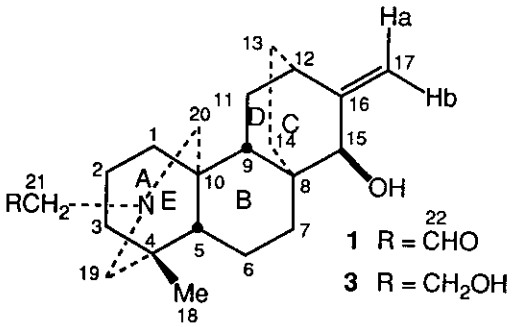
NEW ALKALOIDS FROM CONSOLIDA HELLESPONTICA

Haridutt K. Desai, Balawant S. Joshi, S. William Pelletier*
Institute for Natural Products Research and Department of Chemistry, University of Georgia, Athens, GA 30602-2556, U.S.A.

Bilge Sener, Funda Bingöl, and Turan Baykal
Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, Ankara, Turkey

Abstract – From the aerial parts of Consolida hellespontica (Boiss.) Chater we have isolated the new diterpenoid alkaloids chellespontine (**1**) and azitine (**4**). The norditerpenoid alkaloid 1-*O*-methyldelphisine (**7**) has not been reported earlier as occurring in nature, and the aporphine alkaloid (+)-corydine (**11**) has been isolated for the first time in the Ranunculaceae family. Besides these, the known alkaloids delphinine (**8**), delphisine (**9**) and bullatine C (14-acetylneoline) (**10**) have been isolated from this plant. The structures of these alkaloids were established by chemical correlation and spectroscopic studies.

Consolida hellespontica (Boiss.) Chater [Syn. Delphinium hellespontica (Boiss.), D. tomentosum (Boiss.)] grows in the Zonguldak and Kastamonu regions in Turkey at an altitude of 640 m and no chemical work has been reported for this plant. We have investigated the alkaloids of C. hellespontica and isolated by conventional chromatographic procedures such as vlc[1] and centrifugal chromatography (Chromatotron)[2] seven alkaloids (A-G). The new diterpenoid alkaloid (A), designated as chellespontine (**1**), crystallized as colorless plates, mp 227–230°C, and showed in the ir spectrum: ν_{max} (KBr) 2910, 1730 (CHO), 1655, (C=CH_2) cm^{-1}. The ^1H nmr spectrum of chellespontine showed signals at δ 0.84 (3H, *s*, *tert*-Me), 3.93 (1H, br *s*, C*H*-OH), 5.10, 5.37 (each 1H, br *s*, C=CH_2), 9.43 (1H, *s*, CHO). The eims of chellespontine gave a molecular ion peak at m/z 343 indicating the molecular formula $C_{22}H_{33}NO_2$ for the alkaloid. The ^{13}C nmr spectrum of chellespontine (Table 1) exhibited 21 lines for 22 carbon atoms of the molecule (the signal at δ 25.9 accounts for two carbons) and a DEPT spectrum revealed four non-protonated carbons at δ 156.4, 46.4, 38.1 33.4, five methines at δ 183.5, 75.0, 44.9, 40.1, 36.3, twelve methylenes at δ 109.5, 64.5, 59.5, 58.3, 41.0, 35.0, 31.0, 28.1, 25.9, 25.9, 19.8 19.4, and one methyl group at δ 24.7.



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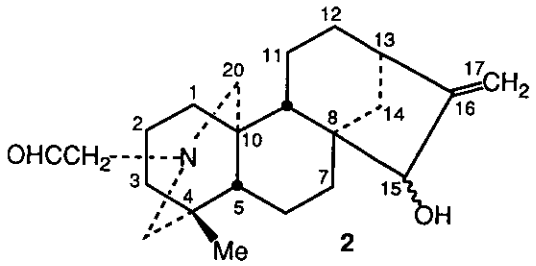

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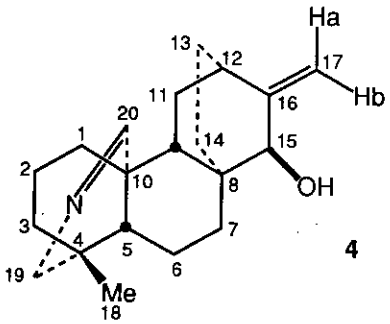

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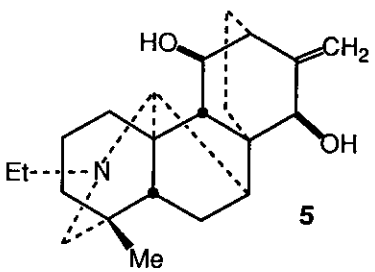

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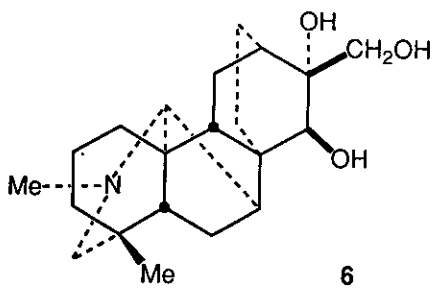

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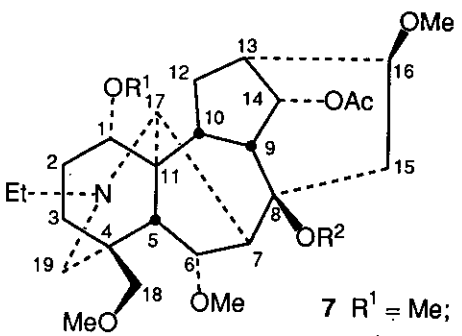
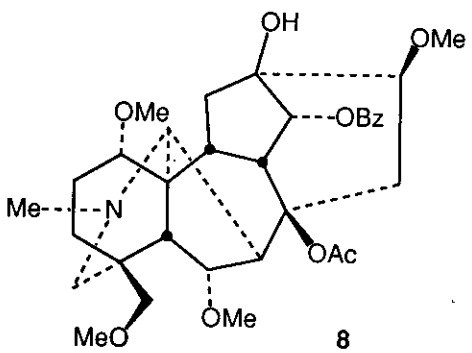


7 R^1 = Me; R^2 = Ac
9 R^1 = H; R^2 = Ac
10 R^1 = R^2 = H



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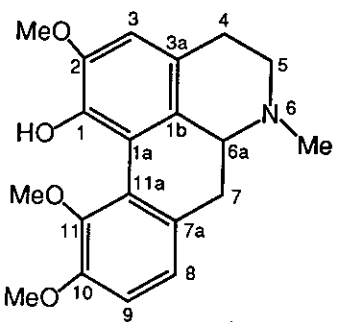

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The diterpenoid alkaloids from the genus Consolida and Delphinium usually conform to two main groups: the norditerpenoid alkaloids (C_{19}) of aconitine and/or lycoctonine-type and the diterpenoid alkaloids (C_{20}) having an atisane or veatchine-type ring skeleton.[3] The former class of compounds are usually methoxylated but not the latter. The 22 carbon atoms of chellespontine confirmed by its ^{13}C nmr spectrum together with the absence of methoxyl groups, excluded the norditerpenoid skeleton. We therefore considered the diterpenoid alkaloid (C_{20}) skeleta for chellespontine. The molecular formula of chellespontine indicated seven degrees of unsaturation, of which two are accounted for by the exocyclic methylene and the aldehydic functions. The characteristic carbon resonances of an atisane- or veatchine-type exocyclic methylene group were readily located at δ 156.4 (s) and δ 109.5 (t) for C-16 and C-17 and the protons at δ 5.10 and 5.37 for the exocyclic methylene group. Of the only two methine doublets downfield of δ 44.9, the signal at δ 183.5 (d) clearly indicated an aldehydic carbon resonance and the signal at δ 75.0 (d) is an oxygenated carbon. The remaining three methines are attached to carbons which are not attached to oxygen or nitrogen atoms. Chellespontine contains an exocyclic methylene, an *N*-CH_2CHO and a secondary hydroxyl group. We noticed that in the ^1H nmr spectrum, the aldehydic proton attached to the methylene group appeared as a singlet and not as the expected triplet at δ 9.43. A literature search showed that in all the cases, the aldehydic proton of *N*-$CH_2C\mathit{H}O$ has been reported to be a singlet or a broad singlet.[4] The hydroxyl group of chellospontine should be located next to the exocyclic methylene group to account for the downfield shift of C-16 (δ 156.4 and 109.5) as in the case of sadosine[5] (δ 155.4 and 110.1), ryosenamine[6] (δ 155.2 and 109.6), and atisine[7] (δ 157.5 and 108.9). On the basis of these data, we arrived at two alternative structures (**1**) and (**2**) for chellespontine. A comparison of the ^{13}C nmr values of **1** with dihydroatisine (**3**), dihydroveatchine[7] and dihydrogarryfoline[8] indicated that the values of the rings B, C and D of **1** are very similar to those of **3** having an atisane skeleton. The chemical shifts of C-8, C-9, C-11, C-14, C-15, C-16 and C-17 in **1** widely differ from the values in dihydrogarryfoline and dihydroveatchine. The ^{13}C nmr spectra of **3** in $CDCl_3$ and C_5D_5N are very similar in their chemical shifts (Table 1). The ^{13}C nmr chemical shift assignments of dihydroatisine (**3**), atisine azomethine (azitine) (**4**) and other diterpenoid alkaloids were essentially made with the help of proton decoupling techniques, additivity relationships and effects owing to specific structural changes in a number of closely related alkaloids.[7,8] Denudatine (**5**) and dictyzine (**6**) are closely similar in their structures to **1**, **3** and **4** except for a bond between C-7 and C-20. Unambiguous ^{13}C chemical shift assignments have been made for denudatine (**5**)[9] and dictyzine (**6**)[10] as a result of detailed nmr studies. Although we have not carried out detailed nmr work on **1**, **3** and **4**, we have assigned the ^{13}C nmr chemical shifts for these alkaloids, by comparison of the values assigned to **5** and **6**. This has necessitated the change of some literature values shown by an asterisk in Table 1.

In selective INEPT experiments,[11] saturation of the H-18 methyl singlet led to an enhancement of the quaternary carbon at δ 33.4 which was assigned to C-4, two bonds removed from H-18. In addition, a

methylene at δ 59.5 assigned to C-19, also showed enhancement three bonds removed from H-18, and an unexpected polarization transfer to C-6 (δ 19.4), four bonds removed. Some other ^{13}C chemical shift assignments of chellespontine (**1**) have been confirmed by selective INEPT studies (Table 2). The structure of chellospontine was confirmed by reduction with $NaBH_4$ to afford a compound identical in all respects (tlc, mp, mixture mp, ir, ^1H and ^{13}C nmr) with dihydroatisine (**3**). The alkaloid (**3**) has been isolated from Aconitum heterophyllum[12] and it has been prepared by the $NaBH_4$ reduction of atisine.[13]

Table 1. ^{13}C Nmr Chemical Shifts and Assignments for Chellespontine (**1**), Dihydroatisine (**3**), Denudatine (**5**), Dictyzine (**6**) and Azitine (**4**).

Carbon	1[a]	3[a]	3[b,8]	5[c,9]	6[d,10]	4[a]	4[b,7]
C-1	25.9	28.4	26.4*	26.1	27.6	25.9	26.1
C-2	19.8	23.1	23.2	20.3	21.8	19.5	19.6*
C-3	41.0	40.8	40.2*	39.8	41.2	34.2	34.1
C-4	33.4	33.7	33.6	33.5	35.3	32.9	32.8
C-5	44.9	50.1	49.6	51.7	54.0	46.9	46.9
C-6	19.4	17.9	17.4	22.5	24.0	20.1	20.0*
C-7	35.0	42.0	41.4*	46.6	44.0	42.3	42.4*
C-8	38.1	38.0	37.4	43.1	43.0	37.3	37.4
C-9	40.1	39.9	39.5	52.2	42.5	38.1	38.1
C-10	46.4	38.3	38.0	45.0	46.9	42.5	42.5
C-11	31.0	32.1	31.5*	71.6	24.7	30.9	31.0*
C-12	36.3	37.1	36.4	41.8	36.5	35.9	36.0
C-13	25.9	26.9	26.4*	24.0	23.0	25.1	25.5*
C-14	28.1	28.4	27.7*	27.7	29.0	28.1	28.1*
C-15	75.0	77.0	76.8	76.7	87.1	75.8	75.2
C-16	156.4	157.5	156.3	154.2	81.1	156.6	156.2
C-17	109.5	109.4	109.6	108.5	67.9	109.2	108.9
C-18	24.7	26.7	26.4	26.5	27.0	25.9	25.8
C-19	59.5	59.8	60.2	57.1	60.8	60.4	60.2
C-20	58.3	61.0	58.0*	71.0	74.7	166.2	166.4
C-21	64.5	54.7	54.0*	50.1	44.5	–	–
C-22	183.5	62.4	60.7	13.5	–	–	–

[a]C_5D_5N; [b]$CDCl_3$; [c]CD_3SOCD_3; [d]CD_3OD.

The alkaloid (B) $C_{20}H_{29}NO$, mp 178-179°C, ms m/z 299 (M^+), designated as azitine (**4**), was isolated during the chromatographic separation of the pH 10 alkaloidal fraction. The ^{13}C nmr spectrum

showed 20 signals for 20 carbon atoms (Table 1). The resonances at 156.6 (s) and 109.2 (t) ppm suggested that the alkaloid is of the atisine-type and these could be assigned to C-16 and C-17, respectively, of the exocyclic methylene group. The two broad signals at δ 5.04 and 5.10 in the ^{1}H nmr spectrum supported the presence of the exocyclic methylene group. The signal at δ 3.69 (δ C 75.8 d)

Table 2. Nmr Data from Selective INEPT Experiments

Irradiation of proton assigned to	δ (ppm)	Enhancement of the carbon signals assigned to*		
Alkaloid 1		**Strong**	**Medium**	**Weak**
CH_3-18	0.84	33.4 (C-4)	59.5 (C-19)	19.4 (C-6)
H-12 (H-9)	2.38	75.0 (C-15) 156.4 (C-16)	40.0 (C-9)	109.5 (C-17)
H-15	3.93	156.4 (C-16)		
H-17$_a$	5.09	36.3 (C-12)		
H-17$_b$	5.40	75.0 (C-15)	156.4 (C-16)	
Alkaloid 4				
H-5	1.02	19.5 (C-6) 42.5 (C-10)	38.1 (C-9)	
H-12	2.40	156.6 (C-16) 75.8 (C-15)	38.1 (C-9) 25.1 (C-14)	109.2(C-17)
H-19	3.41	42.3 (C-3) 166.2 (C-20)	32.9 (C-4)	
H-15	3.70	156.6 (C-16) 38.1 (C-9)	109.2 (C-17)	35.9 (C-12)
H-17$_a$	5.05	35.9 (C-12)	156.6 (C-16)	75.8 (C-15)
H-17$_b$	5.10	156.6 (C-16) 75.8 (C-15)		
H-20	7.90	60.4 (C-19) 46.9 (C-5)	42.5 (C-10)	

*Strong 61-100%, Medium 40-60%, Weak < 40%

is clearly due to the proton attached to a hydroxyl group and the two proton signals at δ 3.41 and 3.42 (δ C 60.4, t) can be assigned to the *N*-CH_2 group. The methine proton far downfield at δ 7.87 indicated the presence of an azomethine function *N*=CH, which is supported by the ^{13}C signal at

166.2 (d) ppm. Structure **4** for azitine is supported by its nmr spectral data. The azomethine group is located on *N*=C(20) and not *N*=C(19) as is clear from the selective INEPT experiments (Table 2). Azitine was shown to be identical with the azomethine (**4**) prepared by $KMnO_4$ oxidation of atisine[14] and its occurrence in nature has not been reported earlier. That the alkaloids (**1**) and (**4**) are not artefacts of atisine generated during the isolation procedure, was shown by the recovery of atisine and partial isomerization to isoatisine after treatment under conditions identical to those used for the isolation of chellespontine (**1**).

Compound (C) was identified as 1-*O*-methyldelphisine (**7**); this is the first report of the natural occurrence of this alkaloid. The compound was prepared earlier by methylation of delphisine with trimethyloxonium tetrafluoroborate and bis-1,8-dimethylaminonaphthalene (proton sponge).[15] The compounds (D), (E) and (F) were identified as the known norditerpenoid alkaloids delphinine[16] (**8**), delphisine[17] (**9**), and bullatine C[18] (**10**), respectively. These alkaloids were found to be identical in their physical and spectral properties when compared with authentic samples. The alkaloid (G) was obtained as a crystalline compound, mp 146-148°C, and its molecular formula $C_{20}H_{23}NO_4$ was derived by its mass spectrum (M^+, m/z 341). The ^1H and ^{13}C nmr spectral data indicated this to be a hydroxy*N*-methyltrimethoxyaporphine. A comparison of the tlc, mixture mp, proton[19] and ^{13}C nmr spectral data showed it to be identical with (+)-corydine (**11**). The ^{13}C nmr chemical shift assignments were based on the δ values recorded for isocorydine[20] and corydine methochlorate.[21] This is the first example of the isolation of an aporphine alkaloid from the Ranunculaceae family.

EXPERIMENTAL

Melting points are corrected and were determined on a Thomas-Kofler hot stage equipped with a microscope and polarizer. Infrared spectra were obtained on a Perkin-Elmer model 1420 spectrophotometer. ^1H (300.13 MHz) and ^{13}C (75.5 MHz) and SINEPT nmr spectra were recorded on a Bruker AC-300 spectrometer. The ^{13}C nmr chemical shift multiplicities were determined from DEPT spectra. Mass spectra were determined on a Finnigan Quadrupole 4023 instrument. Optical rotations were measured on a Perkin-Elmer model 141 polarimeter. Chromatographic separations on a Chromatotron were carried out on rotors coated with 1 mm thick layer of Al_2O_3 (EM 1104-3) or SiO_2 (EM-7749); vlc was carried out with Merck Al_2O_3 (EM 1085).

Plant material: – The aerial parts of Consolida hellespontica were collected by one of the authors (B.S.) from the fields between Zonguldak and Kastamonu, at an altitude of 640 m. A voucher specimen (GUH-1810) is deposited in the herbarium of the Department of Pharmacognosy, Gazi University, Ankara, Turkey.

Isolation of alkaloids: – Dried and powered aerial parts of C. hellespontica (3.0 kg) were extracted by percolation at room temperature with EtOH and evaporation of the extract in vacuo gave a gum (280 g). Part of this (76.1 g) was extracted with hexane (2 l) to give a residue (4.67 g). The defatted material was dissolved in $CHCl_3$ (300 ml) and extracted with 2% (v/v) H_2SO_4 (200 ml x 10). The acidic fraction was washed with $CHCl_3$ (300 ml x 3) and the $CHCl_3$ fractions were combined to give the neutral fraction. The acidic fraction was basified with Na_2CO_3 (pH 10) and extracted with $CHCl_3$ (700 ml x 7) to give the crude alkaloid (2.46 g). This was chromatographed on Al_2O_3 by vlc[1] and eluted with a gradient of hexane, Et_2O and MeOH. Twelve fractions (F_1–F_{12}) (each 150 ml) were collected and combined as per their tlc pattern.

Isolation of 1-*O*-methyldelphisine (C)(**7**) and delphinine (D)(**8**) from fractions F_1–F_3: – The combined fraction F_1–F_3 (520 mg; eluted with hexane: 10, 20 and 30% Et_2O) was chromatographed on an Al_2O_3 rotor and eluted with a gradient of hexane, Et_2O and MeOH and visualized under uv (λ 254 and 365 nm). Fractions 5 and 6 (hexane: 7 and 8% Et_2O, 50 ml each), gave 1-*O*-methyldelphisine (**7**; 111.2 mg), mp 138-139°C. Tlc, ir spectra and mixture mp of the alkaloid were identical with those of an authentic sample.[15] Fractions 9–11 (hexane: 15, 20 and 30% Et_2O, 50 ml each) gave delphinine (**8**; 103.3 mg), mp 192-193°C, identical in its tlc, ir spectrum and mixture mp with those of an authentic sample.[16]

Isolation of delphisine (E)(**9**), bullatine C (F)(**10**) and (+)corydine (G)(**11**): – The fraction F_4 (207 mg, hexane: 40% Et_2O, 450 ml) and fractions 12-15 from the chromatography of F_1-F_3 (42.3 mg) were combined on the basis of their tlc similarity, chromatographed on an Al_2O_3 rotor and eluted with a gradient of hexane, Et_2O and MeOH. Fractions 9–16 (hexane: 20 and 25%Et_2O) gave bullatine C (**10**; 58.9 mg), identical in all respects with an authentic sample.[18]

Fractions 1–5 were rechromatographed on a silica gel rotor and eluted with a gradient of hexane, $CHCl_3$ and MeOH. The first three fractions (hexane: 10, 50 and 100% $CHCl_3$, 100 ml each) afforded delphisine (**9**; 31.3 mg), mp 122-123°C, identical in its properties with those of an authentic sample.[17] *Fraction 4 ($CHCl_3$; 100 ml) gave (+)-corydine (**11**; 4.65 mg), mp 146-148°C.* ^{1}H *nmr ($CDCl_3$):* δ *6.69* (1H, *s*, H-3), 2.56 (3H, *s*, *N*-CH_3), 6.92 (1H, *d* J=9 Hz, H-8), 7.09 (1H, *d* J=9 Hz, H-9), 3.74 (3H, *s*, 11-OCH_3), 3.91, 3.92 (each 3H, *s*, 2,10-OCH_3,), 8.71 (1H, br *s*, 1-OH); ^{13}C nmr ($CDCl_3$): δ 143.9 (C-1), 123.6 (C-1_a), 123.6 (C-1_b), 149.1 (C-2), 110.8 (C-3), 126.6 (C-3_a), 28.6 (C-4), 52.6 (C-5), 43.5 (*N*-CH_3), 62.6 (C-6_a), 35.2 (C-7), 130.5 (C-7_a), 124.3 (C-8), 111.2 (C-9), 151.7 (C-10), 142.3 (C-11), 130.5 (C-11_a). The alkaloid (G) was identical with an authentic sample[19] of (+) corydine, in its tlc, mixture mp, ir, ^{1}H and ^{13}C nmr spectral comparison.

Isolation of chellespontine (A)(**1**) and azitine (B)(**4**): – The highly colored fractions F_{10}–F_{11} (297 mg) obtained by elution with Et_2O and Et_2O:50% MeOH were submitted to acid-base extraction and the

crude alkaloid (210 mg) was chromatographed on a silica gel rotor. Elution with $CHCl_3$ and 10% MeOH gave a mixture (83.5 mg) and further elution with MeOH and MeOH:Et_3N did not elute the blue fluorescent (λ 254 nm) band. The fluorescent band was scraped out and extracted with 2% H_2SO_4 (35 ml). Basification with 20% NaOH (pH 14) and extraction with $CHCl_3$ (100 ml x 3) gave a gum (57.5 mg). This was purified on an Al_2O_3 rotor (1mm; neutral EM 1092) and eluted with $CHCl_3$ and MeOH. Fractions 1-6 ($CHCl_3$ and 1-5% MeOH) gave a residue (17.1 mg). This material was again separated on an Al_2O_3 rotor and eluted with haxane: 40% Et_2O to give azitine (**4**; 9.1 mg), mp 177-179°C, identical in its tlc, mixture mp ,^1H and ^{13}C nmr spectrum with those of an authentic synthetic sample.[7] Fractions 11-23 were obtained by elution with $CHCl_3$ and 5-20% MeOH to afford chellespontine (**1**; 33.2 mg), mp 227-230°C; $[\alpha]_D$ + 14.6° (MeOH, c, 0.56); ms : m/z 343 (M^+, 12%), 342 (M^+-1, 23.4), 328 (M^+-CH_3, 2.9), 314 (M^+-CHO, 5.6), 300 (M^+-$COCH_3$, 2.9), 257 (3.4), 241(0.6), 186 (13.2), 159 (11.4), 105 (6.4), 91 (29), 55 (55.2), 41 (100). For the ^{13}C nmr data see Table 1.

Reduction of chellespontine (**1**) with $NaBH_4$ to dihydroatisine (**3**): – Chellespontine (**1**, 5.1 mg) was dissolved in MeOH (2 ml) and to the solution was added $NaBH_4$ (15 mg) in four portions and the mixture kept overnight. Usual work up gave dihydroatisine (**3**, 3.5 mg), mp 157-159°C, identical in its tlc, mixture mp, ir and ^1H nmr spectrum with those of an authentic sample.[8]

Effect of the isolation procedure of (**1**) on atisine: – Atisine (99 mg) was adsorbed on a silica gel rotor and eluted with a gradient of hexane, $CHCl_3$, MeOH and Et_3N as reported for the isolation of **1**. The silica gel was scraped, extracted with 2% H_2SO_4 and the alkaloidal fraction was isolated after basification with NaOH. This mixture on purification on an Al_2O_3 rotor gave atisine and isoatisine[22] as identified by comparison of their ^1H and ^{13}C nmr spectra.

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