Study of the Acid-Catalyzed Isomerization of Dihydroveatchine

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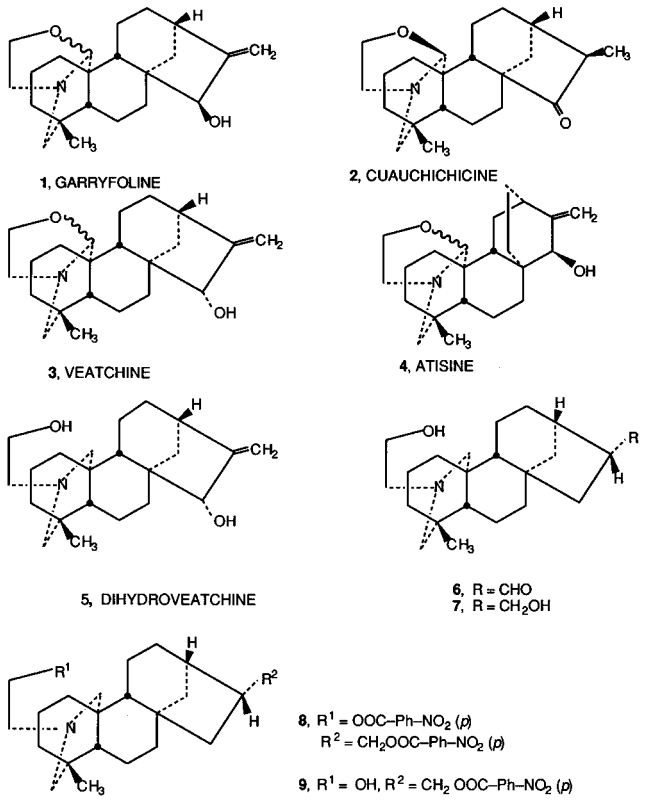
A study of the acid-catalyzed isomerization of dihydroveatchine (**5**) resulted in the isolation of a single major compound, the aldehyde **6**. Structure **6** has been derived from its spectral data. Reduction of **6** with $NaBH_4$ gave compound **7**, which was characterized through detailed NMR studies including 1D, 2D, and selective INEPT experiments, as well as preparation of its mono- and bis(*p*-nitrobenzoyl) derivatives **8** and **9**. A plausible mechanism for the formation of **6**, derived from the spectral data of the isomerized product obtained by deuterium labeling, is reported. Interestingly, the acid-catalyzed isomerization products of the allylic alcohols garryfoline (**1**) and dihydroveatchine (**5**) are different and appear to be dependent on the configurational orientation of the C(15) hydroxyl group. Unambiguous NMR chemical shift assignments for **5** are also reported.

In 1955, the diterpenoid alkaloid garryfoline (**1**) was reported to rearrange rapidly to cuauchichicine (**2**) in dilute mineral acid at room temperature.[1] A similar rearrangement has been observed in other diterpenoid alkaloids, e.g., atisine, kobusine, and napelline.[2] In contrast to the rapid rearrangement of garryfoline, the 15-epimeric veatchine (**3**) is stable even on heating in dilute hydrochloric acid. To explain the facile acid-catalyzed rearrangement of garryfoline compared with veatchine, a nonclassical structure for the intermediate carbocation was suggested.[3] We have reported mechanism studies of the garryfoline−cuauchichicine rearrangement[4] and the acid-catalyzed isomerization of isoatisine.[5]



The biogenetic origin and correlation of veatchine (**3**), with a 3:1:2 bicyclooctane ring system, and atisine (**4**), with a 2:2:2 bicyclooctane ring system, were postulated in an ingenious hypothesis by Wenkert.[6] The hypothesis suggested that compounds **3** and **4** have a common precursor. A study of this hypothesis was conducted by Edwards and co-workers and is recorded in two dissertations.[7,8] Dihydroveatchine (**5**) was vigorously treated with HCl to give a product that showed in its IR spectrum a frequency typical of a carbonyl group attached to a six-membered ring.[8] The product was characterized by its $NaBH_4$ reduction product. They tentatively concluded that the new ketone, tetrahydroketoveatchine, should be identical with a tetrahydroketoatisine derivative. They prepared the latter compound and found that it was not identical with "tetrahydroketoveatchine". The products of acid-catalyzed isomerization of dihydroveatchine and its $NaBH_4$ reduction product were not fully characterized nor were their structures determined.

We now report the acid-catalyzed isomerization of dihydroveatchine (**5**). The major product, an aldehyde **6**, was fully characterized by spectroscopic studies along with studies of the product of its reduction with $NaBH_4$.

Results and Discussion

A pure sample of dihydroveatchine (**5**) was prepared by reduction of veatchine (**3**) with $NaBH_4$.[9] Compound **5** was dissolved in 6 N HCl (aqueous), and the solution was refluxed for 45 min. On workup, a basic compound was obtained that on purification on an Al_2O_3 rotor of a Chromatotron[10] gave a homogeneous amorphous solid. Its molecular formula, $C_{22}H_{35}NO_2$, was derived from its FABHRMS m/z 346.2746 $[M + 1]^+$ and carbon-13 NMR data. Though the molecular formula of the product **6** is the same as that of the starting material (**5**), differences were revealed by TLC comparison and in the ^1H and ^{13}C NMR data. The ^1H NMR spectrum of **6** showed a doublet at δ 9.65 and the disappearance of the signals for the exocyclic methylene (δ 5.06 and 5.20, in **5**). The ^{13}C NMR spectrum of **6** showed a signal at δ 203.4 as a methine carbon and suggested the presence of an oxygenated carbon. Comparing the ^{13}C NMR chemical shifts of **5** and **6** (see Table 1) reveals that chemical shifts for C(1) to C(5) and C(18) to C(22) are identical and the changes in the shifts of **6** occurred for the carbons of the 3:1:2 bicyclooctane ring carbons and the

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Table 1. Carbon-13 Chemical Shifts and Assignments[a,b] for Compounds **5**−**9** and **10**

C no.	5	6	10	7	8	9
1	40.7 t	41.3 t	41.3 t	40.9 t	40.9 t	41.2 t
2	18.4 t	18.8 t	18.7 t	20.0 t	20.1 t	20.1 t
3	41.2 t	40.9 t	40.9 t	41.3 t	41.3 t	41.7 t
4	33.7 s	33.8 s	33.7 s	33.7 s	33.8 s	33.8 s
5	50.1 d	50.1 d	50.1 d	50.1 d	50.1 d	50.1 d
6	18.2 t	20.1 t	20.0 t	23.5 t	23.5 t	22.8 t
7	33.1 t	30.9 t	30.7 t	39.6 t	30.6 t	39.6 t
8	47.2 s	44.8 s	44.6 s	44.2 s	44.6 s	44.6 s
9	50.4 d	52.5 d	52.4 d	52.5 d	52.5 d	52.4 d
10	40.2 s	40.2 s	40.1 s	40.0 s	40.2 s	40.2 s
11	23.4 t	38.4 t	38.4 t	18.7 t	18.7 t	18.6 t
12	32.3 t	23.5 t	23.4 t	31.2 t	31.1 t	31.1 t
13	41.7 d	37.5 d	37.1 d	37.6 d	38.2 d	38.2 d
14	36.7 t	39.2 t	39.0 t	37.9 t	38.1t	38.1 t
15	82.6 d	40.5 t	−	45.3 t	45.3 t	45.3 t
16	159.7 s	53.3 d	−	43.0 d	39.3 d	39.3 d
17	108.5 t	203.2 d	203.4 d	67.3 t	69.9 t	69.9 t
18	26.4 q	26.5 q	26.4 q	26.5 q	26.5 q	26.4 q
19	60.2 t	60.3 t	60.3 t	60.3 t	60.3 t	60.3 t
20	55.9 t	55.8 t	55.7 t	55.6 t	55.7 t	56.0 t
21	60.6 t	60.8 t	60.8 t	60.6 t	60.7 t	63.0 t
22	57.8 t	58.0 t	58.0 t	57.8 t	57.8 t	57.3 t

[a] The aromatic carbons as well as the ester carbonyl carbons of the mono- and the bis(*p*-nitrobenzoyl) derivatives **8** and **9** have identical chemical shifts except that the intensities of the signals in **8** were almost double those in **9**: C=O, 150.4 s; 1′, 130.6 s; 2′,6′, 130.6 d; 3′,5′, 123.5 d; 4′, 135.8 s ppm. [b] The assignments of compounds **5** and **7** are unambiguous and are based on the ^{1}H−^{1}H COSY, HETCOR, and selective INEPT NMR studies.

carbons close to this ring. Analysis of DEPT spectra shows that **5** has four quaternary, four methine, 13 methylene, and one methyl carbon, whereas **6** has three quaternary, five methine, 13 methylene, and one methyl carbon. These results indicate that in the product **6** one of the quaternary carbons, C(16), of **5**, has been transformed into a methine carbon bearing an oxygenated carbon. The disappearance of the quaternary carbon at δ 159.7 assigned to C(16) in **5** shows that the new carbonyl-bearing group in **6** is located at C(16). Also, the methylene carbon at C(17) resonating at δ 108.5 and the oxygenated carbon, C(15) at δ 82.6 in **5**, disappeared in **6**, indicating that the changes in **5** occurred at C(15), C(16), and C(17). These results prove that product **6** is an aldehyde. The presence of an −CHO group is further supported by the reactions carried out on **6**, i.e., reduction with $NaBH_4$ giving **7** bearing an additional $-CH_2$-OH group. The presence of two $-CH_2OH$ groups in **7** was confirmed when it gave a mixture of mono- and bis-(*p*-nitrobenzoyl) derivatives **8** and **9.** The *p*-nitrobenzoyl derivatives of **7** were prepared to obtain a crystalline derivative suitable for X-ray analysis. The structures **7**−**9** are fully supported by their detailed NMR results (see Table 1 for ^{13}C NMR chemical shift assignments and the Experimental Section for the ^{1}H NMR shift assignments). The selective INEPT data for **7** also support the structure (see Table 2).

The stereochemistry of the −CHO group in **6** and of the $-CH_2OH$ group in **7** was determined as follows. Examination of the Dreiding model of compound **7** shows that the angle between H(16β) and H(13β) is almost 90°, whereas the angle between H-16α and H-13β is about 20°. This fact and the lack of coupling observed between H-16 and H-13 indicate that the $-CH_2OH$ group in **7**, and hence, in **6**, is α-oriented.

Further proof that **6** does not contain a 2:2:2 bicyclooctane ring system derives from a comparison of the

Table 2. Selective INEPT Results for Compounds **5** and **7**

	pulsed ^{1}H (δ)	responding carbons (δ)
5	H_3-18 (0.77)	C-19 (60.2), C-5 (50.1), C-3 (41.2) C-4 (33.7)
	H-9 (1.05)	C-15 (82.7), C-8 (47.3), C-10 (40.2)
	H-3$_\alpha$ (1.57)	C-5 (50.1), C-1 (40.7), C-4 (33.7)
	H-7$_\alpha$ (1.71)	C-9 (50.4), C-5 (50.1), C-8 (47.3)
	H-14$_\alpha$ (1.87)	C-16 (159.7), C-15 (82.7), C-12 (32.3)
	H-20$_\beta$ (2.55)	C-21 (60.6), C-19 (60.2), C-5 (50.1) C-10 (40.2)
	H-13 (2.70)	C-15 (82.7), C-8 (47.3)
	H-15$_\beta$ (3.77)	C-13 (41.7), C-14 (36.7)
	H-17A (5.05)	C-15 (82.7), C-13 (41.7)
	H-17B (5.20)	C-15 (82.7), C-13 (41.7)
7	H_3-18 (0.76)	C-19 (60.3), C-5 (50.1), C-3 (41.3) C-4 (33.7)
	H-15 (0.87)	C-17 (67.3), C-9 (52.5), C-8 (44.2), C-16 (42.9), C-7 (39.6)
	H-14$_\alpha$ (1.81)	C-8 (44.2), C-16 (42.9)
	H-13 (2.04)	C-15 (45.3), C-8 (44.2), C-11 (18.7)
	H-19A (2.10)	C-21 (60.6), C-5 (50.1), C-4 (33.6)
	H-19B (2.42)	C-5 (50.1), C-4 (33.6)
	H-20$_\beta$ (2.52)	C-5 (50.1), C-10 (40.0)
	H-20$_\alpha$ (2.72)	C-21 (60.6), C-10 (40.0)
	H-17 (3.37)	C-15 (45.3), C-16 (43.0), C-13 (37.6)
	H-22 (3.60)	C-21 (60.6)

reported[11] ^{13}C NMR chemical shifts assigned to the eight carbons of the two different octane systems (Table 3).

Comparison of the data in Table 3 shows that the pattern of the chemical shifts assigned to the eight carbon atoms of the two ring systems is different. The number of quaternary, methine, and methylene carbons in both systems is the same, but their chemical shifts are different. When these shifts are compared in both series of compounds, the values are close for similar carbon atoms (except in compounds bearing carbonyl groups, i.e., compounds **B**−**D** and **K**−**L**). The ^{13}C NMR chemical shifts for C(8) in a 2:2:2 bicyclooctane ring system range from ∼36 to 38 ppm [except for compounds **B**−**D** where a carbonyl group is adjacent to C(8) and for compound **E**, which has a hydroxyl group on C(7)]. The ^{13}C NMR chemical shifts for C(8) in the 3:1:2 bicyclooctane ring system range from ∼45 to 48 ppm. In both of these systems C(15) bears a hydroxyl group. The ^{13}C NMR chemical shifts for C(14) in both systems are different, as can be seen from Table 3. The ^{13}C NMR chemical shifts assigned to the eight carbons of the octane ring in **6** and **7** (see Table 1) match well with those reported for compounds **I**−**P** (Table 3), and hence, we can conclude that the ring system in the product **6** obtained by acid-catalyzed isomerization of **5** has not changed.

The mechanism involved in the acid-catalyzed isomerization of dihydroveatchine was studied by carrying out the reaction in DCl and D_2O. Its molecular formula, $C_{22}H_{33}D_2NO_2$, was determined from its FABHRMS *m*/*z* 348.2887 $[M + 1]^+$ and carbon-13 NMR data. Two deuterium atoms were incorporated in the molecule (**10**) at C(16) and C(15) as indicated by the collapse of signals at δ 53.3 and 40.5 assigned to C(16) and C(15) in compound **6**, respectively. On the basis of this result, a pinacol-type mechanism that involves dehydration, rehydration and an allylic rearrangement is suggested in Figure 1.

Experimental Section

General Experimental Procedures. Melting points are corrected and were determined on a Thomas-Koffler

Table 3. Comparison of the ^{13}C NMR Chemical Shifts[11] for the Eight Carbons of the Diterpenoid Alkaloids Having 2:2:2 and 3:1:2 Bicyclooctane Ring Systems

	chemical shifts for the carbons							
	8	9	11	12	13	14	15	16
compds with 2:2:2 system								
A, atisine (20α)	37.5	40.0	28.2	36.6	27.7	25.5	77.0	157.5
B, atidine	53.8	41.6	28.0	36.0	26.6	25.3	72.8	151.5
C, atidine diacetate	50.8	42.3	27.8	36.1	26.8	25.6	73.6	149.2
D, atisinone	44.7	44.2	29.6	36.2	27.7	29.3	204.0	147.0
E, dihydroajaconine	42.6	39.5	28.4	36.1	26.4	25.4	71.9	156.3
F, dihydroatisine	37.4	39.5	28.0	36.4	27.7	26.4	76.8	156.3
G, dihydroatisine diacetate	36.8	40.5	28.0	36.4	27.4	26.3	77.2	151.3
H, atisineazomethine acetate	36.7	39.2	28.0	35.9	25.8	25.0	76.2	151.1
compds with 3:1:2 system								
I, veatchine (20α)	47.3	51.6	22.7	31.2	42.4	35.1	82.8	160.7
J, garryfoline (20α)	45.4	43.9	22.8	32.0	40.4	37.4	83.1	159.3
K, cuauchichicine	52.0	47.7	22.7	22.4	33.7	34.7	224.7	49.5
L, dihydrocuauchichicine	52.3	48.6	23.3	24.8	38.4	34.5	224.7	47.8
M, dihydroveatchine	47.2	50.0	23.4	32.3	41.7	36.8	82.3	159.1
N, dihydrogarryfoline	45.4	42.6	23.5	32.9	39.8	36.9	82.4	158.1
O, dihydroovatine	45.8	44.3	23.7	33.3	40.0	37.4	81.8	153.7
P, dihydroveatchine diacetate	47.0	49.9	22.4	32.4	41.9	37.6	82.7	154.8
compd **6** (see Table 1)	44.8	52.5	38.4	23.5	37.5	39.2	40.5	53.3
compd **7** (see Table 1)	44.2	52.5	18.7	31.2	37.6	37.9	45.3	43.0

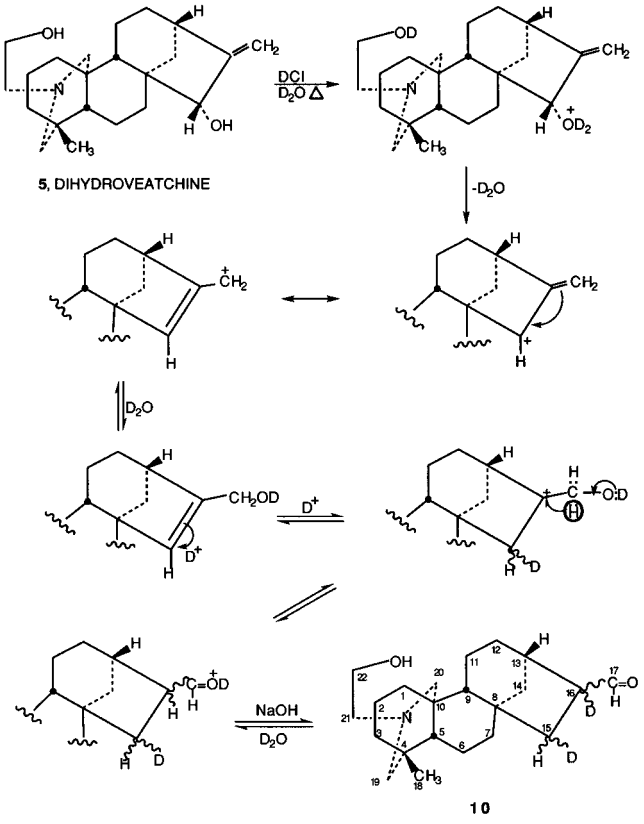

Figure 1.

hot stage equipped with a microscope and a polarizer. Optical rotations were measured on a Perkin-Elmer, Model 141, polarimeter in $CHCl_3$. IR spectra were recorded in Nujol on a Perkin-Elmer Model 1420 spectrophotometer. FABHRMS were recorded on an Autospec FAB^+ spectrometer, and ESIMS were recorded on a Perkin-Elmer SCIEX AP1-1 mass spectrometer. The samples for ESIMS were dissolved in a solvent mixture consisting of AcOH, MeCN, and H_2O. NMR spectra including, DEPT and 2D experiments, were recorded in $CDCl_3$ on Bruker AC 300 spectrometer. The pulse sequences employed for the NMR experiments were those of the standard Bruker software. The pulse sequence for the selective INEPT experiments was obtained by modifying the Bruker standard INEPT sequence as described by Bax.[12] The critical parameters used on our spectrometer were as mentioned in ref 13. Chromatographic separations on a Chromatotron[10] were carried out on rotors coated with 1 mm thick layers of Merck Al_2O_3 60 PF 254, 365 (EM 1104).

Preparation of Dihydroveatchine (5). To a solution of veatchine (**3**) (0.729 mmol) in MeOH (37 mL) was added $NaBH_4$ (9.9 mmol) in small lots during 1 h. The mixture was left for 17 h at room temperature. The solvent was evaporated *in vacuo*, and the residue in H_2O (10 mL) was extracted with $CHCl_3$ (30 mL × 3). The combined $CHCl_3$ extract was dried (Na_2SO_4) and evaporated to dryness. The dry amorphous solid was crystallized from Me_2CO-H_2O to give long thin plates (0.45 mmol): mp 142−143 °C (lit.[9] 148 °C); $[\alpha]_D$ −31.3° (c = 1.5); IR ν max 3350 (−OH), 3030, 1638, 857 cm^{-1} (>C═CH_2); ^1H NMR δ 0.99 and 2.14 (each 1H, m, H-1), 1.36 and 1.67 (each 1H, m, H-3), 1.00 (1H, br s, H-5), 1.35 and 1.71 (each 1H, m, H-7), 1.05 (1H, m, H-9), 1.40 (2H, m, H-12), 2.71 (1H, m, H-13), 1.41 and 1.87 (each 1H, m, H-14), 3.77 (1H, br s, H-15), 5.06 and 5.20 (each 1H, s, H-17), 0.77 (3H, s, H-18), 2.11 and 2.42 (each 1H, d, AB, J = 11.3 Hz, H-19), 2.55 and 2.73 (each 1H, d, J = 4.95 Hz, H-20), 2.40 (2H, t, J = 5.4 Hz, H-21), 3.60 (2H, t, J = 5.5 Hz, H-22). For ^{13}C NMR chemical shifts assignments see Table 1.

Action of Boiling 6 N HCl on 5. A solution of **5** (0.145 mmol) in 6 N HCl (13 mL) was refluxed for 45 min. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in H_2O (7 mL), and the solution was basified to pH 12 in the cold with 10% NaOH and extracted with $CHCl_3$ (5 × 30 mL). The dried (Na_2SO_4) $CHCl_3$ extract gave a gummy residue that showed a major spot (R_f 0.53) on TLC (Al_2O_3, Et_2O) with a minor less polar spot (Dragendorff's reagent). The gummy residue was fractionated on an Al_2O_3 rotor of a Chromatotron, and the faintly visible band (λ 254 nm) eluting was collected (hexane:80% Et_2O). The amorphous residue of **6** (0.123 mmol, 85%) was found to be a homogeneous compound in various TLC systems: $[\alpha]_D$

−74.5° (*c* = 1.1); FABHRMS *m/z* 346.2746 $[M + 1]^+$ (calcd M^+ for $C_{22}H_{33}NO_2$, *m/z* 345.2667); ESIMS *m/z* 346.2 $[M + 1]^+$; IR ν_{max} 3498 (−OH), 2130, 2030 (weak, −CHO), 1725 cm^{-1} (−C═O); ^1H NMR δ 0.76 (3H s, H-18), 3.61 (1H t, *J* = 5.5 Hz, H-22), 9.64 (1H br d, *J* = 1.9 Hz, −CHO). For ^{13}C NMR chemical shifts assignment see Table 1.

Action of 6 N DCl in D_2O on 5. A solution of **5** (0.087 mmol) in 6 N DCl in D_2O (3 mL) was refluxed for 45 min. Workup as described above gave a homogeneous amorphous compound (**10**, 0.047 mmol): FABHRMS *m/z* 348.2887 $[M + 1]^+$ (calcd M^+ for $C_{22}H_{33}D_2NO_2$ *m/z* 347.2793); ESIMS *m/z* 348.2 $[M + 1]^+$; ^1H NMR δ 9.64 (1H br s, −CHO) and signals similar to those of **6**. For ^{13}C NMR chemical shifts assignment see Table 1.

Reduction of 6 with $NaBH_4$. To a solution of **6** (0.116 mmol) in MeOH (13 mL) was added $NaBH_4$ (3.3 mmol) in small lots during 30 min. MeOH was evaporated *in vacuo*, and to the residue H_2O (5 mL) was added. The mixture was extracted with $CHCl_3$ (3 × 30 mL), and the combined extract was washed with water. Evaporation (*in vacuo)* of the dried (Na_2SO_4) $CHCl_3$ extract gave a gummy residue (0.06 mmol) that crystallized from Me_2CO:hexane, giving fine silky needles of **7**: mp 130−132 °C; $[\alpha]_D$ −23.2° (*c* = 0.9); ESIMS *m/z* 348.2 $[M + 1]^+$; IR ν_{max} 3477 cm^{-1} (−OH); ^1H NMR δ 2.13 (1H m, H-1_α), 0.98 (1H m, H-1_β), 1.50 (2H m, H-2), 1.59 and 1.41 (each 1H m, H-3), 0.96 (1H m, H-5), 1.53 (2H m, H-6), 1.41 (2H m, H-7), 0.84 (1H m, H-9), 1.65 (2H m, H-11), 1.43 and 1.27 (each 1H m, H-12), 2.04 (1H m, H-13), 1.81 (1H d, *J* = 11.8 Hz, H-14_α), 0.98 (1H d, *J* = 11.8 Hz, H-14_β), 1.53 (1H m, H-15_α), 0.87 (1H m, H-15_β), 1.90 (1H m, H-16), 3.37 (2H d, *J* = 7.5 Hz, H-17), 0.75 (3H s, H-18), 2.42 (1H d, H-19_B), 2.10 (1H d, H-19_A), 2.73 (1H br d, *J* = 9.1 Hz, H-20_A), 2.53 1H d, *J* = 10.0 Hz, H-20_B), 2.40 (2H m, H-21), 3.60 (2H t, *J* = 5.4 Hz, H-22). For ^{13}C NMR chemical shifts assignment see Table 1.

Preparation of *p*-Nitrobenzoyl Esters of 7. To a solution of **7** (0.105 mmol) in pyridine (2 mL) and benzene (dry, 3 mL) was added 4-nitrobenzoyl chloride (0.43 mmol). The mixture was stirred at room temperature for 68 h. The reaction mixture was passed over a small column of Al_2O_3 (basic), and the column was washed with CH_2Cl_2. The solvents were evaporated *in vacuo*; the TLC (Al_2O_3, hexane:$CHCl_3$ 1:1) of the residue (32.4 mg) indicated it to be mixture of at least two compounds with traces of starting material. The mixture was fractionated on an Al_2O_3 rotor of a Chromatotron. The visible bands (λ 254 nm) eluting with hexane and its mixture with $CHCl_3$ were collected. Fractions 5 and 6 eluted with hexane:$CHCl_3$ (80:20) gave a homogeneous compound (0.014 mmol) that was identified as bis(*p*-nitrobenzoyl) ester (**8**) of **7**; ESIMS *m/z* 646.4 $[M + 1]^+$ (calcd M^+ for $C_{36}H_{43}N_3O_8$ *m/z* 645.4); IR ν_{max} 1728, 1605, 1530, 1451, 1345, 1280, 1170, 1120, 1100, 1015, 970, 870, 751, 720 cm^{-1}. Fractions 9−11 eluted with hexane:$CHCl_3$ (75:25) gave another homogeneous compound (0.009 mmol), which was identified as the mono-*p*-benzoyl ester (**9**) of **7**: ESIMS *m/z* 497.4 $[M + 1]^+$ (calcd M^+ for $C_{29}H_{40}N_2O_5$ *m/z* 496.4); IR ν_{max} 3420, 1725, 1530, 1450, 1235, 1165, 1120, 1100, 852, 751, 750, 720 cm^{-1}. Attempts to crystallize compounds **8** and **9** met with failure.

8: ^1H NMR δ 8.30 (2H dd, *J* = 8.0, 2.2 Hz, H-3′, -5′), 8.20 (2H dd, *J* = 8.0, 2.2 Hz, H-2′, -6′), 4.16 (2H d, *J* = 7.2 Hz, H-17), 3.62 (2H t, *J* = 5.4 Hz, H-22), 0.78 (3H s, H-18).

9: ^1H NMR δ 8.30 (4H dd, *J* = 8.2, 2.3 Hz, H-3′, -5′), 8.20 (2H dd, *J* = 8.0, 2.1 Hz, H-2′, -6′), 8.22 (2H dd, *J* = 8.0, 2.1 Hz, H-2′, -6′). For ^{13}C NMR chemical shift assignments of **8** and **9** see Table 1.

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References and Notes

(1) Djerassi, C.; Smith, C. R.; Lippman, A. E.; Figdor, S. K.; Heran, J. *J. Am. Chem. Soc.* **1955**, *77*, 4801−4807.
(2) Pelletier, S. W.; Mody, N. V. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, Chapter 2, pp 100−216.
(3) Wiesner, K.; Velanta, Z. *Forschr. Chem. Org. Naturst.* **1958**, *16*, 50−53.
(4) Pelletier, S. W.; Desai, H. K.; Mody, N. V. *Heterocycles* **1979**, *13*, 277−280.
(5) Desai, H. K.; Jiang, Q.; Pelletier, S. W. *J. Nat. Prod.* **1990**, *53*, 1374−1378.
(6) Wenkert, E. *Chem. Ind.* **1955**, 282−284.
(7) Edwards, J. A.; The Structure and Stereochemistry of Diterpene Alkaloids. Thesis, University of New Brunswick, Canada, 1955.
(8) King, J. F. Degradation Studies in the Aconite Alkaloid Series. Ph.D. Thesis, University of New Brunswick, Canada, 1957.
(9) Wiesner, K.; Figdor, S. K.; Bartlett, M. F.; Henderson, D. R. *Can. J. Chem.* **1952**, *30*, 608−626.
(10) Desai, H. K.; Trumbull, E. R.; Pelletier, S. W. *J. Chromatogr.* **1986**, *366*, 439−444.
(11) Atta-ur-Rahman. *Hand Book of Natural Products Data*; Elsevier: New York, 1990; pp 239−341.
(12) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314−318.
(13) Desai, H. K.; Pelletier, S. W. *J. Nat. Prod.* **1993**, *56*, 1140−1147.

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