ISOLATION AND STRUCTURE OF RAVEYINE, A NOVEL NORDITERPENOID ALKALOID FROM *CONSOLIDA RAVEYI* (BOISS) SCHRÖD.

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Abstract - From the aerial parts of *Consolida raveyi* (Boiss) Schröd., a new norditerpenoid alkaloid designated as *raveyine* has been isolated along with the known alkaloids ajaconine, azitine, chellespontine and isoatisine. The structure of *raveyine* (**4**) was determined on the basis of homonuclear ^{1}H decoupled ^{13}C, DEPT, 2D ^{1}H phase sensitive COSY, TOCSY, ROESY, ^{1}H-^{13}C HMQC, HMQC-clean TOCSY and HMBC NMR spectral studies.

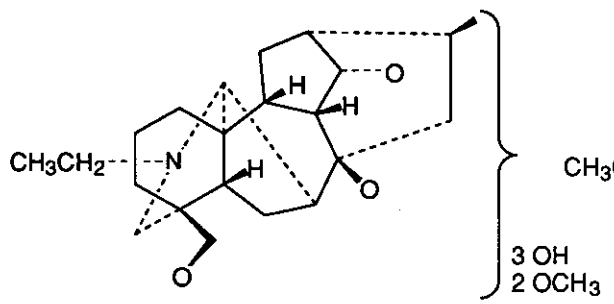
INTRODUCTION

No phytochemical work appears to have been carried out earlier on *Consolida raveyi*, (Boiss) Schröd., a plant endemic to Turkey. In continuation of our studies on the alkaloids of *Consolida* species,[1-7] an investigation of the aerial parts of *C. raveyi* led to the isolation of a novel norditerpenoid alkaloid designated as *raveyine*. *C. raveyi* was collected in Lalahan, Ankara in Central Anatolia at an elevation of 850 m, and extracted to give a crude alkaloid isolated at pH 10. This was purified on an Al_2O_3 column by VLC[8] and six fractions (A-F) were collected. By chromatographic separation of the fourth fraction on an Al_2O_3 rotor, the amorphous homogeneous alkaloid raveyine was isolated.

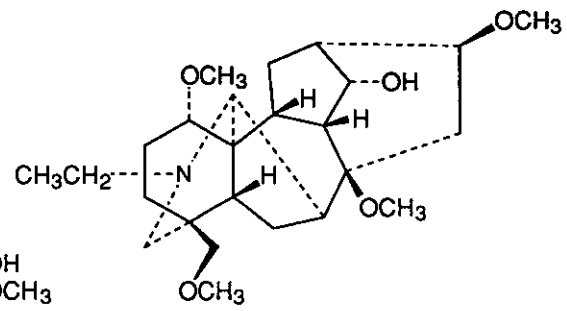
RESULTS AND DISCUSSION

The FAB-HRMS $[M+1]^+$ 408.2728 indicated the molecular formula $C_{23}H_{37}NO_5$ for raveyine. The preliminary ^{1}H and ^{13}C NMR spectra showed that the alkaloid contains an *N*-ethyl group (δ_C 12.9, q; δ_H 1.11, 3H, t, J = 7.5 Hz; δ_C 48.3 t; δ_H 2.48, 2.54, 2H) and two methoxyl groups (δ_C 48.5, q; δ_H 3.14,

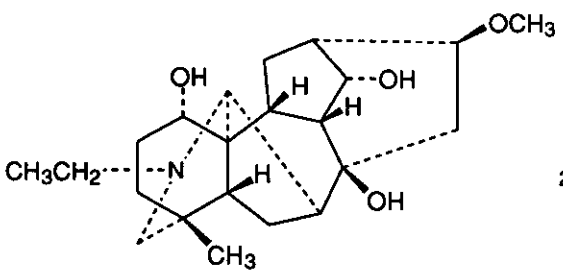
3H, s; δ_C 56.4, q; δ_H 3.38, 3H, s) accounting for four carbons. Biogenetic considerations and the molecular formula $C_{23}H_{37}NO_5$ suggested that raveyine is a norditerpenoid alkaloid. As there are no carbonyl functionalities, ether oxygens or methylenedioxy groups, the alkaloid should contain three hydroxyl groups and two methoxyl groups. Raveyine does not contain a tertiary methyl group at the C-4 position. As no other significant functional groups are observed in the IR and the NMR spectra, a partial structure (**1**) can be written for this alkaloid.



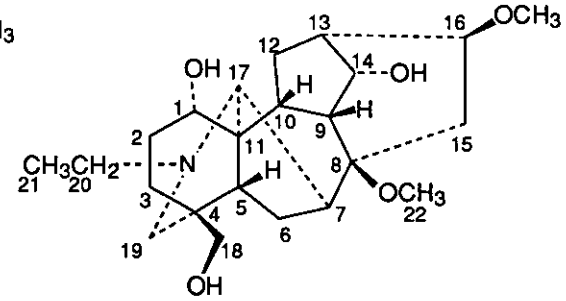
1



2: 8-*O*-Methyltalatizamine



3: Karakoline



4: Raveyine

Assignments of ^1H and ^{13}C chemical shifts, shown in Table 1, were accomplished using a two-stage method. In the first stage, the segments were established by the spin systems identified on the basis of scalar coupling in TOCSY and HMQC-TOCSY spectra. The sequence-specific assignments of ^1H and ^{13}C within a segment were obtained by the ^1H-^1H primary connectivities in COSY spectrum and the ^1H-^{13}C correlations in HMQC spectrum. Then, the overall structure was obtained by the long-range ^1H-^{13}C coupling between the segments in the HMBC spectrum and the inter-segment ^1H-^1H nOe connectivities in the ROESY spectrum (Table 2).

Twenty three carbons were observed using the 1D ^1H-decoupled ^{13}C, DEPT and HMQC spectra, which were determined by their characteristic ^1H and ^{13}C chemical shift patterns as one methyl, two methoxy, eight methylene, nine methine and three quaternary carbons. The quaternary carbon signals at δ 37.8, and 48.8 can be readily assigned to C-4, and C-11. The singlet at δ 78.8 is assigned to C-8 bearing an oxygen function.[9] The methyl quartet at 48.5 ppm strongly indicated

that C-8 bears a methoxyl group as in hokbusine A (δ 49.7),[10] 8-*O*-methyltalatizamine (**2**) (δ 48.3),[11] nuttalianine (δ 48.2),[12] and many other alkaloids bearing an 8-*O*-methyl.[9,13] A comparison of the carbon-13 NMR signals of raveyine showed similarity with the chemical shifts of 8-*O*-methyltalatizamine (**2**), karakoline (**3**)[13] and neolinine, except for the carbons adjacent to C-6, because neolinine has a methoxyl group at C-6.[9,13] The ^{13}C NMR signal at δ 82.7, d suggested that the second methoxyl group should be located at C-16. The general chemical shift range for C-16 in aconitine-type alkaloids not bearing an OH group at C-15 is δ 79.5-84.5.[9] The proton at δ 2.38 assigned to H-13 shows a correlation with C-16 (δ 82.7) in the HMBC spectrum (Table 2).

The problem of locating the three secondary hydroxyls thus remains. One of the hydroxyls is placed at C-1 (δ_C 72.1 d; δ_H, 3.74, 1H, br s). This proton shows a correlation with the H-2 protons in the COSY spectrum and a correlation with C-10 (δ 43.7) and C-3 (δ 26.0) in the HMBC spectrum. The carbon signal at δ 75.4 (δ_H 4.10, 1H, t, J = 4.5 Hz) is clearly assigned to C-14 bearing a hydroxyl group, not having any substituents on the adjacent carbons C-9 and C-13. There are numerous examples in support of this argument.[6,9] The third hydroxyl group should be clearly located on the C-18 methylene, since this carbon appears at δ_C 68.0 t; δ_H, 3.28, 3.45, 2H, AB, indicative of a methylene bearing an oxygen function. Thus, the three hydroxyl groups of the alkaloid are located at C-1, C-14 and C-18 and the methoxyls at C-8 and C-16 in the partial structure (**1**) leading to the structure (**4**) for raveyine. Detailed NMR spectral studies confirmed this structural assignment.

NMR SPECTRAL ASSIGNMENTS

Inspection of the HMQC-TOCSY spectrum (Figure 1) reveals five segments, two isolated methylene and two methoxy groups. Further inspection of the TOCSY spectrum indicates a weak cross peak along the resolved proton at 4.10 ppm, which connects two of the five segments. The weak intensity of this cross peak can be traced to the very small coupling constant due to a nearly perpendicular orientation between the two protons. The primary ^1H-^1H and ^1H-^{13}C correlations within the above four spin systems were obtained using the COSY and HMQC spectra, respectively. The assignments for ^1H signals were initiated at the resolved ^1H resonances such as CH protons at 2.42, 2.71, 3.35 and 3.74 ppm, and methylene protons at (2.14, 2.16), (2.48, 2.54), and (3.28, 3.45) ppm.

The assignments for the three quaternary carbons at 37.7, 48.8 and 78.8 ppm were completed based on the observed HMBC couplings of the resolved protons to these carbons. The H-15 proton chemical shift at 2.14-2.16 ppm (*vide infra*) was used to assign the signal at 78.8 ppm to the C-8 carbon. This proton has a coupling to a single quaternary carbon, and also to C-16 and C-9. The quaternary carbon was readily assigned to C-8, because the coupling of H-15 either to C-11 or to C-4 is expected to be much smaller than to C-8. Both H-10 and H-17 protons were observed to couple to C-8 and another quaternary carbon at 48.8 ppm. This carbon was assigned to C-11 since it is much closer to H-10 and H-17 in the sequence than to the C-4, and the couplings of H-17 and H-10 to C-11 are expected to be larger than that to the C-4 carbon. The H-6 proton showed the long-

range coupling to all three quaternary carbons. The carbon at 37.7 ppm was then assigned to C-4 since the other two quaternary carbons had been already assigned and these were confirmed by the ^{1}H-^{13}C connectivities (HMBC) from other protons to these three carbons. Positions of the two methoxy groups were readily assigned by their HMBC crosspeaks to the attached carbons (H-22 to C-8 and H-23 to C-16) and also confirmed by the ROESY connectivities. The presence of hydroxyl groups at C-1, C-18 and C-14 was supported by the large ^{1}H and ^{13}C chemical shift values at these three positions.

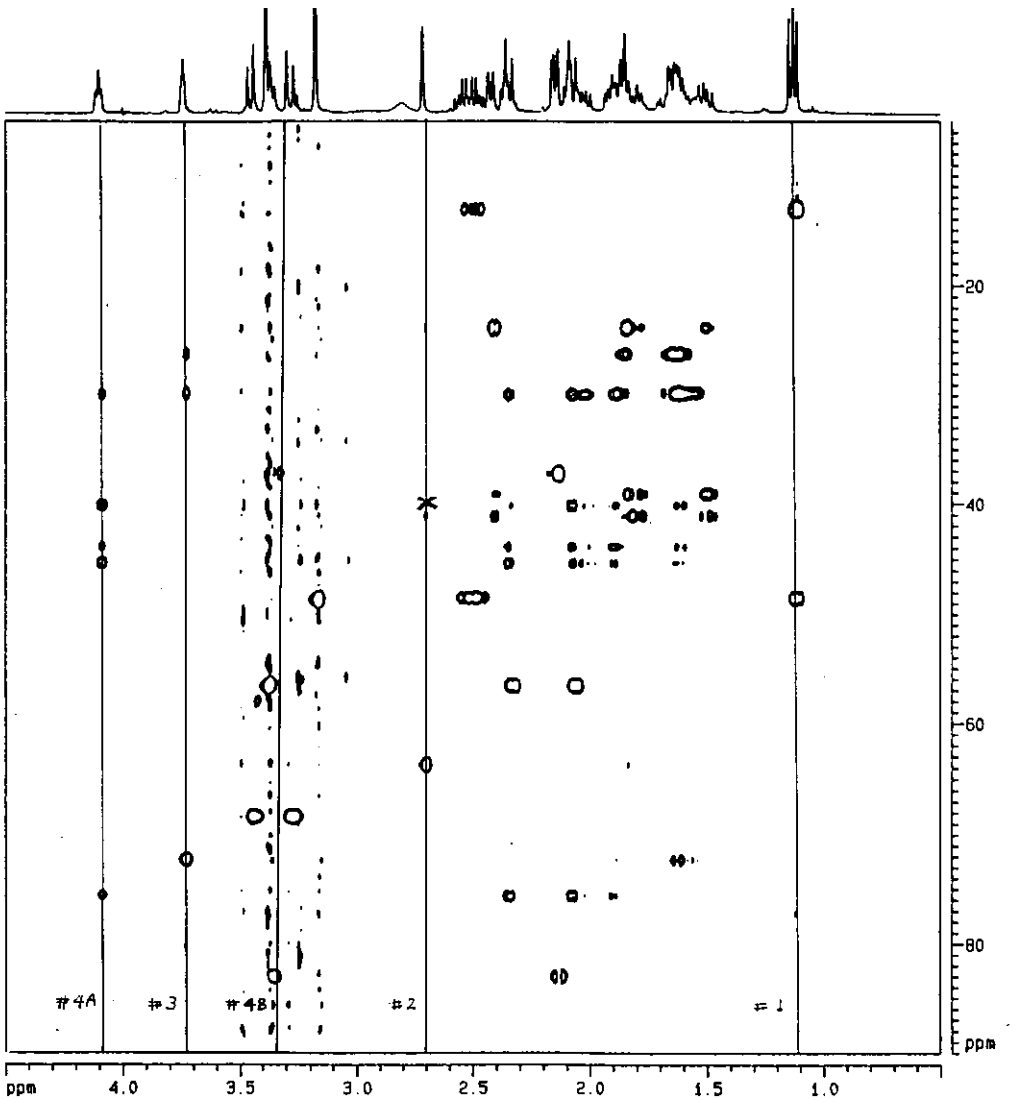


Figure 1. HMQC-clean TOCSY spectrum of raveyine (**4**) with 1D ^{1}H spectrum on top. The identified spin systems are labeled by vertical lines. The isolated methyl and methylene groups are also labeled. The crosspeak marked X (δ_C 38.9) was seen at lower couter level.

Table 1. ^{13}C and ^{1}H NMR Chemical Shifts Assignments of Raveyine (4), in $CDCl_3$ (ppm)

C #	^{13}C		H #	^{1}H		J = Hz
1	72.1	(d)	1_β	3.74	(t)	$J = 2.8$
2	29.6	(t)	2_α	1.64	(m)	
			2_β	1.57	(m)	
3	26.0	(t)	3_β	1.62	(m)	$^{*}J_{3\alpha,3\beta} = 14.8$, $^{*}J_{3\alpha,2\beta} = 10.8$, $^{*}J_{3\alpha,2\alpha} = 5.4$, $^{*}J_{3\beta,3\alpha} = 14.7$,
			3_α	1.87	(m)	$^{*}J_{3\beta,2\alpha} = 6.9$, $^{*}J_{3\beta,2\beta} = 6.9$,
4	37.7	(s)	4	-		
5	40.9	(d)	5	1.85	(d)	$J_{5,6b} = 8.1$
6	23.6	(t)	6_a	1.51	(d,d)	$J_{6a,6b} = 14.3$, $J_{6b,5} = 8.1$
			6_b	1.79	(m)	$J_{6b,6a} = 14.3$, $J_{6b,7} = 8.0$
7	38.9	(d)	7	2.42	(d)	$J_{7,6b} = 8.0$
8	78.8	(s)	8	-		
9	45.1	(d)	9	2.09	(d,d)	$^{*}J_{9,10} = 10.4$, $^{*}J_{9,14} = 4.7$
10	43.7	(d)	10	1.92	(m)	
11	48.8	(s)	11	-		
12	29.7	(t)	12_a	2.04	(m)	$^{*}J_{12a,12b} = 13.4$, $^{*}J_{12a,13} = 7.9$
			12_b	1.62	(m)	Overlap
13	40.0	(d)	13	2.38	(m)	
14	75.4	(d)	14	4.10	(t)	$J_{14,9} = 4.7$
15	37.0	(t)	15_a	2.14	(m)	$J_{15,16a} = 9.0$
			15_b	2.16	(d,d)	$J_{15a,15b} = 10.3$, $J_{15a,16} = 9.0$
16	82.7	(d)	16	3.35	(t)	$J_{16,15} = 9.0$
17	63.5	(d)	17	2.71	(br s)	$1/2_w = 3.2$
18	68.0	(t)	18_a	3.45	(AB)	$J_{gem} = 10.4$
			18_b	3.28	(AB)	$J_{gem} = 10.4$
19	56.4	(t)	19_a	2.34	(AB)	$J_{gem} = 11.7$
			19_b	2.07	(AB)	$J_{gem} = 11.7$
20	48.3	(t)	20_a	2.54	(octet)	
			20_b	2.48	(octet)	
21	12.9	(q)	21	1.11	(t)	$J = 7.5$
22	48.5	(q)	22	3.14	(s)	
23	56.4	(q)	23	3.38	(s)	

$^{*}J$ Constants are measured using HMQC spectrum

Table 2. Summary of HMBC, ROESY and COSY Correlation Data of Raveyine (**4**)

Obs. ^{1}H	HMBC	ROESY	COSY
H-1$_\alpha$	C-3, C-10, H-12$_a$, H-17	H-2$_\alpha$, H-2$_\beta$, H-10, H-12$_b$,	H-2$_\alpha$, H-2$_\beta$
H-2$_\alpha$	C-4, C-5, C-10, C-11	H-1$_\beta$, H-3$_\beta$	H-1$_\beta$, H-3$_\beta$
H-2$_\beta$	C-5, C-10, C-11	H-1$_\beta$, H-5	H-1$_\beta$, H-3$_\beta$
H-3$_\alpha$	C-11	H-19$_a$	H-3$_\beta$
H-3$_\beta$	C-1, C-2, C-11, C-19	H-2$_\alpha$, H-18$_b$	H-2$_\alpha$, H-2$_\beta$, H-3$_\alpha$
H-5	C-4, C-11, C-17, C-18, C-19	H-2$_\beta$, H-6$_a$, H-6$_b$, H-9, H-18$_a$, H-19$_b$	H-6$_a$, H-17
H-6$_a$	C-4, C-8	H-5, H-6$_b$, H-7, H-9, H-22	H-5
H-6$_b$	C-4, C-8, C-11	H-5, H-6$_a$, H-7, H-18$_a$, H-18$_b$, H-19$_a$, H-22	H-7
H-7	C-8, C-9, C-11, C-17	H-6$_a$, H-6$_b$, H-15, H-17, H-19$_b$,H-22	H-6$_b$
H-9	C-7,C-8, C-12, C-13 C-14, C-16	H-5, H-6$_a$, H-10, H-12$_a$, H-14	H-10, H-14
H-10	C-8, C-11	H-1, H-9, H-12$_b$, H-14	H-9, H-12$_b$
H-12$_a$	-	H-1, H-12$_b$, H-13, H-14	H-12$_b$, H-13
H-12$_b$	C-14, C-16	H-1, H-10, H-12$_a$, H-13, H-16, H-17	H-10, H-12$_a$
H-13	C-14, C-15, C-16	H-12$_a$, H-12$_b$, H-14, H-16	H-12$_a$, H-14
H-14	C-8, C-16	H-9, H-10, H-12$_a$, H-13	H-9, H-13, H-16 (W)
H-15	C-7, C-8, C-16	H-7, H-16, H-17, H-22	H-16
H-16	C-12, C-14, C-23	H-7, H-12$_b$, H-13, H-15	H-15, H-14 (W)
H-17	C-5, C-6, C-8, C-10, C-11, C-19	H-7, H-12$_b$, H-15, H-16, H-20, H-21	H-5
H-18$_a$	C-3, C-19	H-5, H-6$_b$, H-18$_b$, H-19$_a$	-
H-18$_b$	C-3, C-5, C-19	H-3$_\beta$, H-6$_b$, H-18$_a$, H-19$_a$, H-19$_b$	-
H-19$_a$	C-3, C-18, C-20	H-3$_\alpha$, H-18$_b$, H-20	-
H-19$_b$	C-3, C-4, C-5, C-17	H-6$_b$, H-7, H-18$_a$, H-18$_b$, H-20	-
H-20	C-17, C-19, C-21	H-17, H-19$_a$, H-19$_b$,H-21	H-21
H-21	C-11	H-20, H-23	H-20
H-22	C-8	H-6$_a$, H-6$_b$, H-7, H-15	-
H-23	C-16	H-21	-

Starting with the methyl resonance frequency of δ_H 1.11 (δ_C 12.9,) TOCSY and HMQC-TOCSY spectra showed that this methyl triplet is scalar-coupled to a pair of methylene protons at 2.48, 2.54 ppm (δ_C 48.3). Thus, the two carbons were assigned to C-21 and C-20, respectively. The H-21 protons have a long-range ^1H-^{13}C coupling to a quaternary carbon at 48.8 ppm in the HMBC spectrum already assigned to C-11. The H-20 methylene protons showed ROESY connectivity to the methine proton at 2.71 ppm of segment #2 (see Figure 1) and to the isolated methylene protons at 2.07, 2.34 ppm and ^1H-^{13}C couplings in the HMBC spectrum to their carbons at 63.5 and 56.4 ppm, respectively. The methine proton at 2.71 ppm was unambiguously assigned to H-17 while the methylene protons were assigned to H-19_a and H-19_b. The H-19 protons show ^1H-^{13}C couplings in the HMBC spectrum to several carbons including the methylene carbon at 26.0 and the quaternary carbon at 37.7 ppm of segment #3, methine carbon at 40.9 of segment #2 (which is assigned to C-5), and the methine carbon at 63.5 ppm assigned to C-17. The H-19 proton also showed coupling with C-18 (δ_C 68.0) and C-20 in the HMBC and a ROESY crosspeak with the H-3_α proton. The sequence of segment #3 was determined as CH (^1H, 3.74 ppm, ^{13}C, 72.1 ppm)-CH_2 (^1H, 1.57, 1.64 ppm, ^{13}C, 29.6 ppm)-CH_2 (^1H, 1.62, 1.87 ppm, ^{13}C, 26.0 ppm) by the ^1H-^1H and ^1H-^{13}C correlations in COSY and HMQC spectra, respectively. The HMBC crosspeaks of H-19 protons to two methylene carbons of the segment, combined with the ROESY crosspeak of H-17 to the methine proton of the segment confirmed the assignments for this segment as C1-C2-C3 between the two quaternary carbons C-4 and C-11. The C-1 and H-1 chemical shifts indicated that a hydroxyl group is attached to C-1 carbon. One of the H-19 protons showed ^1H-^{13}C coupling with a quaternary carbon at 37.7 ppm already assigned to C-4. The isolated methylene carbon at 68.0 ppm was assigned to C-18 on the basis of the ^1H-^{13}C couplings of H-19 to this carbon and its methylene protons to the C-3 carbon. Several other ^1H-^{13}C couplings were also observed between the proton of the segment to nearby carbons, such as the couplings of H-3 to C-11 and H-2 to C-4.

The COSY correlation pattern indicated that segment #2 contains a sequence of CH (1.85 ppm)-CH_2 (1.51, 1.79 ppm)-CH (2.42 ppm). The ^1H-^{13}C couplings of this methine to C-4, C-17, C-18 and C-19, the ROESY connectivities to H-18_a and to H-19_b determined the positions of the segment as H-5 (1.85 ppm), H-6 (1.51, 1.79 ppm), H-7 (2.42 ppm). Several ^1H-^{13}C couplings were observed for H-17 proton to other carbons including C-5, C-6, C-8,C-10, C-11, C-19.

The assignment of the last spin system, segment #4 (4A and 4B in Figure 1), was initiated at the resolved methine proton at 4.10 ppm and methylene protons at 2.14, 2.16 ppm. The HMQC-TOCSY spectrum showed this proton to correlate with four carbons (three methines and one methylene) plus its own carbon at 75.4 ppm. In the TOCSY spectrum this proton showed a weak crosspeak to another proton at 3.35 ppm in addition to the correlations with the protons attached to the above four carbons in segment 4A. The sequence of this segment was identified by the COSY correlations of H-10 to H-9 and H-12, H-12 to H-13, H-9 to H-14, H-13 to H-14, and H-15 to H-16. A COSY correlation between H-13 and H-16 protons was not observed, but the connectivity of H-16 to H-13

is supported by the TOCSY crosspeaks of H-16 to both H-14 and H-9 and ^{1}H-^{13}C couplings of H-12 to C-16 and H-14 to C-16 in the HMBC spectrum. The assignment for this spin system was also confirmed by the ROESY connectivities (Table 2). The ^{1}H-^{13}C couplings of H-1 to C-10, H-10 to C-11, H-7 to C-9 and H-15 to C-8 in the HMBC spectrum were then used to complete the assignments of the segment in the structure (**4**).

The stereochemistry of raveyine (Figure 2) was determined using the ROESY cross peaks from the protons of asymmetric carbons to other nearby protons. The ROESY crosspeak between H-17 proton and H-16 proton indicates that the methoxy group at C-16 is in an equatorial configuration. The ROSEY crosspeak of H-17 to the H-12_b proton at 1.62 ppm determines its configuration. The stereochemistry of the OH at C-14 is based on the observation of the ROESY crosspeak of H-12_a (2.04 ppm) to H-14. The C-14 hydroxyl is axial and the methoxyl at C-16 is equatorial in the twist boat configuration of the ring formed by C-8, C-9, C-14, C-13, C-16 and C-15. The H-14 proton also has ROESY correlation with H-10 proton. The α-orientation of the C-1 OH group enables hydrogen bonding to the nitrogen when the A ring adopts a boat conformation.[14] The α-configuration of the hydroxyl group at C-1 was confirmed by the ROESY correlation of H-10 to H-1 proton. Furthermore, the orientation of H-19 protons was determined as H-19a (2.34 ppm) and H-19_b (2.07 ppm) using the NOEs of H-6b and H-7 to H-19_b and of H-3_α to H-19_a. The six-membered ring containing nitrogen orients below the ring defined by C-1 to C-5 and C-11 carbons because H-18_a shows an NOE in the ROESY spectrum with H-5 proton. Thus, the hydroxymethyl group on C-18 is above the ring on the same side of H-5 proton. Both the methoxy group at C-16 and the methyl group (C-21) face in to each other. This orientation is supported by the NOE in the ROESY spectrum between H-21 and H-23 protons. The methoxy protons at C-8 also face towards the C-21 and C-23 groups, indicated by the ROESY crosspeaks of H-22 to H-7 and H-15 protons. The C-18 hydroxyl group is close to H-3_β based on the correlation of H-18 protons to H-6_b and H-5.

Particular emphasis was placed on the weak COSY cross peak of H-17 to the methine at 1.85 ppm which was assigned to H-5. The weak correlation is not from the three bond ^{1}H-^{1}H coupling of H-17 to H-7 because the two protons are in perpendicular orientation to each other, where C-17 is in the location connecting three rings and C-7 connects two rings. The assignments of H-5 and H-7 were made based on the fact that H-5 has ^{1}H-^{13}C couplings in the HMBC spectrum to C-4, C-18 and C-19, whereas H-7 has the couplings to C-8 and C-9. The assignments were also supported by the strong NOEs in the ROESY spectrum from H-5 to H-18_a and H-7 to H-15. If the weak COSY cross peak was due to the correlation of H-17 to H-7, the above ^{1}H-^{13}C couplings and strong NOEs could not be observed since H-7 and H-5 are five bonds away to C-18 and to C-9, respectively, and H-7 is far removed from H-18_a as is H-5 from H-15. By chromatographic separation of the fractions (B) and (D), the previously reported diterpenoid alkaloids ajaconine, azitine, chellospontine, and isoatisine were isolated.

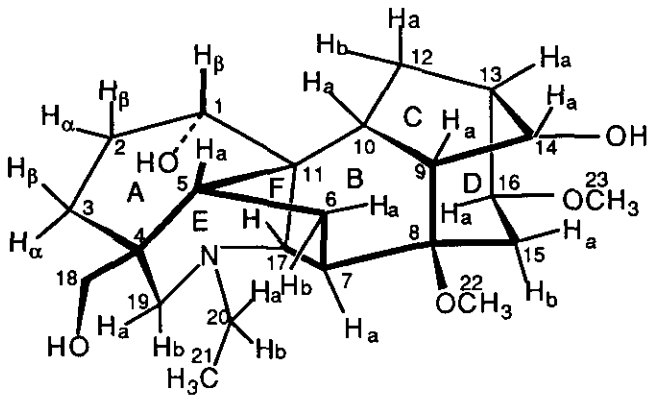


Figure 2. Stereostructure of raveyine (**4**)

EXPERIMENTAL

General Experimental Procedures.– IR spectra were recorded neat on a Perkin-Elmer Model 1420 spectrophotometer. EIMS and HRMS were determined on a Perkin-Elmer SCIEX API-1 and Autospec-FAB+ mass spectrometers, respectively. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter. Chromatographic separations on a Chromatotron were carried out on rotors coated with 1 mm thick layers of Merck Al_2O_3 60 PF 254, 365 (EM 1104).

All NMR data were acquired at 25° C on a Bruker AMX400 spectrometer (400.13 MHz, ^1H) using 36 mg of the compound dissolved in 0.5mL of $CDCl_3$. ^1H and ^{13}C chemical shifts at 25° C were referenced to TMS, via the $CDCl_3$ resonance frequency at 7.27 and 77.0 ppm, respectively. The 2D ^1H phase sensitive COSY[15,16] and clean-TOCSY[17] spectra were obtained using a spectral width of 2.0 kHz for both dimensions, while 2D ROESY[18] experiments were acquired with a spectral width of 4.0 kHz. For 2D TOCSY experiments, a spin lock field of 8 kHz was used during spin lock time of 60 ms, which includes 2 ms trim pulses. ROESY spectra were recorded with a spin lock field of 1.8 kHz during the 500-ms mixing time. For 2D ^1H-^{13}C heteronuclear experiments, a spectral width of 10 kHz was used in the ^{13}C dimension for HMQC[19], HMQC-clean-TOCSY[20] and HMBC[21]. ^1H-^{13}C coupling constants of 150 Hz and 10 Hz were used in HMQC and HMBC experiments, respectively. HMQC data was acquired with a BIRD[16] sequence to suppress the signals from protons bound to ^{12}C and with GARP[22] decoupling during acquisition, Quadrature detection in the indirectly observed dimensions was obtained using TPPI[23] (time proportional phase increment) method for all 2D experiments. Typically, the data were acquired with acquisition time of 500 ms, 16 scans for each of 512 FID's in the homonuclear experiments, and 32 scans for each of 256 FID's in the heteronuclear experiments.

The 2D ^1H data were processed with 60°-shifted sine-bell-squared functions for ROESY and TOCSY spectra and with 5°-shifted sine-bell-squared functions for the phase sensitive COSY spectrum. The data sets were zero-filled to a final matrix size of 2048 X 2048 real points prior to

Fourier transformation. All homonuclear spectra were plotted without symmetrization. The 2D ^{1}H-^{13}C HMQC and HMQC-clean-TOCSY were processed with 45°-shifted sine-bell-squared functions in ^{1}H dimension and 90°-shifted sine-bell-squared functions in ^{13}C dimension, while HMBC was processed with 0°-shifted sine-bell-squared functions in both dimensions. The data sets were zero-filled to 2048 X 1024 real data points prior to Fourier transformation. The HMBC was presented in magnitude mode after Fourier transform to gain maximum sensitivity of the spectrum.

Plant Material.– The aerial parts of *Consolida raveyi* were collected in June 1996, in Lalahan, Ankara, Central Anatolia at an elevation of 850 m and identified by A. H. M. and F. M. A voucher specimen has been deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul, AEF: 19590.

Extraction of Crude Alkaloids. – Dried and powdered aerial parts of *C. raveyi* (3.2 kg) were extracted exhaustively by percolation at rt for 3 days with 95% EtOH (20 L). Evaporation (*in vacuo*) of the combined extracts gave a gummy residue (60 g) which was dissolved in CH_2Cl_2 (500 mL) and extracted with 2% H_2SO_4 (200 mL x 10). The acidic extract was washed with CH_2Cl_2 (200 mL x 3) and then basified to pH 10 with cold aq. 10% NaOH. Extractions with CH_2Cl_2 (250 mL x 5) and evaporation of the combined extracts in *vacuo* gave a crude mixture of alkaloids (4.05 g).

Purification of the Alkaloidal Mixture - The crude alkaloidal mixture was chromatographed by VLC [8] on an Al_2O_3 column. The eluting solvent was a gradient of hexane, EtOAc and MeOH and six fractions (A-F) were collected. These were separated on Al_2O_3 rotors of a Chromatotron. Fraction (B) was chromatographed on an Al_2O_3 rotor and eluted with a gradient of hexane, EtOAc, MeOH to afford azitine[4] (3 mg) from fraction 14-15 and ajaconine[24] (5 mg) from Fraction 37, as amorphous products.

Fraction (D) (433 mg) was chromatographed on a basic Al_2O_3 rotor and 55 fractions (25 mL each) were collected by elution with a gradient of hexane-$CHCl_3$-MeOH. Elution with $CHCl_3$-MeOH (92:8) afforded isoatisine[25] (62 mg) in fractions (14-16), chellespontine [4](83 mg) in fractions (36-37) and raveyine (**4**) (36 mg; amorphous) in fractions(31-32); $[\alpha]_D$ -4.1° (c,1.03, $CHCl_3$). EIMS: m/z 407; Calcd for $C_{23}H_{37}NO_5$, 407; FAB-HRMS: Found , $[M+H]^+$ m/z 408.2728; Calcd for $C_{23}H_{37}NO_5$ $[M+H]^+$ m/z 408.2749; IR (neat): ν_{max} 3400, 2930, 2880, 1500, 1390, 1300, 1220, 1150, 1090, 1070, 920, 730 cm^{-1}. For ^{1}H and ^{13}C NMR spectra, see Table 1. The identities of the known compounds were established by comparison of the TLC, ^{1}H and ^{13}C NMR spectra and comparison with authentic samples.

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