Diterpenoid Alkaloids from the Roots of *Delphinium scabriflorum*

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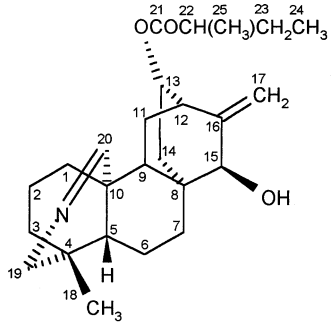
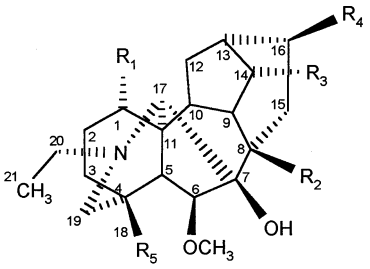
Chemical investigation of the $CHCl_3$ extracts from the roots of *Delphinium scabriflorum* has resulted in the isolation of a new diterpenoid alkaloid, 13-(2-methylbutyryl)azitine (**1**), along with 11 known alkaloids, delbine (**2**), 14-deacetyl-14-isobutyrylajadine (**3**), methyllycaconitine (**4**), 14-deacetylnudicauline (**5**), delectinine (**6**), deltatsine (**7**), dictysine (**8**), geyerline (**9**), ajacine (**10**), lycoctonine (**11**), and delcosine (**12**). The structure of **1** was determined by spectroscopic data interpretation. Complete NMR data for alkaloids **2**−**8** are presented. Some earlier ^{13}C NMR assignments made for alkaloids **4**−**7** were revised.

In Nepalese folk medicine, the roots of *Delphinium scabriflorum* D. Don (Ranunculaceae) are used for the treatment of rheumatism and fever, and the juice of the leaves is used for wound healing.[1] In the course of our studies on diterpenoid alkaloids from *Aconitum* and *Delphinium* species we have investigated the alkaloids of the roots of *D. scabriflorum* collected in Nepal, which have led to the isolation of one new alkaloid, 13-(2-methylbutyryl)-azitine (**1**), as well as 11 known diterpenoid alkaloids. The known compounds were identified as delbine[2] (**2**), 14-deacetyl-14-isobutyrylajadine[3] (**3**), methyllycaconitine[4] (**4**), 14-deacetylnudicauline[5] (**5**), delectinine[6] (**6**), deltatsine[7] (**7**), dictysine[8] (**8**), geyerline[9] (**9**), ajacine[10] (**10**), lycoctonine[11] (**11**), and delcosine[10] (**12**). A literature survey showed that no previous phytochemical study of this species has been reported.

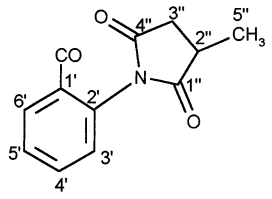


1

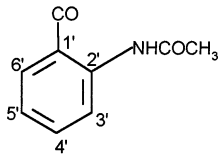
The ESIMS of alkaloid **1** gave a protonated molecular ion peak ($[M + H]^+$, *m*/*z* 400) suggesting a molecular formula of $C_{25}H_{37}NO_3$. The IR spectrum showed the presence of a hydroxy group (3425 cm^{-1}) and an azomethine group (1651 cm^{-1}). The ^1H NMR spectrum displayed a signal for an exocyclic methylene group at δ_H 5.08 and 5.17, which was also observed at δ_C 152.9 and 109.9 in the ^{13}C NMR spectrum, and the lack of methoxyl groups. The ^1H NMR spectrum also indicated the presence of an angular methyl at δ_H 0.86 and two oxygenated methines at δ_H 3.74 and 5.04. The absence of methoxyl, *N*-ethyl, and methyl groups and the presence of an exocyclic methylene signal indicated that the alkaloid is a C_{20}-diterpenoid alkaloid. The downfield signal at δ_H 7.93 was consistent with the presence of an azomethine function.



	R_1	R_2	R_3	R_4	R_5
2	-OH	-OH	-OH	$-OCH_3$	-OH
3	$-OCH_3$	-OH	$-OCOCH(CH_3)_2$	$-OCH_3$	$-CH_2OB$
4	$-OCH_3$	-OH	$-OCH_3$	$-OCH_3$	$-CH_2OA$
5	$-OCH_3$	-OH	-OH	$-OCH_3$	$-CH_2OA$
6	$-OCH_3$	-OH	-OH	$-OCH_3$	$-CH_2OH$
7	-OH	$-OCH_3$	-OH	$-OCH_3$	$-CH_2OCH_3$
9	$-OCH_3$	-OH	$-OCH_3$	-OAc	$-CH_2OA$
10	$-OCH_3$	-OH	$-OCH_3$	$-OCH_3$	$-CH_2OB$
11	$-OCH_3$	-OH	$-OCH_3$	$-OCH_3$	$-CH_2OH$
12	-OH	-OH	-OH	$-OCH_3$	$-CH_2OCH_3$



A



B

The ^{13}C NMR spectrum of **1** showed 24 signals for 25 carbon atoms. Among these were three methyl quartets at δ_C 25.8, 16.9, and 11.7, 10 methylene triplets at δ_C 19.3, 19.9, 25.5, 28.2, 26.7, 31.9, 33.6, 42.3, 60.0, and 109.9, six methine doublets at δ_C 38.0, 35.5, 44.9, 41.3, 70.8, and 72.6, and five quaternary carbons at δ_C 34.3, 37.4, 42.0 152.9, and 178.2 (Table 1). The ^{13}C NMR spectrum also showed signals for a 2-methylbutyryl ester group at δ_C 178.2, 41.3, 26.7, 16.9, and 11.7. The presence of the 2-methylbutyryl group was also indicated by the loss of 102 amu in the mass spectrum. The resonances for the exocyclic methylene group observed at δ_H 5.08 and 5.17 indicated the presence of a β-hydroxy group at C-15.[12] The signal at δ_C 70.8 (δ_H 3.74) was assigned to C-15, carrying a hydroxy group. The

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Table 1. NMR Data for Compound **1**

position	δ_C (multiplicity)		δ_H multiplicity (J in Hz)	COSY
1	33.6 (t)	H-1α	1.72 brd (14.5)	1*β*, 2α
		H-1*β*	1.06 brd (12.7)	1α
2	19.9 (t)	H-2α	1.48 dd (6.6, 13.8)	1α, 3*β*
		H-2*β*	n[a]	
3	42.3 (t)	H-3α	1.42 dd (5.1, 18.0)	2α, 3*β*
		H-3*β*	1.24 m	1α, 2α, 3α
4	34.3 (s)			
5	44.9 (d)	H-5	n[a]	
6	19.3 (t)	H-6α	1.60 m	
		H-6*β*	1.19 m	6α, 7α
7	31.9 (t)	H-7α	2.05 m	7*β*
		H-7*β*	1.33 m	7α
8	37.4 (s)			
9	38.0 (d)	H-9	1.94 brd (8.4)	11α, 11*β*
10	42.0 (s)			
11	28.2 (t)	H-11α	1.78 m	9, 11*β*
		H-11*β*	1.62 m	9
12	35.5 (d)	H-12	2.38 m	11*β*
13	72.6 (d)	H-13*β*	5.04 dd (4.7, 11.9)	14α, 14*β*
14	25.5 (t)	H-14α	1.65 m	13, 14*β*
		H-14*β*	1.30 m	13, 14α
15	70.8 (d)	H-15α	3.74 brt	17a
16	152.9 (s)			
17	109.9 (t)	H-17a	5.08 brs	15, 17b
		H-17b	5.17 brs	17a
18	25.8 (q)	H-18	0.86 s	
19	60.0 (t)	H-19	3.45 d (10.7)	
20	n[a]	H-20	7.93 brd	
21	178.2 (s)			
22	41.3 (d)	H-22	2.57 m	25
23	26.7 (t)	H-23α	1.70 m	23*β*, 24
		H-23*β*	1.50 m	23α, 24
24	11.7 (q)	H-24	0.92 t (7.3)	23α, 23*β*
25	16.9 (q)	H-25	1.16 d (7.0)	22

[a] n = peak not observed.

methine proton showed a correlation with an exocyclic methylene proton (δ_H 5.08) in the COSY spectrum.

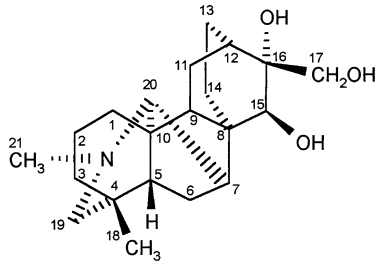
The ^{13}C NMR chemical shifts of **1** were comparable to those of azitine[13] except for the resonance of C-13. The difference is due to the substitution of H-13 in azitine by a methylbutyryl group in **1**. The presence of this group was also supported by the mass spectrum (*m*/*z* 399), which was 100 amu more than that of azitine. The chemical shift of C-13 bearing a hydroxy group is at about δ_C 70−73, whereas it is at about δ_C 75 when there is a hydroxyl at C-11.[14] The ^1H NMR chemical shift of H-13 of this alkaloid was comparable with those found for cardiopine,[15] venudelphine,[16] and cossonine.[17] Therefore, the ^{13}C NMR signal at δ_C 72.6 was attributed to a 2-methylbutyryl ester group at C-13. As in the COSY spectrum, the downfield signal δ_H 5.04 was coupled with the vicinal protons at C-14 (δ_H 1.65, H-14α, δ_H 1.30, H-14*β*), and the 2-methylbutyryl ester group has to be placed at C-13. By analogy with other diterpenoid alkaloids possessing an oxygen function at C-13 (fissumine,[14] cardiopine,[15] venudelphine,[16] cossonine[17]), the α-configuration was assigned to the C-13-ester group.

Delbine (**2**) was previously isolated from *Delphinium bonvalotti* Franch by Jiang and Sung.[2] The complete NMR assignments presented here have not been reported previously. The NMR assignments given in Table 2 are based on 1D and 2D NMR data and the mass spectra and on comparison with the ^{13}C NMR data of diacetyldelbine.[2] 14-Deacetyl-14-isobutyrylajadine (**3**) was isolated from *Delphinium stapeliosum* Brühl.[3] Herein, we report the complete ^1H NMR assignments of this same alkaloid isolated from *D. scabriflorum*, along with those of **4**−**7** (Table S1, Supporting Information). Based on 1D and 2D NMR spectra, complete NMR data for alkaloid **8** are presented

Table 2. NMR Data for Compound **2**

position	δ_C (multiplicity)		δ_H multiplicity (J in Hz)	COSY
1	72.6 (d)	H-1*β*	3.64 t (4.0)	2*β*, 3α
2	29.0 (t)	H-2α	1.60 m	
		H-2*β*	1.71 m	1*β*, 3α, 3*β*
3	35.2 (t)	H-3α	1.81 m	1*β*, 2*β*, 3*β*
		H-3*β*	2.12 m	2*β*, 3α
4	70.4 (s)			
5	52.6 (d)	H-5	1.79 s	6α, 17
6	89.6 (d)	H-6α	4.17 s	5
7	88.1 (s)			
8	77.8 (s)			
9	45.3 (d)	H-9	2.95 dd (5.3, 1.1)	14*β*
10	43.8 (d)	H-10	1.95 m	9, 12α
11	49.9 (s)			
12	30.0 (t)	H-12α	1.60 m	10, 12*β*
		H-12*β*	2.06 m	12α, 13
13	39.2 (d)	H-13	2.39 dd (5.1, 7.4)	12*β*, 14*β*
14	75.6 (d)	H-14*β*	4.13 t (4.6)	9, 13
15	34.3 (t)	H-15α	1.68 m	15*β*, 16α
		H-15*β*	2.76 m	15α, 16α
16	81.9 (d)	H-16α	3.36 m	15α, 15*β*
17	65.2 (d)	H-17	2.87 s	5
19	60.5 (t)	H-19α	2.71 d (10.1)	19*β*
		H-19*β*	2.82 d (11.1)	19α
20	50.0 (t)	H-20α	2.88 m	20*β*, 21
		H-20*β*	3.00 m	20α, 21
21	14.1 (q)	H-21	1.11 t (7.2)	20α, 20*β*
CH_3O-6	58.2 (q)	CH_3O-6	3.40 s	
CH_3O-16	56.4 (q)	CH_3O-16	3.37 s	

(Table S2, Supporting Information). Several ^{13}C NMR shift asssignments for alkaloids **4**−**7** have been revised (see Experimental Section).



8

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler hot stage and were uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. The UV spectra were obtained on a Perkin-Elmer Lambda 5 UV/vis spectrometer. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer as KBr pellets. The NMR spectra were taken on Bruker 200 and Bruker DRX 500 spectrometers with TMS as internal standard. Chemical shifts are given in ppm downfield of TMS. LCMS and multiple mass spectra were obtained on a Finnigan LCQ G-2 mass spectrometer in the electrospray ionization mode with positive ionization. Chromatographic separations were carried out by column chromatography on Merck Kieselgel 0.05−0.20 mm and Merck aluminum oxide 90 active neutral 0.063−0.20 mm. TLC was performed on Merck Si gel 60 F_{254} plates (0.20 and 0.25 mm) and aluminum oxide 60 F_{254} plates (0.25 mm). TLC spots were visualized by exposure to iodine vapor and/or by spraying with Dragendorff's reagent.

Plant Material. Plants were collected at Phulchoki Hill, Kathmandu Valley, Nepal, in August 1997 and identified by comparison with the authentic herbarium specimens at the National Herbarium Laboratory, Plant Research Division, Department of Plant Resources, Kathmandu, Nepal. A voucher

specimen (NPRL 97-8) has been placed in the herbarium of the Natural Products Research Laboratory, Dr. A. Katz, Basel.

Extraction and Isolation. Air-dried and ground roots (60 g) of *Delphinium scabriflorum* were percolated with diethyl ether (200 mL). The defatted root powder was brought to pH 9 with 25% aqueous NH_4OH and extracted four times by shaking with 250 mL each of $CHCl_3$. The $CHCl_3$ extracts were evaporated to dryness to give 0.83 g of a crude alkaloidal mixture. Subsequently, the root powder was basified to pH 12 with 2 N NaOH and extracted with $CHCl_3$ (3 × 300 mL) to yield 0.49 g of additional crude alkaloidal mixture. Since the TLC patterns of the pH 9 and pH 12 extracts were the same, the two extracts were combined. The mixture was dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to dryness to yield a crude $CHCl_3$ extract (1.22 g). This material was chromatographed over a column of Kieselgel (0.05−0.20 mm) eluting with a gradient system of cyclohexane−chloroform−methanol−diethylamine. Thirty-four column fractions of 50 mL each were collected.

Column fraction 3, eluted with cyclohexane−chloroform−diethylamine (15:4:1), was rechromatographed over Kieselgel with a gradient system of cyclohexane−chloroform−diethylamine, giving nine fractions (10 mL each). Further workup of fraction 2 (column chromatographed over aluminum oxide) gave 15 subfractions (5 mL each). Subfraction 6, after repeated preparative TLC on aluminum oxide plates (cyclohexane−chloroform−ethanol, 23:75:2), gave 2.1 mg of **1**.

Repeated preparative TLC of column fraction 4 on aluminum oxide (cyclohexane−chloroform−ethanol, 55:44:1) and silica gel plates (cyclohexane−chroloform−diethylamine, 7:2:1) afforded **3** (1.4 mg). Column fractions 5−7 gave **4** (34.2 mg), **7** (9.6 mg), **9** (7.2 mg), and **10** (7.4 mg) after repeated preparative TLC on silica gel and aluminum oxide plates. Similarly, column fractions 8 and 9 gave **5** (3.2 mg) **11** (10.1 mg), and **12** (7.1 mg). Column fractions 10 and 11 afforded **6** (14.9 mg), while column fraction 12 gave **8** (2.0 mg). Alkaloid **2** (9.4 mg) was obtained from column fractions 16−29 after repeated preparative TLC on aluminum oxide plates.

13-(2-Methylbutyryl)azitine (1): amorphous; $[\alpha]^{20}_D$ −7.6° (*c* 0.2, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 214 nm (3.43); IR (KBr) ν_{max} 3425, 2926, 1731, 1651, 1461, 1265, 903 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 1; ESIMS *m/z* 400 $[M + H]^+$ (100), 386 (31), 382 (8), 298 (100), 280 (100), 270 (11), 263 (33), 252 (13), 224 (5).

Delbine (2): crystal (acetone−ether); mp 112−114 °C (lit.[2] 116−118 °C); $[\alpha]^{20}_D$ +51.1° (*c* 0.43, $CHCl_3$); IR (KBr) ν_{max} 3424, 2928, 2856, 1653, 1459, 1085, 1015, 951 cm^{-1}; ^1H NMR, see Table 2; ^{13}C NMR, see Table 2; ESIMS *m/z* 448 $[M + Na]^+$ (100), 426 $[M + H]^+$ (73), 408 (31), 394 (17), 390 (15), 376 (100), 358 (100), 344 (74), 340 (17), 330 (37), 326 (32), 316 (34).

14-Deacetyl-14-isobutyrylajadine (3): UV (EtOH) λ_{max} (log ϵ) 210 (4.09), 238 (3.74), 248 (3.70), 290 (3.39) nm; IR (KBr) ν_{max} 3421, 2925, 2856, 1737, 1527, 1378, 1259, 1164, 1091, 804, 757 cm^{-1}; ^1H NMR, see Table S1; ^{13}C NMR data were identical with the published data.[3]

Methyllycaconitine (4): $[\alpha]^{20}_D$ +35.5° (*c* 0.45, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 228 (4.13), 276 (3.43) nm; IR (KBr) ν_{max} 3446, 2929, 1706, 1680, 1590, 1451, 1383, 1298, 1260, 1089, 756, 704 cm^{-1}; ^1H NMR, see Table S1; ^{13}C NMR revised data δ 50.2 (C-5), 43.2 (C-9), 46.1 (C-10), 38.2 (C-13). The other assignments were identical with the published data.[4]

14-Deacetylnudicauline (5): $[\alpha]^{20}_D$ +28.8° (*c* 0.32, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 228 (3.98), 276 (3.26) nm; IR (KBr) ν_{max} 3449, 2925, 2853, 1770, 1715, 1603, 1494, 1457, 1393, 1293, 1088, 714 cm^{-1}; ^1H NMR, see Table S1; ^{13}C NMR revised data δ 50.3 (C-5), 45.2 (C-9). The other assignments were identical with the published data.[5]

Delectinine (6): IR (KBr) ν_{max} 3423, 2926, 1736, 1640, 1514, 1461, 1378, 1297, 1088 cm^{-1}; ^1H NMR, see Table S1; ^{13}C NMR revised data δ 49.5 (C-5), 45.0 (C-9), 46.0 (C-10), 36.4 (C-13). The other assignments were identical with the published data;[6] ESIMS *m/z* 454 $[M + H]^+$ (100), 436 (46), 422 (100), 421 (6), 404 (22), 390 (93), 386 (3), 376 (21), 372 (24), 362 (8), 360 (6), 358 (22), 354 (4), 344 (18), 340 (11), 330 (4), 312 (5).

Deltatsine (7): $[\alpha]^{20}_D$ +26.5° (*c* 0.47, $CHCl_3$); IR (KBr) ν_{max} 3432, 2934, 2860, 1731, 1654, 1459, 1389, 1296, 1195, 1095 cm^{-1}; ^1H NMR, see Table S1; ^{13}C NMR revised data δ 49.0 (C-5), 39.9 (C-9). The other assignments were identical with the published data.[7]

Dictysine (8): IR (KBr) ν_{max} 3421, 2926, 2844, 1726, 1458, 1383, 1272, 1070 cm^{-1}; ^1H NMR, see Table S1; ^{13}C NMR, see Table S2; ESIMS *m/z* 348 $[M + H]^+$ (100), 330 (88), 318 (50), 317 (54), 312 (64), 299 (28), 281 (51), 269 (25), 263 (46), 253 (31), 251 (47), 241 (28), 239 (100), 235 (28), 225 (35), 223 (45), 221 (84), 211 (40), 209 (37), 207 (33), 199 (32).

Geyerline (9): UV (EtOH) λ_{max} (log ϵ) 228 (4.05), 276 (3.41) nm; IR (KBr) ν_{max} 3451, 2929, 2856, 1716, 1656, 1494, 1456, 1391, 1257, 1189, 1088, 713 cm^{-1}; ESIMS *m/z* 733 $[M + Na]^+$ (48), 711 $[M + H]^+$ (100), 710 (15), 693 (19), 679 (70), 651 (100), 650 (23), 647 (22), 633 (12), 619 (100), 618 (2), 601 (30), 587 (31), 573 (15), 569 (19), 541 (7), 354 (9), 336 (5). ^1H NMR and ^{13}C NMR data were identical with the published data.[9]

Ajacine (10): $[\alpha]^{20}_D$ +32.1° (*c* 0.45, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 223 (4.31), 252 (4.05), 310 (3.68) nm; IR (KBr) ν_{max} 3450, 2925, 2855, 1691, 1591, 1526, 1451, 1378, 1298, 1089, 758 cm^{-1}. ^1H NMR and ^{13}C NMR data were identical with the published data.[10]

Lycoctonine (11): $[\alpha]^{20}_D$ +34.8° (*c* 0.32, $CHCl_3$); ESIMS *m/z* 468 $[M + H]^+$ (100), 450 (14), 437 (13), 436 (100), 418 (21), 405 (14), 404 (75), 390 (19), 387 (4), 386 (18), 376 (7), 372 (26), 358 (18), 354 (9), 344 (4), 340 (3). ^1H NMR and ^{13}C NMR data were identical with the published data.[11]

Delcosine (12): IR (KBr) ν_{max} 3518, 3473, 3356, 2945, 2868, 1638, 1464, 1392, 1270, 1087 cm^{-1}. ^1H NMR and ^{13}C NMR data were identical with the published data.[10]

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Supporting Information Available: Tables of ^1H NMR data for **3**−**7** and NMR data for **8**. This information is available free of charge via the Internet at http://pubs.acs.org.

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