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^{1}H-NMR SPECTRA OF NORDITERPENOID ALKALOIDS. A REVIEW[1]

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ABSTRACT.—The ^{1}H-nmr spectra of the diterpenoid moiety of 52 norditerpenoid alkaloids are dealt with in this review. The norditerpenoid alkaloids have been classified into six types. For each of these categories the average chemical shifts of the protons are represented in tables and discussed in the text. Dihedral angles, multiplicities, and *J* values are tabulated.

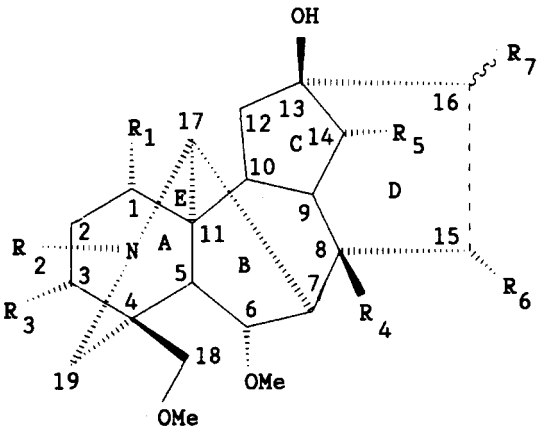
Diterpenoid alkaloids occur in plants that grow throughout the Northern Hemisphere, species of the Ranunculaceae (*Aconitum, Delphinium*), Garryaceae (*Garrya*), Compositae (*Inula royleana*), Saxifragaceae (*Anopterus*), and Rosaceae (*Spiraea japonica*). Due to their high toxicity and varied pharmacological properties (2,3), they have attracted much interest.

Two classes of diterpenoid alkaloids can be differentiated. One class includes the less toxic C_{20}-alkaloids. The second group comprises the highly toxic C_{19}-alkaloids, usually called norditerpenoid alkaloids, of which their ^{1}H-nmr data are the subject of this review. The norditerpenoid alkaloids display more oxygenation centers in the form of hydroxyl, *O*-ester and methoxyl groups than do the C_{20}-type alkaloids. The alkaloids dealt with in this review have been classified into six types (I–VI) and are oxygenated at C-1, C-6 (except type V and compound **51**), C-8 (except artifacts **12** and **13**), C-14, C-16, and C-18. In types I–IV the 6-*O*-substituent is α-orientated, while in type VI β-orientation prevails. Depending on the position of the additional oxygen groups these six types can be distinguished as follows:

I. Aconitine Type: Additional hydroxyl groups occur at C-3, C-13, and C-15.
II. Pseudaconitine Type: The additional hydroxyls are at C-13 and C-15 only.
III. Bikhaconitine Type: There is only one additional hydroxyl, which is at C-13.
IV. Neoline Type: There is no additional oxygenation at C-3 (except falconerine [**39**]), C-13, or C-15 (except 8-acetyl-15α-hydroxyneoline [**40**] and 15α-hydroxy-1-*epi*-neoline [**41**]).
V. Isotalatizidine Type: There is no oxygenation at C-3, C-6, C-13, or C-15.
VI. Lycoctonine Type: Oxygenation at C-7 is typical for this type. Oxygen substitution at C-6 is in most cases in the β- position. There is no oxygenation at C-3, C-13, or C-15.

Although complete ^{13}C-nmr spectra of many norditerpenoid alkaloids have been reported, only a few complete ^{1}H-nmr data compilations are available in the literature (4–6). The systematic studies in this laboratory on complete ^{1}H-nmr spectra of norditerpenoid alkaloids (1, 7–12; S.J. Desai, unpublished results) has provided a ^{1}H-nmr data bank of 46 compounds. The chemical shift assignments were based on one-dimensional ^{1}H-nmr spectra in conjunction with spin-spin decoupling experiments, two-dimensional ^{1}H-^{1}H COSY, and in some cases on confirmation with ^{1}H-^{13}C HETCOR. Furthermore, we have included in this review compounds **5** (13), **6** (14), **8** (15), **10** (16), **42** (17), and **52** (18), for which complete ^{1}H-nmr data are available in the literature. Tables 1–7 show the average chemical shifts and shift ranges. They serve as the basis for the following discussion of the ^{1}H-nmr spectra of compounds **1–52** . Table 8 summarizes the dihedral angles of the CH-bonds, the ^{1}H multiplicities and the

[1]Communication No. 15 on *Aconitum*. For communication No. 14, see Hanuman and Katz (1).



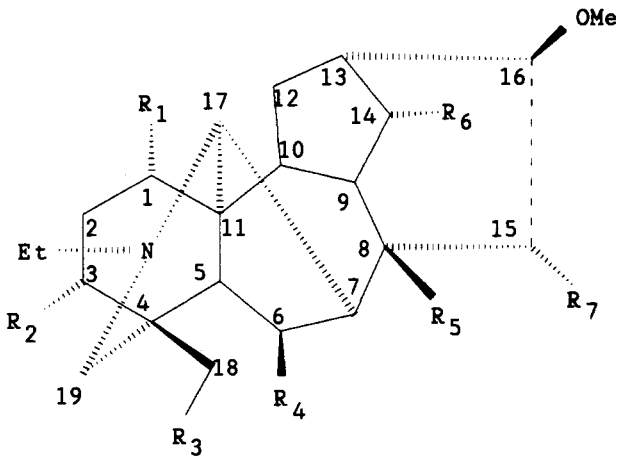
Structures **1–32**

No.	Compound	R_1[a]	R_2[a]	R_3[a]	R_4[a]	R_5[a]	R_6	R_7	Source[b]
I.	Aconitine type								
1	Aconitine	OMe	Et	OH	OAc	OBz	OH	β-OMe	N
2	Benzoylaconine	OMe	Et	OH	OH	OBz	OH	β-OMe	N
3	Aconine	OMe	Et	OH	OH	OH	OH	β-OMe	S
4	8-*O*-Methylaconine	OMe	Et	OH	OMe	OH	OH	β-OMe	S
5	14-Benzoyl-8-*O*-ethylaconine	OMe	Et	OH	OEt	OBz	OH	β-OMe	N
6	Polyschistine A	OMe	Et	OAc	OEt	OBz	OH	β-OMe	N
7	Mesaconitine	OMe	Me	OH	OAc	OBz	OH	β-OMe	N
8	Hokbusine A	OMe	Me	OH	OMe	OBz	OH	β-OMe	N
9	Hypaconitine	OMe	Me	H	OAc	OBz	OH	β-OMe	N
10	1-Demethylhypaconitine	OH	Me	H	OAc	OBz	OH	β-OMe	N
11	3-Deoxyaconitine	OMe	Et	H	OAc	OBz	OH	β-OMe	N
12	Desbenzoylpyroaconitine	OMe	Et	OH	H	OH	=O	β-OMe	S
13	16-*epi*-Desbenzoylpyro-aconitine	OMe	Et	OH	H	OH	=O	α-OMe	S
II.	Pseudaconitine type								
14	Pseudaconitine	OMe	Et	OH	OAc	OVr	H	β-OMe	N
15	Veratroylpseudaconine	OMe	Et	OH	OH	OVr	H	β-OMe	N
16	Pseudaconine	OMe	Et	OH	OH	OH	H	β-OMe	N
17	8-Lipopseudaconitine	OMe	Et	OH	Olip.	OVr	H	β-OMe	N
18	Yunaconitine	OMe	Et	OH	OAc	OAs	H	β-OMe	N
19	8-Lipoyunaconitine	OMe	Et	OH	Olip.	OAs	H	β-OMe	N
20	8-Deacetylyunaconitine	OMe	Et	OH	OH	OAs	H	β-OMe	N
21	Indaconitine	OMe	Et	OH	OAc	OBz	H	β-OMe	N
22	8-Lipoindaconitine	OMe	Et	OH	Olip.	OBz	H	β-OMe	N
23	Ludaconitine	OMe	Et	OH	OH	OBz	H	β-OMe	N
24	3-Acetylpseudaconitine	OMe	Et	OAc	OAc	OVr	H	β-OMe	S
25	3-Acetylyunaconitine	OMe	Et	OAc	OAc	OAs	H	β-OMe	N
26	3-Acetylveratroylpseudaconine	OMe	Et	OAc	OH	OVr	H	β-OMe	S
III.	Bikhaconitine type								
27	Bikhaconitine	OMe	Et	H	OAc	OVr	H	β-OMe	N
28	Veratroylbikhaconine	OMe	Et	H	OH	OVr	H	β-OMe	N
29	8-Lipobikhaconitine	OMe	Et	H	Olip.	OVr	H	β-OMe	N
30	Bikhaconine	OMe	Et	H	OH	OH	H	β-OMe	N
31	Chasmaconitine	OMe	Et	H	OAc	OBz	H	β-OMe	N
32	Crassicauline A	OMe	Et	H	OAc	OAs	H	β-OMe	N

[a]Me=methyl; Et=ethyl; Ac=acetyl; Vr=veratroyl; lip.=mixture of lipoyl fragments (palmitoyl, stearoyl, oleoyl, linoleyl, linolenoyl); As=anisoyl.

[b]N=natural compound, S=semi-synthetic compound.

calculated, as well as the observed *J* values. Joshi and Pelletier (19) reviewed the work done on the basis of X-ray studies regarding the conformation of rings A–F. Rings A, B, and E of aconitine are in the chair form, and ring C is in the envelope form with C-



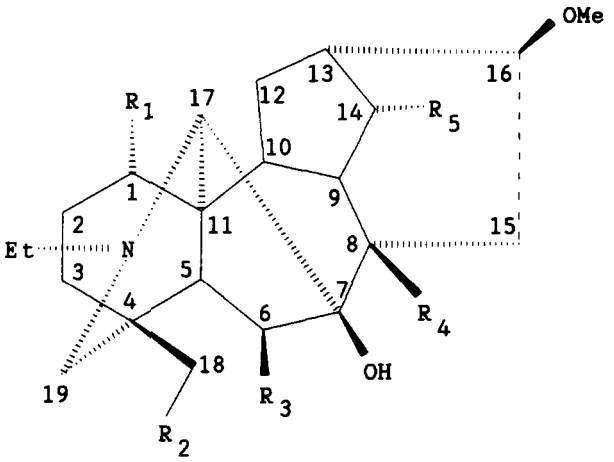
Structures **33–46**

No.	Compound	R_1[a]	R_2[a]	R_3[a]	R_4[a]	R_5[a]	R_6[a]	R_7	Source[b]
IV.	Neoline type								
33	Neoline	α-OH	H	OMe	OMe	OH	OH	H	N
34	Senbusine A	α-OH	H	OMe	OH	OH	OH	H	N
35	14-*O*-Acetylsenbusine A	α-OH	H	OMe	OH	OH	OAc	H	N
36	1,6,14-Triacetylsenbusine A	α-OAc	H	OMe	OAc	OH	OAc	H	S
37	1,6-Dehydro-14-*O*-acetyl-senbusine A	=O	H	OMe	=O	OH	OAc	H	S
38	Falconericine	α-OMe	H	OMe	OMe	OAc	OVr	H	N
39	Falconerine	α-OMe	OH	OMe	OMe	OH	OVr	H	N
40	8-Acetyl-15α-hydroxyneoline	α-OH	H	OMe	OMe	OAc	OH	OH	N
41	15α-Hydroxy-1-*epi*-neoline	β-OH	H	OMe	OMe	OH	OH	OH	N
42	1,14-Diacetylneoline	α-OAc	H	OMe	OMe	OH	OAc	H	N
V.	Isotalatizidine type								
43	Isotalatizidine	OH	H	OMe	H	OH	OH	H	N
44	Columbianine	OH	H	OH	H	OH	OH	H	N
45	Talatisamine	OMe	H	OMe	H	OH	OH	H	N
46	14-*O*-Acetyltalatisamine	OMe	H	OMe	H	OH	OAc	H	N

[a]Me=methyl; Ac=acetyl; Vr=veratroyl.
[b]N=natural compound, S=semi-synthetic compound.

14 at the flap. Ring D is in the boat form with the end at C-15 flattened, and ring F is in the half-chair form (20).

RING A.—Depending on the oxygenation in ring A, two patterns of coupling systems can be observed. Compounds of types I and II, which are oxygenated at C-1 and C-3, exhibit an ABXY system, whereas an A_2B_2X is noted in compounds of the 3-deoxy types III–VI, and in compounds **9** and **11** of type I. The average chemical shift of X (H-1β) of ABXY is 3.12±0.06 ppm and of Y (H-3β), 3.77±0.09 ppm. A (H_a-2) of ABXY resonates at 2.06±0.18 ppm and B (H_b-2) at 2.36±0.04 ppm, both as multiplets. In compounds of type II, acetylation of 3α-OH causes downfield shifts of AB ($H_{a,b}$-2) and Y (Hβ-3), which resonate at 2.37±0.02 and 4.90±0.01 ppm, respectively. These downfield shifts are due to an α-effect on the C-3 proton and an anisotropic effect of the acetyl carbonyl group on the C-2 methylene protons. In types III-VI an A_2B_2X spin system is observed. In 1α-methoxy compounds, X (Hβ-1) of A_2B_2X appears at 3.04±0.11, A_2 (H_2-3) at 1.59±0.20, and B_2 (H_2-2) at 2.1±0.20 ppm. In 1α-hydroxy compounds of types IV-VI, X (Hβ-1) resonates at 3.68±0.05, A_2 (H_2-2) at 1.59±0.13,



Structures **47–52**

No.	Compound	R_1[a]	R_2[a]	R_3[a]	R_4[a]	R_5[a]	Source[b]
VI.	Lycoctonine type						
47	Gigactonine	OH	OH	β-OMe	OH	OMe	N
48	Lycoctonine	OMe	OH	β-OMe	OH	OMe	N
49	14-Methyldelphinifoline	OH	OMe	β-OH	OH	OMe	N
50	Demethylenedelcorin	OMe	OMe	β-OH	OH	OMe	N
51	Virescenine	OH	OMe	H	OH	OH	N
52	Pubescenine	OH	OMe	α-OH	OMe	OAc	N

[a]Me=methyl; Ac=acetyl
[b]N=natural compound.

and B_2 (H_2-3) at 1.74±0.22 ppm, while in the 1β-hydroxy compound of type IV, X (Hβ-1) is noted at 3.90, A_2 (H_a-2, H_a-3) at 1.36, and B_2 (H_b-2, H_b-3) at 2.96/1.85 ppm, with a shift difference of 1.60 and 0.49 ppm between the A and B protons.

RING B.—In compounds of types I–IV, oxygenation is observed at C-6α and C-8, in type V at C-8, in type VI at C-6β (except **52**: C-6α), C-7, and C-8. An ABX and AB_2C spin system could be expected in types I–IV and V, respectively. However, due to the dihedral angle of ca. 110° between Hβ-6 and H-7 (8), an AX pattern is observed. In 8-OH compounds, H-7 resonates at 1.97±0.11 ppm, while in 8-OAc alkaloids it exhibits a downfield shift to 2.90±0.12 ppm due to deshielding by the acetyl carbonyl. In 6α-methoxy compounds of types I–IV, A (H-5) of AX resonates at 2.06±0.09 and X (Hβ-6) at 4.05±0.11 ppm. In the 6β-methoxy compounds of type VI, A (H-5) appears at 1.78±0.09 and X (Hβ-6) at 3.92±0.07 ppm. In the 6α-hydroxy compounds of type IV, X (Hβ-6) resonates at 4.74±0.03 ppm, and in 6α- and 6β-hydroxy compounds of type VI X (Hβ- and Hα-6) at 4.41±0.09 ppm. This is a downfield shift of 0.69 and 0.49 ppm, respectively, compared with 6α- and 6β-methoxy compounds. The 6-deoxy compounds of type V display an A_2BC pattern, while the 6-deoxy compound **51** of type VI shows an A_2B system due to the tertiary hydroxyl substituent at C-7. The A_2 signal (Hβ-5/H_a-6) in both cases appears at 1.76±0.11/1.56±0.06 ppm, whereas the B resonance (H_b-6) of type VI appears at lower field (at 2.30 ppm) than B of type V, which resonates at 1.90±0.04 ppm. The C signal (Hα-7) of the A_2BC system in type V appears as a multiplet at 2.10±0.02 ppm.

RING C.—The oxygen substituents in ring C are located at either C-13 and C-14

TABLE 1. ^{1}H-Nmr Data of Ring A of Norditerpenoid Alkaloids.

Position	Type											
	I		II		III	IV			V		VI	
	1α-OMe	1α-OMe 15-dehydro	1α-OMe	3-OAc	1α-OMe	1α-OMe	1α-OH	1β-OH	1α-OMe	1α-OH	1α-OMe	1α-OH
H-1	3.14±0.04	3.00±0.02	3.10±0.04	3.10±0.04	3.01±0.02	3.03±0.00	3.67±0.03	3.90	3.11±0.04	3.72±0.01	2.94±0.01	3.66±0.03
H_a-2	1.97±0.09	2.16±0.01	2.13±0.11	2.37±0.02	1.97±0.03	1.96±0.01	1.54±0.02	1.36	1.98±0.00	1.67±0.04	2.00±0.10	1.52±0.06
H_b-2	2.34±0.02	2.34±0.02	2.36±0.04	2.37±0.02	2.28±0.02	2.27±0.03	1.88±0.04	2.96	2.22±0.00	1.85±0.01	2.08±0.08	1.75±0.21
H_a-3	3.82±0.05	3.65±0.01	3.73±0.05	4.90±0.01	1.59±0.09	1.63±0.00	1.54±0.02	1.36	1.38±0.01	1.67±0.04	1.39±0.12	1.63±0.09
H_b-3	—	—	—	—	1.62±0.05	1.63±0.00	1.54±0.02	1.85	1.80±0.00	1.67±0.04	1.67±0.16	1.75±0.21

TABLE 2. ^{1}H-Nmr Data of Ring B of Norditerpenoid Alkaloids.

Position	Type									
	I	II	III	IV		V	VI			
	6α-OMe	6α-OMe	6α-OMe	6α-OH	6α-OMe	6-H	6-H	6β-OMe	6β-OH	6α-OH
H-5	2.06±0.06	2.05±0.06	2.04±0.04	2.10±0.08	2.10±0.01	1.76±0.11	1.79	1.78±0.09	1.59±0.11	2.13
H_a-6	4.02±0.07	4.08±0.07	3.98±0.04	4.10±0.07	4.74±0.03	1.56±0.06	1.60	3.92±0.07	4.41±0.09	4.45
H_b-6	—	—	—	—	—	1.90±0.04	2.30	—	—	—
H-7	2.89±0.21	2.96±0.07 (8-OAc) 1.97±0.11 (8-OH)	2.96±0.06 (8-OAc) 2.08±0.01 (8-OH)	2.81±0.03 (8-OAc) 2.01±0.01 (8-OH)	— 1.93±0.00 (8-OH)	2.10±0.02	—	—	—	—

TABLE 3. ^{1}H-Nmr Data of Ring C of Norditerpenoid Alkaloids.

Position	Type												
	I		II		III		IV			V		VI	
	8-OAc 14-OAr	8-OH 14-OAr	8-OAc 14-OAr	8-OH 14-OAr	8-OAc 14-OAr	8-OH 14-OAr	8-OH 14-OAc	8-OH 14-OAr	8-OH 14-OH	8-OH 14-OH	8-OH 14-OAc	8-OH 14α-OMe	6-H 14α-OH
H-9	2.90±0.01	2.52	2.91±0.02	2.54±0.02	2.90±0.01	2.54±0.00	2.33±0.19	2.43±0.00	2.19±0.05	2.25±0.03	2.35	3.10±0.14	2.22
H-10	2.01±0.11	2.13	2.10±0.07	2.10±0.07	2.06±0.03	2.06±0.03	1.93±0.12	1.95±0.01	1.93±0.12	1.78±0.08	1.63	1.94±0.04	1.81
H_a-12	2.01±0.11	2.13	2.10±0.07	2.10±0.07	2.06±0.03	2.06±0.03	1.69±0.28	1.96±0.01	1.69±0.28	1.70±0.10	1.90	1.75±0.04	1.55
H_b-12	2.66±0.30	2.58	2.72±0.20	2.54±0.10	2.78±0.02	2.59±0.00	2.26±0.29	2.38±0.07	2.26±0.29	1.98±0.08	2.14	2.25±0.17	2.06
H-13	—	—	—	—	—	—	2.59±0.07	2.67±0.10	2.30±0.05	2.35±0.01	2.65	2.40±0.07	2.35
H-14	4.89±0.09	5.00 3.91 (8,14-OH)	4.87±0.02	5.14±0.02 4.01 (8,14-OH)	4.87±0.02	5.15±0.00 3.99 (8,14-OH)	4.78±0.04	5.10±0.06	4.16±0.05	4.18±0.05	4.83	3.65±0.05	4.24

TABLE 4. ^{1}H-Nmr Data of Ring D of Norditerpenoid Alkaloids.

Position	Type								
	I	II		III		IV	V		VI
	8-OAc 14-OAr	8-OAc 14-OAr	8-OH 14-OAr	8-OAc 14-OAr	8-OH 14-OAr	8-OH 14-OAc	8-OH 14-OH	8-OH 14-OAc	8-OH 14α-OMe
H_a-15	4.51±0.06	2.45±0.05	2.28±0.06	2.45±0.03	2.29±0.03	2.09±0.16	2.07±0.01	1.90	1.69±0.09
H_b-15	—	3.06±0.08	2.57±0.04	3.05±0.03	2.55±0.03	2.37±0.13	2.43±0.01	2.42	2.80±0.20
OH-15	4.40±0.09	—	—	—	—	—	—	—	—
H-16	3.29±0.10 3.88 (16α-OMe)	3.34±0.05	—	3.37±0.05	—	3.20±0.17	3.39±0.02	3.20	3.29±0.10

TABLE 5. ^{1}H-Nmr Data of Ring E of Norditerpenoid Alkaloids.

Position	Type									
	I	II	III	IV		V			VI	
	1α-OMe	1α-OMe	1α-OMe	8-OAc	8-OH	1-dehydro	1α-OH	1α-OMe	1α-OH	1α-OMe
H-17	3.02±0.22	2.96±0.11	3.02±0.12	2.94±0.05	2.60±0.07	3.34±0.00	2.80±0.01	3.10±0.07	2.95±0.20	2.89±0.01
H_a-19	2.44±0.13	2.35±0.09	2.37±0.11	2.15±0.21	2.15±0.21	2.15±0.21	2.07±0.01	2.02±0.01	2.44±0.09	2.40±0.14
H_b-19	2.89±0.04	2.85±0.09	2.99±0.10	2.70±0.16	2.70±0.16	2.70±0.16	2.34±0.00	2.53±0.02	2.61±0.18	2.62±0.02

TABLE 6. ^{1}H-Nmr Data of 4-Methoxymethyl Side-Chain of Norditerpenoid Alkaloids.

Position	Type											
	I		II			III		IV	V		VI	
	3α-OH	3α-OAc	3α-OH	3α-OAc	8-OH	8-OAc	8-OH	8-OH	18-OH	18-OMe	18-OH	18-OMe
H_a-18	3.56±0.12	2.96	3.49±0.01	2.98±0.02	3.74±0.03	3.14±0.02	3.31±0.01	3.20±0.16	3.27	3.00±0.01	3.35±0.01	3.19±0.15
H_b-18	3.61±0.08	3.83	3.63±0.01	3.93±0.09	—	3.60±0.01	3.68±0.02	3.59±0.14	3.41	3.13±0.02	3.64±0.01	3.28±0.06

TABLE 7. ^{1}H-Nmr Data of the *N*-Ethyl Side-Chain of Norditerpenoid Alkaloids.

Position	Type						
	I	II	III	IV		V	VI
	15-OH	15-H	15-H	15-H	15-OH	15-H	15-H
H_a-20	2.46±0.09	2.54±0.04	2.53±0.06	2.50±0.05	2.36±0.05	2.49±0.03	2.89±0.05
H_b-20	2.69±0.07	—	—	—	2.69±0.09	—	—
H_3-21	1.09±0.01	1.10±0.01	1.07±0.01	1.08±0.05	1.08±0.05	1.09±0.03	1.07±0.03

TABLE 8. Dihedral Angles, Multiplicities, and *J* Values of Norditerpenoid Alkaloids.[a]

Position	Angle		Configuration	Multiplicity	Expected *J* Value	Observed *J* Value
	Chair	Boat				
H_e-1/H_e-2	70°	55°				
H_e-1/H_a-2	50°	60°			6.0	
H_a-1/H_a-2	180°	180°	Hβ-1	t	6.5	6.0–8.8
				dd		5.8–7.5
H_a-1/H_e-2	50°	65°			7.6	7.5–11.0
				m	—	—
H_e-2/H_e-3	70°	50°				
H_e-2/H_e-3	50°	65°	Hβ-3	t	5.0	8.2
				dd		4.0–6.0
H_a-2/H_a-3	165°	180°			9.0	8.0–13.0
				m	—	—
H_a-2/H_e-3	50°	65°			5.0	
H-5/H_a-6	25°		Hβ-5	d	6.0	4.2–7.0
				m	—	—
H-5/H_e-6	95°				0.4	
H_a-6/H-7	110°				1.0	
H_e-6/H-7	10°		Hβ-6	d	7.4	6.0–8.0
				dd		5.0, 11.0
				m	—	—
H-9/H_a-10	20°				6.5	6.5–6.6
				m	—	—
H-9/H_a-14	30°		Hβ-9	t	5.6	6.0
				dd		4.7–5.1
H-10/H_a-12	0°					
H-10/H_e-12	120°				4.4	
H_e-12/H-13	80°				6.0	
H_a-12/H-13	40°					
H_a-14/H-13	75°		Hβ-14	d	1.8	4.0–6.0
				m	—	—
H-13/H_a-16	130°				6.0	
H_a-15/H-8	40°				2.5	4.0–16.0
H_e-15/H_e-8	80°					
H_a-15/H_a-16	170°		Hβ-15	t	9.6	4.0
				d		2.0–6.1
				dd		2.0–7.0
				m	—	—
H_e-15/H_a-16	50°		OHα-15	d	1.8	2.0–4.0
			Hα-16	d		4.0–8.0
				dd		4.5–7.0
						8.0–10.0
				m	—	—
H_e-17/H_a-7	90°		Hα-17	br s	1.0	
H_a-18/H_b-18	120°		H-18	d s	4.4	8.0–10.0
H_a-19/H_b-19	120°		H-19	d	4.4	10.0–12.0
						6.0–9.0
				dd		16.0
H_a-20/H_b-20	120°		H-20	t	4.4	7.2
				dd		4.0–8.0
						7.0–14.0
				m	—	—
			H-21	t		6.0–8.0

[a]Angles measured ± 5° on Dreiding models with a Büchi Torsiometer; *J* values expressed in Hz.

(types I–III) or at C-14 only (types IV–VI). In the 13-hydroxy alkaloids (types I–III), an AX of H-9 and H-14 and an A_2B system of H_2-12 and H-10 are observed, whereas in types IV-VI we find the ABX system of H-13, H-9, and H-14, and the ABC system caused by H_2-12 and H-10. In 8-OAc compounds of types I–III, the A (H-9) of the AX system resonates at 2.91±0.02 ppm, and in 8-OH compounds at 2.44±0.12 ppm. In 8-OAc, 14α-*O*-aryl ester compounds of types I–III, X (Hβ-14) resonates at 4.89±0.09 ppm, while in 8-OH, 14α-*O*-aryl ester compounds it appears at 5.08±0.08 ppm, whereas in aconines (8-OH, 14α-OH) the resonance is further upfield at 3.96±0.05 ppm. In the 13-deoxy types IV–VI the A (H-9) of ABX appears at 2.33± 0.19 ppm with the exception of the 14α-OMe alkaloids **47–50**, where it appears at 3.10±0.14 ppm. The B (H-13) signal of ABX in 8-OH, 14α-*O*-ester compounds appears at 2.64±0.12 ppm, whereas in aconines (8-OH, 14α-OH), it resonates at 2.30±0.05 ppm. The X (Hβ-14) of ABX appears in 8-OH, 14α-*O*-acetyl esters at 4.78±0.04 ppm, in 8-OAc, as well as in 8-OH, 14α-*O*-aryl esters at 5.10±0.06 ppm, and in aconines (8-OH, 14α-OH) at higher field at 4.16±0.05 ppm. In types I–III A_2 (H_a-12, H_b-12) of A_2B resonates at 2.03±0.13 ppm and B (H_b-12) appears at 2.66±0.30 ppm. In contrast, in types IV–VI the A (H_a-12) signal of ABC appears at 1.69±0.28 ppm, B (H-10) at 1.84±0.21 ppm, and C (H_b-12) at 2.26±0.29 ppm.

RING D.—The alkaloids of type I, as well as compounds **40** and **41** (type IV) are oxygenated at C-15 and C-16. They exhibit an XY (Hβ-15, Hα-16) spin system, in contrast to all other types which display an ABX (H_2-15, Hα-16). In 8-OAc compounds, the X (Hα-16) of XY resonates at 3.29±0.10 ppm, and in the semi-synthetic 15-dehydro-16β-epimer **13** it resonates at 3.88 ppm. The Y (Hβ-15) of XY resonates at 4.51±0.06 ppm as a doublet of doublets due to coupling both with X (Hα-16) and H of 15α-OH. In 8-OAc, 14α-*O*-aryl ester compounds of types II and III, A (H_a-15) and B (H_b-15) of ABX resonate at 2.45±0.05 and 3.06±0.08 ppm, respectively, with X (Hα-16) at 3.37±0.05 ppm, whereas in 8-OH, 14α-*O*-aryl ester compounds, A (H_a-15) resonates at 2.28±0.06 ppm, B (H_b-15) at 2.57±0.04 ppm with a difference of 0.17 and 0.49 ppm, and X (Hα-16) at 3.37±0.05 ppm. In 8-OH, 14α-OAc compounds of types IV and V, A (H_a-15), B (H_b-15) and X (Hα-16), in turn, resonate at 2.07±0.17, 2.37±0.13 and 3.20±0.17 ppm as multiplets, against shifts of 1.69±0.09, 2.80±0.20, and 3.29±0.10 ppm displayed in 8-OH, 14α-OMe compounds of type VI.

RING E.—In ring E, C-17 and C-19 are bridged by a nitrogen atom resulting in relatively downfield resonances of H-17 and H_2-19. In most of the norditerpenoid alkaloids, H-17 appears as a broad singlet without any splitting due to the bonding angle of 100° with the neighboring H-7. All 1α-methoxy compounds show this singlet at 3.02±0.22 ppm; in the 1α-hydroxy, 8-OH compounds **33–35** of type IV, it appears relatively upfield at 2.60±0.07 ppm. In the 1-dehydro compound **37**, due to deshielding by the carbonyl group, a marked downfield shift to 3.34 ppm is observed.

The H_a and H_b of C-19 exhibit an AB spin system. In C-3 *O*-substituted compounds of types I and II, A of H_2-19 resonates at 2.42±0.15 ppm and B at 2.92±0.16 ppm. The chemical shift differences of A and B are in the range of 0.46±0.51 ppm. The C-3 deoxy compounds of type I deviate from these values in a way which can not be analyzed until more compounds are available. In deoxyaconitine the shift difference of 0.78 ppm is particularly large. It results from a relatively low A of 2.13 ppm. In contrast, in hypaconitine the shift difference of 0.19 ppm results from a low value (2.55 ppm) of B. In compounds of type III, the chemical shift difference between H_a- and H_b-19 in 8-OAc, 14α-*O*-aryl esters is 0.54 ppm, in 8-OH, 14α-*O*-aryl esters 0.31 ppm, and in 8-OH, 14α-OH alkaloids, it is 0.14 ppm. The 3-*O*-substituted alkaloids (types I and II) do not show

these decreasing differences between H_a- and H_b-19. In types IV–VI, H_a-19 resonates at 2.14±0.16 ppm, and H_b-19 at 2.56±0.22 ppm.

N-ETHYL SIDE-CHAIN.—In 15α-OH compounds of type I the methylene protons of the *N*-ethyl side-chain ($H_{a,b}$-20) display an AB system with a 0.23±0.13 ppm shift difference [A (H_a-20) resonates at 2.46±0.09 ppm and B (H_b-20) at 2.69±0.07 ppm], whereas in 15-deoxy compounds the AB signals appear as multiplets. In compounds of types II–IV, AB signals (H_a/H_b-20) appear as multiplets at 2.52±0.07 ppm (except in the C-15-OH compounds **40** and **41** of type IV which show the same resonances as type I) and in type VI at 2.89±0.05 ppm. This can be explained by considering a non-bonded electron interaction of 15α-OH and the nitrogen atom due to unfavored parallel disposition. As a result the non-bonded nitrogen electrons orient themselves close to the C-20 methylene protons, thus causing the shift difference. In all types the terminal methyl group appears as a triplet at 1.08±0.05 ppm.

C-18 SIDE-CHAIN.—H_2-18 displays an AB system. In 3α-OH compounds of type I and II, as well as in compound **39** of type IV the shift difference of A (H_a-18) and B (H_b-18) is 0.065±0.065 ppm, while in the 3α-OAc compounds, due to the anisotropic effect of the acetyl carbonyl, the difference is 0.94±0.01 ppm. The 3-deoxy alkaloids in types I, III, and IV show differences of 0.47±0.13, in V of 0.13±0.01, and in VI of 0.22±0.07 ppm. The influence of the various substituents on these shift differences can not be evaluated.

On examining Dreiding models of norditerpenoid alkaloids, *W*-conformation is noted among the following protons: 3β-H/19-H_a, 1α-OMe/3α-H or OH, **5-H/17-H**, **5-H/19-H_e**, 8-OH/10-H, 9-H/13-OH, 9-H/15α-OH, 12α-H/14α-OH, **14β-H/16β-OMe**, 16β-OMe/8-OH, **H-16/13-OH**, and 17-H/19-H_e. The long-range couplings set in bold type were observed in the ^{1}H-^{1}H COSY nmr spectra of most of these alkaloids (8–12). In some cases they could not be read due to other, overlapping signals.

ESTER SUBSTITUENTS.—These present the well-known shifts and connectivities of veratroyl-, anisoyl-, benzoyl-, and acetyl- groups, and therefore are not dealt with in this review.

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