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THE STRUCTURES OF SACHACONITINE AND ISODELPHININE FROM *ACONITUM MIYABEI* NAKAI

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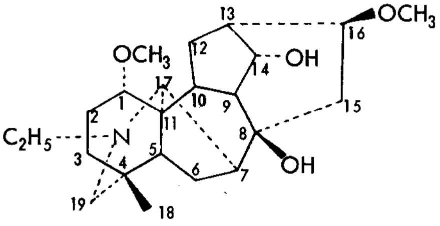
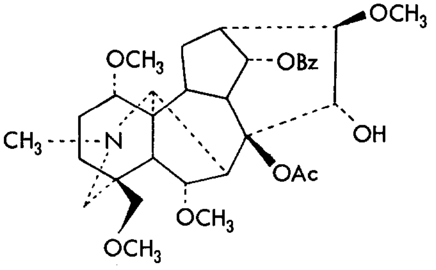
We wish to report the structure determination for sachaconitine (1) and isodelphinine (base D) (2), two C_{19}-diterpenoid alkaloids occurring in the roots of *Aconitum miyabei* Nakai, a plant native to Hokkaido, Japan. These two alkaloids were isolated and partially characterized by Katsui and co-workers$^{1-3}$ in 1959.



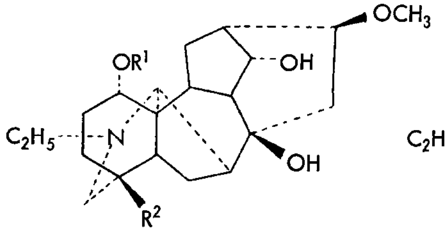
1 Sachaconitine



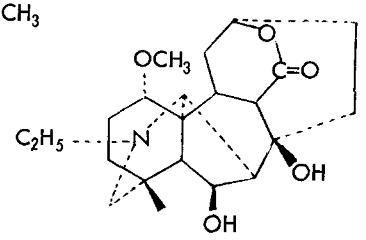
2 Isodelphinine

Sachaconitine, $C_{23}H_{37}NO_4$, mp 129-130°C, $[\alpha]^{20}$ D -13.1° (c 2.35 in 95% EtOH) shows IR absorption at 3500 and 3300 (two hydroxyl groups), 1100 (ether linkage) cm^{-1} and other characteristic peaks of the C_{19}-diterpenoid alkaloid skeleton. The 100 MHz ^1H NMR spectrum of sachaconitine in $CDCl_3$ gave signals at δ 0.8 (3H, singlet, C-4 methyl), 1.06 (3H, triplet, J=7Hz, N-CH_2-$\underline{CH_3}$), 3.28 and 3.37 (3H, singlet, C-1 and C-18 OCH_3) and 4.15 (1H, doublet of doublets, C-14βH). The IR and ^1H NMR spectra of 1 are similar to those of the related alkaloids, aconosine^4 (3), talatizamine^5 (4) and karakoline^6 (5).

A correlation of sachaconitine with available related alkaloids talatizidine^7 (6), heteratisine^8 (7) and chasmanine^7 (8) was made through a study of their ^{13}C NMR spectra (Table 1). The comparison of ^{13}C NMR spectrum of 1 with alkaloids 6 to 8 afforded evidence for the presence of a C-4 methyl, an N-CH_2CH_3 and two hydroxyl groups at the C-8 (singlet at 72.8 ppm) and C-14 (doublet at 75.7 ppm) positions in 1. The two methoxyl groups at C-1 and C-16 are assigned by observing two doublets at 86.7 and 82.3 ppm and two quartets at 56.3 and 56.9 ppm in 1, respectively. The chemical shifts of the A and D rings further confirmed the presence of two methoxyl groups at C-1 and C-16 in sachaconitine. All other signals are also in agreement with the assigned structure (1) for sachaconitine.



3 R^1 = CH$_3$ R^2 = H
4 R^1 = CH$_3$ R^2 = CH$_2$OCH$_3$
5 R^1 = H R^2 = CH$_3$
6 R^1 = H R^2 = CHOCH$_3$



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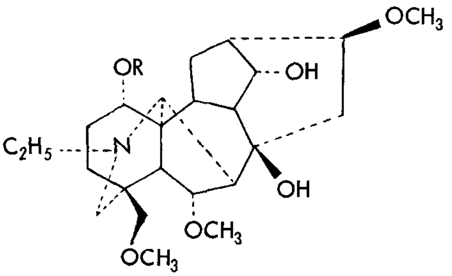
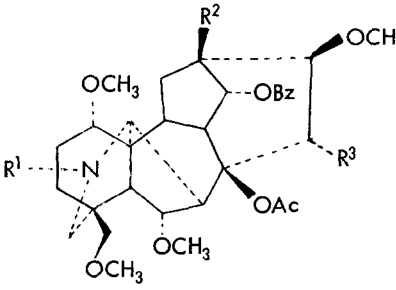
In 1959 Katsui[2] reported that isodelphinine has the same molecular formula and functional groups as delphinine[9] and that the infrared spectra of isodelphine (2) and delphinine (9) are similar except in the region of the ester carbonyl groups: isodelphinine shows two bands at 1705 and 1720 cm^{-1}, while delphinine has one band at 1720 cm^{-1}. He postulated that the benzoyl group in delphinine is *trans* to the C-13 hydroxyl, while in isodelphinine it is *cis*, or in other words delphinine and isodelphinine are C-14 epimers. Since then no further work clarifying the relationship between delphinine and isodelphinine has been reported.



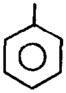
8 R = CH$_3$
12 R = H



9 R^1 = CH$_3$ R^2 = OH R^3 = H
10 R^1 = C$_2$H$_5$ R^2 = R^3 = OH
11 R^1 = C$_2$H$_5$ R^2 = R^3 = H

Isodelphinine, $C_{33}H_{45}NO_9$, mp 167-168°C, $[\alpha]^{20}$ D + 20.1° (c 2.05, 95% EtOH), shows IR absorption at 3500 (hydroxyl group), 1705 and 1720 (ester groups), 1600 (an aromatic ring), 1275 (acetate group), 1100 and 1115 (ether linkage) and 720 (monosubstituted aromatic ring) cm^{-1}. The 100 MHz ^{1}H NMR spectrum of isodelphinine in CDCl$_3$ reveals the presence of an acetoxyl group (3H, singlet) at δ 1.45, an N-methyl group (3H, singlet) at δ 2.36, four methoxyl groups (3H, singlets) at δ 3.20 and δ 3.54, and (6H, singlet) at δ 3.32. The spectrum also shows signals at δ 5.06 (doublet of doublets) attributable to a proton attached to a carbon (C-14) carrying an aromatic ester group and signals for the aromatic protons of the benzoyl group between δ 7.40 and δ 8.20. The highly shielded acetate singlet[10] at δ 1.45 confirms that a C-14 benzoate — C-8

Table 1. Carbon-13 Chemical Shifts and Assignments for Sachaconitine 1, Isodelphinine 2 and Other Related C_{19} - Diterpenoid Alkaloids[a]

Carbon	1	6	7	8	2	9	10	11
1	86.7	72.3	83.5	86.1	85.1	84.9	85.0	72.2
2	26.3	29.2	26.9	26.0	26.4	26.3	26.3	29.5
3	37.8	29.7	36.8	35.2	34.9	34.7	35.2	30.1
4	34.7	37.3	34.7	39.5	39.3	39.3	39.0	38.9
5	49.5	41.7	50.9	48.8	47.9	48.8	49.1	44.4
6	25.2	25.0	72.9	82.5	83.7	83.0	83.3	84.0
7	45.9	45.3	49.3	52.8	44.5	48.2	45.1	48.2
8	72.9	74.3	75.4	72.6	92.1	85.4	92.0	85.9
9	47.1	46.7	57.8	50.3	44.7	45.1	44.6	43.5
10	38.5	40.4	42.8	38.4	38.7	41.0	41.0	38.2
11	51.0	48.7	49.3	50.4	50.0	50.2	49.9	49.9
12	27.8	26.8	33.1	28.6	29.4	35.7	36.7	29.5
13	45.9	44.1	75.8	45.7	43.9	74.8	74.0	43.2
14	75.7	75.6	176.0	75.5	76.4	78.9	78.8	75.7
15	38.0	42.3	29.1	39.2	78.8	39.3	79.0	38.9
16	82.3	82.4	29.2	82.2	89.3	83.7	90.2	82.8
17	62.5	63.7	62.2	62.4	62.2	63.3	61.2	63.0
18	26.3	79.0	26.2	80.8	80.2	80.2	80.2	79.9
19	57.5	56.6	58.3	54.0	56.5	56.1	53.3	56.6
$N\text{-}CH_{2(3)}$	49.5	48.4	49.0	49.3	42.6	42.3	49.1	48.3
CH_3	13.7	13.0	13.5	13.6	-	-	13.4	13.0
1'	56.3	56.2	55.2	56.3	56.1	56.1	56.0	-
6'	-	59.3	-	57.2	57.7	57.6	57.9	57.9
16'	56.9	-	-	55.9	58.0	58.6	60.9	56.9
18'	-	-	-	59.2	59.1	58.9	59.0	59.1
-C=O	-	-	-	-	172.3	169.4	172.2	169.6
CH_3	-	-	-	-	21.5	21.4	21.3	21.6
-C=O	-	-	-	-	166.1	166.0	165.9	166.0
	-	-	-	-	133.1	132.8	133.1	133.0
	-	-	-	-	130.1	130.4	129.9	130.3
	-	-	-	-	129.7	129.6	129.5	129.7
	-	-	-	-	128.6	128.4	128.5	128.4

[a] In ppm downfield to Me_4Si, solvent deuterochloroform.

acetate substitution pattern is present in isodelphinine. The ^{1}H NMR spectrum of isodelphinine (**2**) is similar to that of delphinine (**9**) except that the C-14 β proton appears as a doublet of doublets at δ 5.06 in **2**, but as only a doublet at δ 4.94 in **9**; also the singlet due to the C-8 acetate group also appears upfield ($\Delta\delta = 0.15$ ppm) at δ 1.30 in **9** as compared to **2**.

Further correlation of isodelphinine with delphinine (**9**), deoxyaconitine (**10**), and 8-acetyl-14-benzoxylneoline (**11**) was made through a study of their ^{13}C NMR spectra (Table 1). The pattern of chemical shifts in isodelphinine is similar to that of alkaloids **9** to **11** with a few exceptions. The shifts of C-8, C-14, C-15 and C-16 of **2** resemble those of **10**. Similarly, the ^{13}C chemical shifts of C-12 and C-13 also resemble those of chasmanine (**8**) and compound **11**. These characteristic shifts of isodelphinine indicate that the hydroxyl group is present at C-15 (78.9 ppm, doublet) and no group is substituted at C-13 in **2**. The downfield singlets at 92.3 and 172.3 ppm of C-8 and the carbonyl group of the C-8 acetate also confirm the presence of hydroxyl at C-15 in isodelphinine. Therefore isodelphinine is *not* the C-14 epimer of delphinine, but shows a novel pattern of substitution, with C-15 being substituted while C-13 is not. The chemical shifts of the remaining carbons are in agreement with the assigned structure **2** for isodelphinine.

Sachaconitine and isodelphinine are interesting alkaloids for biogenetic speculation. Sachaconitine may be a biogenetic intermediate between the alkaloids aconosine (**3**) and talatizamine (**4**). Also sachaconitine and karakoline (**5**) provide an additional example of C-1 α-hydroxyl-methoxyl pair along with the other known pairs, neoline-chasmanine[11], isotalatizidine-talatizamine[5] and lapaconidine-lappaconine.[12] This additional example suggests the possible existence of other such pairs in nature. It is interesting to note that isodelphinine is the first naturally occurring example of an alkaloid with the C-15 hydroxyl in the absence of the C-13 hydroxyl group. Thus far, all diterpenoid alkaloids bearing a C-15 hydroxyl also feature a hydroxyl at C-13 e.g., aconitine, jesaconitine, mesaconitine, deoxyaconitine and hypaconitine.[13]

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