance unit full scale (a.u.f.s.); temperature, 40 °C.

A, hokbusine A; B, mesaconitine; C, aljesaconitine A; D, aconitine; E, jesaconitine.

## Acute Toxicity of 8-*O*-Alkyl Derivatives

Acute toxicity and the other biological activities of aconitine-type alkaloids have been reported by many investigators[11] and it was suggested that the substituent at C-8 is important for the biological activities.[11a]

Table III shows oral and subcutaneous $LD_{50}$ values of some 8-*O*-alkyl derivatives in addition to the methanol and water extracts of this plant. In the toxicity experiment, characteristic aconitine syndromes[11b] were observed; the 8-*O*-alkyl derivatives still had high toxicities.

### Experimental

All melting points are uncorrected. Optical rotations were measured with a JASCO DIP-4 polarimeter. Infrared (IR) spectra were taken with a JASCO IRA-2 spectrometer. Ultraviolet (UV) spectra were measured in EtOH solution with a Shimadzu D-300 spectrometer. NMR spectra were measured in $CDCl_3$ solution with a JEOL FX-100 spectrometer using tetramethylsilane as an internal standard, and the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectra (MS) were measured with a Shimadzu LKB-9000B spectrometer. Column chromatography was performed on silica gel (0.063—0.200 mm, Merck) and alumina (activity II-III, 0.063—0.200 mm, Merck). Thin-layer chromatography (TLC) was performed on Silica gel 60 $F_{254}$ (Merck). Elemental analyses and high-resolution MS were performed by the Analytical Center, Hokkaido University. HPLC was carried out on a Shimadzu LC-3A equipped with an SPD-2A detector and a Chromatopac C-R1A recorder using a reverse-phase column of Nucleosil $C_{18}$ (Nagel Co.).

**Isolation Procedure**——Fraction B (91 g) obtained previously from the extract (234 g) of *A. japonicum* THUNB. was chromatographed over alumina (1.5 kg) to afford the following fractions: $CHCl_3$–hexane (4 : 1, 2 l) gave Fr-B-1 (8.3 g), $CHCl_3$–hexane (1 : 1, 2 l) gave Fr-B-2 (13.4 g), $CHCl_3$ (2 l) gave Fr-B-3 (23.0 g), ethyl acetate (2 l) gave Fr-B-4 (34.5 g), $CHCl_3$–MeOH (1 : 1, 2 l) gave Fr-B-5 (8.2 g), and MeOH (2 l) gave Fr-B-6 (2.4 g). Fr-B-1, 2, and 3 were combined and chromatographed on silica gel with a mixture of hexane and $CHCl_3$ saturated with 28% aqueous $NH_3$. The content of hexane was decreased gradually. Purification by repeated column chromatography gave **1** (20 mg), **2** (22 mg), **3** (234 mg), **4** (224 mg), **5** (105 mg), and **6** (124 mg, mp 205—207 °C). Compounds **7** (8 mg) and **8** (11 mg) were purified by HPLC under the following conditions: column, Nucleosil 5-$C_{18}$ (300 × 10 mm, i. d.); mobile phase, 0.05 M phosphate buffer–acetonitrile, pH 2.5 (70 : 30); flow rate, 3.0 ml/min; temperature, 40 °C.

**Aljesaconitine A (7)**——Amorphous powder, $[\alpha]_D^{20} = +7.5°$ ($c = 0.93$, EtOH). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 255 (4.03). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3450, 1720, 1610, 1505, 1250, 1110. $^1$H-NMR ($\delta$): 1.13 (3H, t, $J = 7.0$ Hz), 3.15 (3H, s), 3.28 (3H, s), 3.29 (3H, s), 3.31 (3H, s), 3.64 (3H, s), 3.87 (3H, s), 4.55 (1H, d, $J = 6.0$ Hz, $C_{14\beta}$ –H), 6.92 (2H, d, $J = 9.0$ Hz), 8.00 (2H, d, $J = 9.0$ Hz). MS (*m/z*): 647 ($M^+$), 632 ($M^+ - CH_3$), 616 ($M^+ - OCH_3$, base peak), 135 (anisoyl cation). High-resolution MS Calcd for $C_{34}H_{49}NO_{11}$: 647.328. Found 647.330.

**Aljesaconitine B (8)**——Amorphous powder, $[\alpha]_D^{20} = +5.8°$ ($c = 1.18$, EtOH). UV $\lambda_{max}^{EtOH}$ nm (log $\varepsilon$): 255 (4.02). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3450, 1720, 1610, 1515, 1260, 1100. $^1$H-NMR ($\delta$): 0.64 (3H, t, $J = 6.0$ Hz), 1.11 (3H, t, $J = 7.0$ Hz), 3.28

(3H, s), 3.33 (3H, s), 3.75 (3H, s), 3.88 (3H, s), 4.60 (1H, d, $J=6.0$ Hz, $C_{14\beta}-H$), 6.93 (2H, d, $J=9.0$ Hz), 8.00 (2H, d, $J=9.0$ Hz). MS *m/z*: 661 ($M^+$), 646 ($M^+-CH_3$), 630 ($M^+-OCH_3$, base peak), 135 (anisoyl cation). High-resolution MS Calcd for $C_{35}H_{51}NO_{11}$: 661.346. Found 661.349.

**Transformation of 2 into 7**——i) A solution of **2** (100 mg) in MeOH (30 ml) was stirred at room temperature for 7 d. The solvent was evaporated off and the residue was purified by TLC to give **7** (10 mg, 10%). ii) At 60 °C for 3 d, the yield was increased to 82%. The products (i and ii) were identical with the natural product form *A. japonicum* in terms of the IR, NMR, and MS.

**Transformation of 2 into 8**——A solution of **2** (100 mg) in EtOH (30 ml) was stirred at 60 °C for 5 d. The solvent was evaporated off and the residue was purified by TLC to give **8** (72 mg, 72%). The derivative was identical with the natural product in terms of the IR, NMR, and MS.

**Transformation of 3 into 5**——A solution of **3** (300 mg) in MeOH (180 ml) was stirred at 60 °C for 7 d, then worked up as described above to give **5** (280 mg, 98%). The derivative was identical with hokbusine A based on a comparison of the IR, $^1H$- and $^{13}C$-NMR, and MS with the literature data.[3] Hokbusine A perchlorate: mp 169—177 °C (dec.). *Anal.* Calcd for $C_{32}H_{45}NO_{11}\cdot HClO_4\cdot H_2O$: C, 53.22; H, 6.70; N, 1.94. Found: C, 53.54; H, 6.62; N, 1.64.

**Transformation of 3 into 9**——A solution of **3** (300 mg) in EtOH (180 ml) was stirred at 60 °C for 10 d, then worked up as described above to give **9** (285 mg, 97%). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3450, 1715, 1600, 1580, 1270, 1090. $^1H$-NMR ($\delta$): 0.57 (3H, t, $J=6.6$ Hz), 2.34 (3H, s), 3.27 (3H, s), 3.28 (3H, s), 3.31 (3H, s), 3.73 (3H, s), 4.08 (1H, d, $J=7.6$ Hz, $C_{6\beta}-H$), 4.54 (1H, d, $J=6.0$ Hz, $C_{15\beta}-H$), 4.81 (1H, d, $J=4.7$ Hz, $C_{14\beta}-H$), 7.27—8.08 (5H, m). $^{13}C$-NMR (ppm, carbon atom): 15.3 (q, 8-*O*-$CH_2\underline{C}H_3$), 34.1 (t, 2), 36.3 (t, 12), 41.3 (d, 10), 42.0 (d, 9), 42.5 (q, *N*-$CH_3$), 43.4 (s, 4), 45.3 (d, 7), 45.6 (d, 5), 49.5 (t, 19), 50.5 (s, 11), 56.3 (q, 1′), 57.1 (t, 8-*O*-$\underline{C}H_2CH_3$), 58.6 (q, 6′), 59.1 (q, 18′), 62.3 (d, 17), 62.4 (q, 16′), 71.3 (d, 3), 74.7 (s, 13), 76.4 (t, 18), 78.3 (d, 15), 79.4 (d, 14), 82.0 (s, 8), 82.7 (d, 1), 83.3 (d, 6), 93.4 (d, 16), 128.3 (d, 3″), 129.6 (d, 2″), 130.3 (s, 1″), 132.8 (d, 4″), 166.1 (s, $C_6H_5-\underline{C}O$). MS *m/z*: 617 ($M^+$), 602 ($M^+-CH_3$), 586 ($M^+-OCH_3$, base peak), 540 (586-EtOH), 105 (benzoyl cation). High-resolution MS Calcd for $C_{33}H_{47}NO_{11}$: 617.320. Found 617.321.

**Treatment of Mesaconitine *N*-Oxide with MeOH**——A solution of mesaconitine *N*-oxide (20 mg) in MeOH was stirred at 60 °C for 7 d. The mixture was worked up as above to afford only the starting material.

**Conditions of HPLC for Quantitative Determination**——See the legend to Fig. 1.

**Preparation of Extract for Analysis**——Chloroform extract was prepared according to the method reported by Hikino *et al.* (Chart 2).[10] The procedure shown in Chart 2 was repeated three times, but water was added only the first time.

**Standard Sample**——Compounds **1**—**3** isolated from this plant and **5** and **7** derived from **3** were used as standard samples.

**Calibration Curve**——About 1 mg of standard sample, accurately weighed, was dissolved in the same solvent as used for the mobile phase in HPLC and made up to exactly 1 ml. The area of the chromatogram was measured. The calibration curves were linear and the correlations ($y$, area; $x$, mg) were as follows ($N=5$ in all cases): aconitine, $y=9.17\times10^6x-8750$ ($r=0.992$); jesaconitine, $y=7.43\times10^6x-4610$ ($r=0.999$); mesaconitine, $y=1.09\times10^7x-6270$ ($r=0.999$); hokbusine A, $y=4.95\times10^6x-258$ ($r=0.999$).

**Determination of Alkaloids in *A. japonicum* THUNB.**——The content of each alkaloid is shown in Table II. The recovery of added standard mesaconitine was 96.0—96.5% in the MeOH, $CHCl_3$, and ether extracts.

**Acute Toxicity in Mice**——Male mice, weighing 27—30 g, were used to determine the subcutaneous and peroral $LD_{50}$s. Mortality was recorded 24 h after administration. $LD_{50}$s were calculated by the up-and-down method described in the textbook.

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