DITERPENOID ALKALOIDS FROM DELPHINIUM NUDICAULE TORR. AND GRAY

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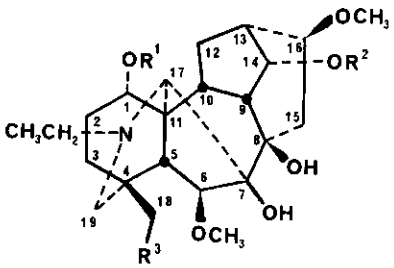
Abstract - Eight known and three apparently hitherto undescribed diterpenoid alkaloids were isolated from D. nudicaule: hetisine, 2-dehydrohetisine, 6-deoxydelcorine, dictyocarpine, dihydrogadesine, methyllycaconitine, lycoctonine, and takaosamine; and nudicaulamine, nudicauline, and nudicaulidine, the structures of which were deduced.

We report the results of a study of the alkaloids of Delphinium nudicaule Torr. and Gray an attractive red-flowered plant native to N. California and Oregon, horticultural strains of which are available from several seed-houses in N. America and Europe.

Our initial work was carried out with whole-plants collected in the wild. By conventional procedures, described previously[1], the alkaloids were isolated, saponified, and the resultant bases fractionated by column chromatography over neutral alumina. Four compounds were thus obtained, and characterised spectroscopically (IR, MS, ^{1}H- and ^{13}C-nmr). Two of these alkaloids were thus recognised[2] to be lycoctonine (1) and hetisine (2), which are well-known and commonly encountered diterpenoids of Aconitum and Delphinium. The third base was identified as 6-deoxydelcorine (3), a compound which had been described once before[3] as an isolate from D. corumbosum, on the basis of the following evidence: m/z 463 (2) and 432 (94), consistent with the required $C_{26}H_{41}NO_6$ M^+ ion of 3, and loss of the C-1 substituent methoxyl[4]; i.r. no OH or C=O absorptions; ^{1}H-nmr ($CDCl_3$) δ 3.42, 3.33, 3.29 and 3.26 (each 3H, s, 4 x OCH_3), 5.01 and 4.91 (each 1H, s, $-OCH_2O-$), 1.06 (3H, t, J = 7Hz, CH_3 of N-ethyl) and 3.64 (1H, t, J = 5Hz, H-14), all in reasonable agreement with the reported values[3,5]; and the ^{13}C-nmr of the perchlorate salt (see Table I) was also in accord[5] with the proposed structure 3. Our material, which was amorphous (lit.[3,5] mp 93-95°C), had $[\alpha]_D$-34° (c 0.14, $CHCl_3$) and formed a crystalline perchloric acid salt, mp 217-219°C.

The fourth compound, $[\alpha]_D$-27°C (c 0.36, $CHCl_3$), also refused to crystallise, although it gave a perchloric acid salt, mp 212-214°C. The structure 4 was deduced for this alkaloid on the basis of the following data: m/z 449 (4) and 418 (100) consistent with expectation for a $C_{25}H_{39}NO_6$ lycoctonine-skeleton, with a methoxy group at C-1; ν_{max} (film) 3460 (br), 1455, and 1100 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.36, 3.30 and 3.26 (each 3H, s, 3 x $-OCH_3$), 5.05 and 4.96 (each 1H, s, $-OCH_2O-$), 1.07 (3H, t, J = 7Hz, CH_3 of N-ethyl), and 4.04 (1H, t, J = 5Hz, for H-14). The ^{13}C-nmr data (see Table I) provided



1 $R^1 = R^2 = CH_3$, $R^3 = OH$

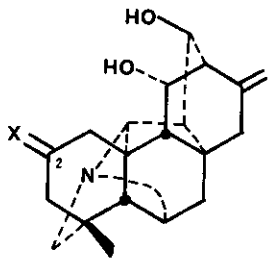
8a $R^1 = CH_3$, $R^2 = R^3 = H$

8b $R^1 = CH_3$, $R^2 = Ac$, $R^3 = H$

10a $R^1 = R^2 = R^3 = H$

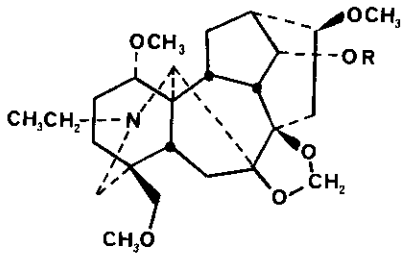
10b $R^1 = R^2 = Ac$, $R^3 = H$

12 $R^1 = R^2 = H$, $R^3 = OH$



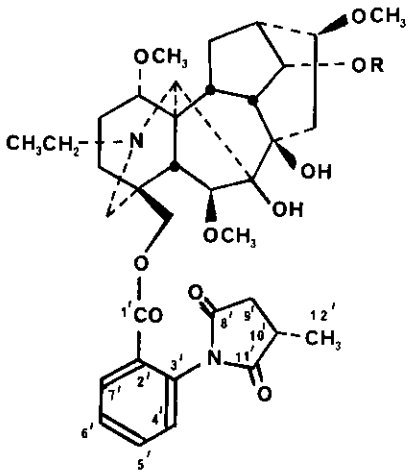
2 X = α-OH, β-H

9 X = O



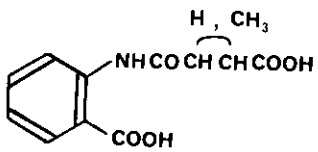
3 R = CH_3

4 R = H

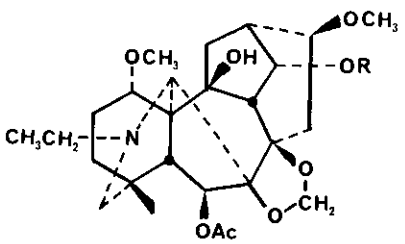


6 R = CH_3

7 R = Ac



5 (mixed isomers)



11a R = H

11b R = Ac

TABLE I. ^{13}C-Chemical shifts[a] for 6-deoxydelcorine perchloric acid salt (3.$HClO_4$), nudicaulamine (4) and its perchlorate, nudicauline (7), nudicaulidine (8a), and takaosamine (12).

	3.$HClO_4$	4	4.$HClO_4$	7	8a	12
C-1	83.1	84.9 d	82.9 d	83.8 d	85.5 d	72.6 d
2	21.8	26.0 t	21.7 t	26.0 t	25.9 t	26.9 t
3	30.1	31.9 t	30.1 t	32.0 t	37.3 t	29.3 t
4	38.8	38.3 s	38.8 s	37.5 s	34.3 s	38.2 s
5	39.6	44.0 d	39.6 d	42.5 d	55.0 d	44.8 d
6	33.1	31.6 t	33.1 t	90.5 d	90.8 d	90.1 d
7	87.6	88.3 s	87.8 s	88.2 s	89.2 s	87.8 s
8	85.1	79.2 s	84.9 s	77.4 s	b	78.0 s
9	46.1	47.5 d	46.4 d	49.9 d	45.1 d	43.9 d*
10	39.0	36.2 d	40.8 d	38.1 d	36.5 d	45.2 d*
11	53.7	50.1 s	53.5 s	48.9 s	48.5 s	48.8 s
12	25.5	26.6 t	25.5 t	28.1 t	27.6 t	26.9 t
13	43.3	46.2 d	45.8 d	45.7 d	46.0 d	39.3 d
14	84.0	74.2 d	74.9 d	75.9 d	75.3 d	75.7 d
15	34.0	32.4 t	33.8 t	33.7 t	33.1 t	34.4 t
16	81.8	81.6 d	81.7 d	82.3 d	81.7 d	81.9 d
17	63.4	62.6 d	63.5 d	64.5 d	65.0 d	66.3 d
18	78.3	78.9 t	78.2 t	69.3 t	26.8 q	66.8 t
19	58.6*	52.6 t	58.6 t*	52.2 t	56.6 t	57.0 t
NCH_2	52.6*	50.8 t	52.6 t*	51.0 t	51.2 t	50.4 t
CH_3	11.0	14.1 q	11.0 q	14.1 q	14.3 q	13.7 q
CH_3-1	56.6	56.0 q	56.4 q	55.8 q	56.0 q	-
6	-	-	-	58.1 q	58.5 q	57.8 q
14	57.8	-	-	-	-	-
16	56.4	56.5 q	56.5 q	56.2 q	56.5 q	56.3 q
18	59.6	59.5 q	59.6 q	-	-	-
-C=O	-	-	-	171.9 s	-	-
CH_3	-	-	-	21.5 q	-	-
$-OCH_2O-$	95.6	93.6 t	95.6 t	-	-	-

C-18 Ester of 7: C-1' 164.0 s 4' 130.0 d 7' 129.4 d 10' 37.0 t
2' 126.9 s 5' 131.0 d 8' 175.8 s 11' 179.8 s
3' 133.0 s 6' 133.7 d 9' 35.2 d 12' 16.4 q

a Measured at 50.3 MHz, of solutions in $CDCl_3$, except for $HClO_4$ salts which were dissolved in CD_3OD, and expressed in ppm units relative to TMS = 0. Signal multiplicities in off-resonance spectra are as indicated: s = singlet; d = doublet; t = triplet; q = quartet. Ambiguities are marked * in any column.

b Signal obscured by solvent.

powerful support for the structure 4: note in particular that this established the location of a methoxyl function at C-18 and that the concordance of shifts for C-1, -14 and -16 with those in model-compounds with closely related structures[5] establishes the orientation as well as the location of the oxygen functions. This alkaloid does not appear to have been described before, and we have named it nudicaulamine.

Acidification of the aqueous alkaline phase remaining after removal of the allkaloids from the saponification liberated methyllycoctonic acid (5) from which we infered the presence in the plant of ester-alkaloids such as methyllycaconitine (6). We therefore examined the unsaponified alkaloids obtained from a horticultural strain of D. nudicaule grown in Calgary, as well as the seeds themselves. Qualitatively, there was little difference in the TLC patterns (Silica gel 60, MeOH-$CHCl_3$ 1:4 v/v) of the alkaloids from the seeds or plants, and fractionation of these bases as before, by chromatography on alumina, yielded seven compounds.

The first of these proved[2] to be the anticipated methyllycaconitine (6). But a second, closely related alkaloid, to which we ascribe the structure 7 appears to be new. The evidence which led us to the structure of this alkaloid, which we have named nudicauline, may be summarised as follows: m/z 710 (2) and 679 (36) consistent with a $C_{38}H_{50}N_2O_{11}$ lycoctonine-type alkaloid with C-1 methoxy-function; ν_{max} (KBr) 3480 (br), 1718 (br), 1493, 1457, 1390, 1254 and 1088 cm^{-1}; ^{1}H-nmr (CD_3OD) δ 3.35, 3.30 and 3.28 (each 3H, s, 3 x $-OCH_3$), 2.00 (3H, s, CH_3COO-), 1.07 (3H, t, J = 7 Hz, CH_3 of N-ethyl), 1.39 (3H, d, J = 7Hz, CH_3 of methylsuccinimido-unit), 3.92 (1H, br s, H-6), 4.73 (1H, t, J = 5 Hz, H-14), 4.15 (centre of 2H AB pair, H-18), 7.34 (1H, dd, J = 7.5 and 2 Hz, H-4'), 7.60 (1H, dt, J = 7.5 and 2 Hz, H-5'), 7.74 (1H, dt, J = 2 and 7.5 Hz, H-6') and 8.10 (1H, dd, J = 7.5 and 2 Hz, H-7'). Note that the alternative arrangement of the acyl units at H-14 and H-18 can be excluded because the H-14 appears at ca. δ 5.0-5.5 in 14-aryl esters[5]. The ^{13}C-nmr spectrum of nudicauline (see Table I) differed significantly from that of 6[5,6] only in the expected way: the presence of signals for an acetate function instead of a methoxy at C-14, and the shift of C-14 resonance. Thus we deduced nudicauline to have the structure and stereochemistry depicted in 7. The alkaloid had $[\alpha]_D$+47° (c 0.42, $CHCl_3$). It was amorphous, but formed a pale cream-coloured crystalline hydroiodide salt, mp 228-230°C.

Another apparently unknown alkaloid was also obtained in amorphous form. This compound, $[\alpha]_D$+42° (c 0.15, $CHCl_3$), which we have named nudicaulidine, was deduced to have the structure 8a on the basis of the following evidence: m/z 437 (3), 422 (18) and 406 (100) consistent with a $C_{24}H_{39}NO_6$ lycoctonine-type alkaloid with C-1 methoxy function; ν_{max} (film) 3470 (br), 1460, and 1093 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 3.41, 3.36 and 3.24 (each 3H, s, 3 x OCH_3), 1.04 (3H, t, J = 7Hz, CH_3 of N-ethyl), 0.98 (3H, s, CH_3-C-), 3.84 (1H, br s, H-6) and 3.96 (1H, t, J = 5Hz, H-14). Upon acetylation (Py-Ac_2O) nudicaulidine gave a monoacetate 8b in which the H-14 signal appeared at δ 4.75 (1H, t, J =

5Hz). The ^{13}C-nmr spectrum of nudicaulidine (see Table I) was in complete agreement with the structure including stereochemistry shown in 8a.

Besides these compounds we also isolated 2-dehydrohetisine (9)[2] (but not hetisine) from both seeds and plants. As well we obtained a mixture of two alkaloids which co-chromatographed in a number of solvent systems but which we were able to separate after acetylation (Py-Ac_2O/25°C) by PTLC (Silica gel 60, $CHCl_3$-MeOH 7:1 v/v) to yield as major component the 1,14-diacetate (10b) of dihydrogadesine (10a), and as minor the 14-acetate (11b) of dictyocarpine (11a). The evidence for these identifications can be summarised as follows.

For 10b: ^{1}H-nmr ($CDCl_3$) δ 0.99 (3H, s, quaternary-CH_3), 1.08 (3H, t, J = 7 Hz, CH_3 of N-ethyl), 2.04 and 2.06 (each 3H, s, 2 x CH_3COO-), 3.32 and 3.41 (each 3H, s, 2 x CH_3O-), 3.90 (1H, br s, H-6), 4.70 (1H, t, J = 5Hz, H-14), and 4.73 (1H, dd, J = 10.5 and 7 Hz, H-1).

For 11b: ^{1}H-nmr ($CDCl_3$) δ 0.88 (3H, s, quaternary-CH_3), 1.06 (3H, t, J = 7Hz, CH_3 of N-ethyl), 2.06 (6H, s, 2 x CH_3COO-), 3.26 and 3.30 (each 3H, s, 2 x CH_3O-), 4.87 and 4.95 (each 1H, s, -OCH_2O-), 5.23 (1H, t, J = 5Hz, H-14), and 5.42 (1H, br s, H-6). This data is in good agreement with that reported[5,6] for 11b. With their acetates identified it was possible to analyse the ^{1}H- and ^{13}C-nmr spectra of the mixture of parent alkaloids, and to see the signals required for 10a[5,7] and 11a[5,6,8].

Finally, from the seed alkaloids alone we isolated another alkaloid as an amorphous solid and identified this as 12 on the basis of the following measurements: m/z 439 (17) and 424 (95) consistent with a $C_{23}H_{37}NO_7$ lycoctonine-type alkaloid with C-1 methoxy function; ν_{max} (KBr) 3430 (br), 1455 and 1080 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.10 (3H, t, J = 7 Hz, CH_3 of N-ethyl), 3.37 and 3.40 (each 3H, s, 2 x CH_3O), 4.00 (1H, br s, H-6) and 4.12 (1H, t, J = 5Hz, H-14). This ^{1}H-nmr data is in excellent agreement with that reported[5,9] for takaosamine, an alkaloid isolated from A. japonicum and assigned structure 12, although that alkaloid was reported[5,9] to have mp 174-175°C. The ^{13}C-nmr spectrum of our base (see Table I) also supports the suggested structure; and the $[\alpha]_D$ +61.6° (c 0.19, $CHCl_3$) also agrees with the literature value[5,9] of $[\alpha]_D$+61.2° ($CHCl_3$) for takaosamine. Thus we isolated and characterised a total of eleven diterpenoid alkaloids from D. nudicaule, three of which appear to be new compounds.

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