ALKALOIDS OF *ACONITUM COLUMBIANUM* NUTT.

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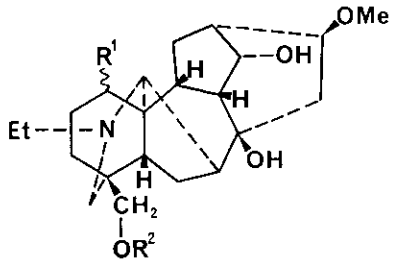
Abstract - The alkaloidal constituents of *Aconitum columbianum* Nutt. ssp. *columbianum* have been investigated. In addition to the known alkaloids cammaconine (12), deltaline (10), dictyocarpine (11), talatizamine (3), and 8-*O*-methyltalatizamine (7), a new base columbidine (**4**) has been isolated and its structure elucidated. The structure was derived on the basis of spectral data and chemical correlation with talatizamine. Synthesis of **7** from talatizamine is described and the ^{13}C-nmr spectrum of 14-dehydrotalatizamine has been recorded. Certain ^{13}C-nmr signals for these compounds have been reassigned.

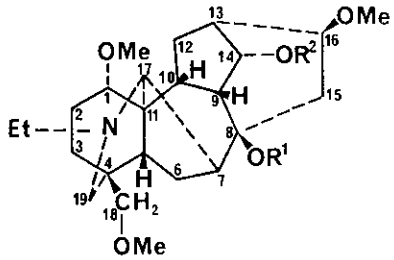
Aconitum species have a long history of medicinal and toxic properties. Loss of life in livestock and humans has occurred from ingestion of *Aconitum* plants or their extracts. Many species have not been carefully investigated with regard to chemical constituents and toxicity.[1] Concern and some confusion exists among livestock producers and others pertaining to livestock poisoning by *Aconitum* species.[2] Detailed chemical investigations, such as the present study, correlated with animal toxicological studies are needed.

Aconitum columbianum Nutt. ssp. *columbianum* is a perennial shrub growing in the western parts of the United States. The presence of aconitine and aconine has been recorded, although no reference has been cited for their original isolation.[3] Some preliminary studies on the isolation of amorphous alkaloids from the roots[4] and assays of the toxicity to sheep and cattle have been reported.[5,6] A study of the alkaloids of a Canadian variety of this plant reported as major alkaloids, talatizamine and cammaconine, and as minor alkaloids, sachaconitine, talatizidine (1A), isotalatizidine (1B), 14-*O*-acetyltalatizamine, 8-*O*-methyltalatizamine (7) and columbianine (2).[7]

In the course of our studies of the chemical constituents of the Ranunculaceae occurring in the United States,[8,9,10] we have investigated the alkaloids of *Aconitum columbianum* Nutt. ssp.

On leave from CIMAP, Lucknow, India.





1A R^1 = -OH; R^2 = CH_3 Talatizidine
1B R^1 = -OH; R^2 = CH_3 Isotalatizidine
2 R^1 = -OH; R^2 = H Columbianine
12 R^1 = $-OCH_3$; R^2 = H Cammaconine

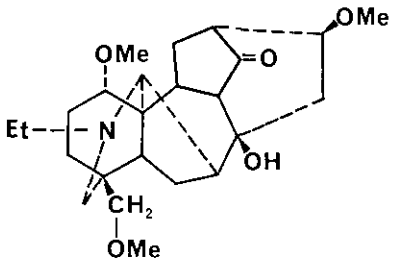
3 R^1 = R^2 = H Talatizamine
4 R^1 = C_2H_5; R^2 = H Columbidine
5 R^1 = C_2H_5; R^2 = Ac
6 R^1 = R^2 = Ac
7 R^1 = CH_3; R^2 = H 8-*O*-Methyltalatizamine
8 R^1 = CH_3; R^2 = Ac

columbianum. The crude alkaloid mixture (E_1) isolated at pH 5 from the ethanol extract was chromatographed on alumina to afford four homogeneous compounds, one of which is a new alkaloid designated as *columbidine*. The molecular formula $C_{26}H_{43}NO_5$ (M^+, m/z 449) together with the ^1H nmr and ^{13}C nmr spectral data indicates that columbidine is a C_{19}-diterpenoid alkaloid of the aconitine type.[11] Its ^1H nmr spectrum shows the presence of three singlets due to methoxyl groups appearing at δ 3.20, 3.23 and 3.29 ppm and two triplets assigned to primary methyl groups at δ 1.05 (J = 7.5 Hz) and 1.08 ppm (J = 7.5 Hz). The fully decoupled ^{13}C nmr spectrum shows 26 lines due to twenty-six carbon atoms of the molecule and indicates close resemblance to the spectrum of talatizamine (**3**) (see Table 1). When compared with **3**, extra signals were observed at 55.8 and 16.2 ppm, appearing as a triplet and a quartet, respectively in the SFORD spectrum. This evidence suggests the presence of an ethoxyl group, which could be located either at C(8) or C(14) in **3**. The two lowfield signals at 85.8 ppm and 82.5 ppm are assigned to C(1) and C(16), respectively, each bearing a methoxyl group. If the ethoxyl group is to be placed at C(14), this carbon should show a resonance about 80.5 - 82.5 ppm. Columbidine does not exhibit any signal in this region and tne resonance at 75.1 ppm is attributed to C(14) bearing a hydroxyl group. The ethoxyl should therefore be placed at C(8) leading to structure (**4**) for columbidine. A hydroxyl group at C(14) is supported by the ^1H nmr spectrum of acetylcolumbidine (**5**) which exhibits the C(14)-proton as a triplet at δ 4.68 ppm (J = 4.5 Hz) as in the case of 14-*O*-acetyltalatizamine[12] and 8,14-di-*O*-acetyltalatizamine (**6**). With a view to correlate columbidine (**4**) with a known compound, it was heated with aqueous sulfuric acid to afford talatizamine (**3**). The demethylation of C_{19}-diterpenoid alkaloids having a methoxyl group at C(8) has precedence in the case of alkaloid A[13] from *Delphinium bicolor* Nutt. and deltatsine.[14]

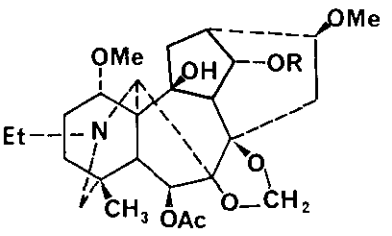
The 8-acetyl group of C_{19}-diterpenoid alkaloids can be replaced by an alkoxyl group by treatment with the corresponding alcohol under reflux or in a sealed tube at 110-130°C. 8-Acetyltalatizamine has not been isolated from a natural source and we were unable to isolate it from *A. columbianum*. Talatizamine does not furnish columbidine when heated with ethanol at 50° for 100 h. Therefore we believe that columbidine is not an artifact formed during isolation, although its

formation from some unisolated intermediate cannot be discounted.

The fraction which eluted after columbidine was identified as 8-*O*-methyltalatizamine (7)[7] from its ^{1}H nmr and ^{13}C nmr spectral properties. This identification was confirmed by comparison with an authentic sample prepared from talatizamine. Heating 8,14-Di-*O*-acetyltalatizamine (6) with methanol in a sealed tube afforded 14-acetyl-8-*O*-methyltalatizamine (8)



9 14-Dehydrotalatizamine



10 R = CH_3 Deltaline
11 R = H Dictyocarpine

which on alkaline hydrolysis gave (7). Dealkylation of 7 with 3 M aqueous sulfuric acid also gave talatizamine.

The major alkaloid, mp 145°C, which eluted after the separation of 8-*O*-methyltalatizamine was found to be identical with talatizamine (3).[15] The ^{13}C nmr spectral data were almost identical with those reported earlier[16] for 3 (Table 1), but some of the assignments need to be revised. The signal at 38.7 ppm assigned to C(5) is much upfield and this carbon should be assigned the resonance at 45.9 ppm as in cardiopetaline[17], and sachaconitine.[18] The assignments for C(10) and C(13) also should be reversed. For most of the C_{19}-diterpenoid alkaloids, the higher field resonance appearing in the range 37-43 ppm previously has been ascribed to C(10) and the lower field signal at around 43-46.5 ppm has been attributed to C(13).[19,20] These values for C(10) and C(13) need to be reversed for most of these alkaloids, as was initially reported by Jones and Benn for some lycoctonines.[21] This reversal of the assigned values for C(10) and C(13) is in conformity with the expected downfield shift of approx. 8.0 ppm of the carbon β- to the hydroxyl group (β-effect) and an upfield shift of about 2-4 ppm of the γ-carbon (γ-effect),[22] when a hydroxyl group is situated at C(9), as in the case of ranaconine[23], lappaconine[24] or episcopalisinine.[25]

14-Dehydrotalatizamine (9) is reported to have been isolated from *Aconitum saposhnikovii*.[26] As the ^{13}C nmr spectrum of this alkaloid has not been recorded, we have prepared 9, mp 129-130°C, by oxidation of talatizamine with chromium trioxide in acetic acid.

The fraction which eluted subsequent to the isolation of talatizamine, mp 185-187°C, was identified as deltaline (10) by comparison of its physical and spectral properties with those of an authentic sample.[27,28] Further elution afforded dictyocarpine (11) which was identified by com-

parison with an authentic specimen and its spectral data.[29,30] The crude alkaloid isolated at pH 9 (E_2) was purified by vacuum liquid chromatography (v.l.c.) on alumina, to afford a compound, mp 135-137°C, identified as cammaconine (**12**).[31] The revised ^{13}C nmr data for **12** are given in Table 1.

TABLE 1. ^{13}C nmr chemical shifts and assignments for talatizamine (**3**), 8,14-di-*O*-acetyltalatizamine (**6**), columbidine (**4**), 8-*O*-methyltalatizamine (**7**), 14-acetylcolumbidine (**5**), 14-acetyl-8-*O*-methyltalatizamine (**8**), 14-dehydrotalatizamine (**9**), and cammaconine (**12**).

Carbons	3	4	7	5	6	8	9	12
C(1)	86.3 d	85.8 d	85.9 d	85.7	85.4	85.7	85.5	86.4 d
C(2)	25.8 t	26.1 t	26.0 t	26.5	26.4	26.5	25.7	25.9 t
C(3)	32.8 t	32.6 t	32.6 t	32.6	32.6	32.6	32.6	32.3 t
C(4)	38.7 s	38.5 s	38.6 s	38.1	37.6	38.4	38.8	39.2 s
C(5)	45.9* d	46.2* d	46.2* d	46.0*	45.8*	46.0*	45.8*	45.9*d
C(6)	24.8 t	23.9 t	23.7 t	24.1	24.8	24.0	25.2	24.6 t
C(7)	46.0* d	40.7 d	40.0 d	41.0	44.8*	40.0	45.8	45.9*d
C(8)	72.9 s	78.1 s	77.8 s	77.6	86.0	77.7	82.8	73.0 s
C(9)	47.0* d	45.5* d	45.9* d	43.2	42.3	43.2	55.3	47.0 d
C(10)	46.0* d	45.8* d	45.6* d	45.2*	49.3	45.2*	46.2*	45.6*d
C(11)	48.8 s	48.8 s	48.8 s	49.1	48.7	49.0	48.9	48.9 s
C(12)	27.7 t	28.7 t	28.4 t	29.0	28.7	29.0	24.6	27.7 t
C(13)	37.7 d	38.7 d	38.0 d	38.4	38.3	38.0	43.9	37.7 d
C(14)	75.6 d	75.1 d	75.0 d	75.6	75.3	75.8	216.2	75.6 d
C(15)	38.5 t	34.7 t	33.3 t	36.3	41.4	35.5	36.8	38.4 t
C(16)	82.3 d	82.5 d	82.3 d	83.4	82.8	83.3	86.2	82.3 d
C(17)	62.9 d	62.5 d	62.8 d	61.8	61.9	61.9	63.8	63.0 d
C(18)	79.5 t	79.6 t	79.6 t	79.6	79.4	79.8	79.3	68.9 t
C(19)	53.3 t	53.1 t	53.1 t	53.2	52.9	53.1	53.1	53.1 t
N-CH_2	49.5 t	49.3 t	49.4 t	49.3	49.3	49.4	49.4	49.6 t
CH_3	13.6 q	13.6 q	13.6 q	13.5	13.5	13.6	13.7	13.7 q
C(1)'	56.3 q	56.1 q	56.3 q	56.3	56.2	56.3	56.1	56.6 q
C(8')	-	-	48.3 q	-	-	48.2	-	-
C(16)'	56.5 q	56.3 q	56.3 q	56.3	56.4	56.3	56.3	56.4 q
C(18)'	59.5 q	59.4 q	-	59.5	59.4	59.5	59.5	-
C(8)-O-CH_2	-	55.8 q	-	55.6	-	-	-	-
CH_3	-	16.2 q	-	16.4	-	-	-	-
C = O	-	-	-	171.4	169.5, 171.0	171.6	170.2	-
CH_3	-	-	-	21.5	22.4, 21.3	21.4	21.7	-

a Chemical shifts in ppm downfield from TMS, solvent deuterochloroform.

b Values given for primed carbons refer to chemical shifts for methoxyls.

* These assignments may be interchanged in any vertical column.

EXPERIMENTAL

MP's are corrected. Spectra were recorded on the following instruments: Ir, Perkin-Elmer Model 1430; ^{1}H nmr, Perkin-Elmer EM-390, 90 MHz; ^{13}C nmr, JEOL FT models FX-60 and FX-90Q; and mass spectra, Finnegan Quadrupole 4023.

Extraction and separation — *Aconitum columbianum* Nutt. ssp. *columbianum* was collected in the Davis Basin area (elevation 6900 feet) northeast of Clifton, Idaho. The collection (Poisonous Plant Research Lab #79-16) consisted of plants primarily in the prebud stage of growth (estimated 90%) with about 9% in the early bud stage and some in full bud with occasional flowers. The aerial parts of plants were air dried, ground, (9 kg) and extracted in a large stainless steel pot with 40 liters of 85% ethanol solution. After soaking for several days, percolation was begun with 85% ethanol at room temperature (18-24°C). Percolation was continued at irregular intervals until a total of 260 liters of ethanol extract was withdrawn (280L total in, 260L out). The ethanol extract was reduced in volume by carefully controlled distillation under vacuum (large-size stainless steel apparatus) with a water bath temperature ranging from 50 to 60°C, resulting in a distilling vapor temperature ranging from 32 to 36°C. The condensed extract weighed 3990 g.

Part of this residue (695 g) was dissolved in 1300 ml chloroform and extracted with 2% aqueous sulfuric acid (18 x 150 ml). The acidic extract was basified with $NaHCO_3$ (pH 5) and extracted with $CHCl_3$ (20 x 500 ml) to afford a crude alkaloid residue (E_1; 12.5 g). The aqueous layer was again basified in the cold with saturated Na_2CO_3 (pH 9) and extracted with $CHCl_3$ (15 x 500 ml) to afford a crude alkaloid mixture (E_2; 12.4 g). The aqueous layer was made alkaline (pH 12) with NaOH solution and extracted with $CHCl_3$ (6 x 500 ml) to give a crude alkaloid fraction (E_3; 1.6 g).

Part of fraction E_1 (8.5 g) was chromatographed on an alumina column (Act. III; 300 g) and eluted with hexane containing increasing amount of methanol (0.05-2%). Fractions (25 ml each) were collected and the chromatographic separation was monitored by t.l.c.

Isolation of columbidine (4). — Fractions 225-300 from E_1 (hexane: 0.5-0.6% MeOH) were combined to give a colorless homogeneous residue (300 mg) which was light sensitive. It was further purified by v.l.c. over a well-packed column of t.l.c. grade alumina (E. Merck 10 g, type E, H basic). Elution was carried out under vacuum with hexane containing increasing amount of ethyl acetate and fractions (50 ml each) were collected. Fractions 18-49 (hexane: 5-20% EtOAc) afforded columbidine (220 mg) as an amorphous product that showed a single spot on t.l.c.; $[\alpha]_D^{25°}$ -6.4° (c 1.4, $CHCl_3$); ir (nujol): 3530, 2965, 2920, 2870, 2815, 1493, 1455, 1382, 1348, 1295, 1260, 1223, 1193, 1158, 1110, 1090, 1060, 1010, 990, 978, 967, 940, 900, 876 and 800 cm^{-1}; ^{1}H nmr (90 MHz, $CDCl_3$, TMS): δ 1.05, 1.08 (each 3H, t, J = 7.5 Hz, N-CH_2-CH_3 and O-CH_2-CH_3), 3.20, 3.23, 3.29 ppm (each 3H, s, OCH_3). Found: C, 69.32; H, 9.68; N, 3.06. Calc. for $C_{26}H_{43}NO_5$: C, 69.49; H, 9.58; N, 3.12. MS: m/z 449 (M^+, 1%), 434 (M-CH_3, 1), 418 (M-OCH_3, 100), 404 (M-OCH_2CH_3, 14), 386 (404-HOH, 10), 373 (418-OCH_2CH_3, 5). For the ^{13}C nmr spectrum see Table 1.

Isolation of 8-*O*-methyltalatizamine (7) — Fractions 302-326 (hexane: 0.6% MeOH) were pooled and purified by v.l.c. on a short alumina column. The elution was carried out with hexane containing increasing amount of ethyl acetate and 100 ml fractions were colleted. Fractions 30-43 (5% EtOAc) afforded (7; 65 mg) as an amorphous product which showed a single spot on t.l.c. $[\alpha]_D^{29.5}$ - 4° (c, 1.16, $CHCl_3$), ir (nujol): 3530, 2960, 2925, 2870, 2820, 1493, 1461, 1453, 1381, 1349, 1295, 1255, 1223, 1192, 1158, 1105, 1090, 1070, 1040, 1003, 988, 976, 966, 940, 908, 874, 842, 800, 765, 748 cm^{-1}. MS: m/z 435; ^1H nmr (90 MHz; $CHCl_3$, TMS): δ 1.03 (3H, t, J = 7 Hz, N-CH_2-CH_3), 3.08, 3.20, 3.23 and 3.30 (each 3H, s, OCH_3) and 3.88 ppm (1H, t, C(14)-β-H). For the ^{13}C nmr spectrum see Table 1.

Isolation of talatizamine (3) — Fractions 332-405 (hexane: 0.6% MeOH) on crystallization from hexane afforded talatizamine (3 g), mp 145°C. MS: m/z 421. Its m.mp., co-t.l.c. and ir spectrum were identical with those of an authentic sample of talatizamine. ^1H nmr (90 MHz; $CDCl_3$, TMS) displayed the following signals: δ 1.08 (3H, t, J=7Hz, N-CH_2-CH_3), 3.05 and 3.15 (each 1H, d, C(18)-H_2), 3.25, 3.29 and 3.35 (each 3H, s, OCH_3), and 4.12 ppm (1H, t, C(14)-β-H); For the ^{13}C nmr spectrum refer to Table 1.

Isolation of deltaline (10) — Fractions 420-500 (hexane: 0.6-0.8% MeOH) were purified by v.l.c. and elution was carried out with hexane containing (5-25% EtOAc). Fractions 17-25 (20% EtOAc) afforded deltaline (120 mg) which on crystallization from a mixture of ether-acetone gave colorless plates, mp 185-187°C, $[\alpha]_D^{29}$ -28° (MeOH); MS: M/z 507. Comparison of the m.mp, co-t.l.c., ir, ^1H and ^{13}C nmr spectrum with those of an authentic sample of deltaline[26,27] showed them to be identical. Found: C, 64.07; H, 8.30. Calc. for $C_{27}H_{41}NO_8$: C, 63.90; H, 8.09%.

Isolation of dictyocarpine (11) — Fractions 501-517 (hexane: 0.8% MeOH) were purified by v.l.c. on alumina and elution was carried out with hexane containing 15-60% $CHCl_3$. Fractions 6-8 (40% $CHCl_3$) afforded dictyocarpine (15 mg), which on crystallization from MeOH gave colorless needles, mp 201-203°C. Comparison of the m.mp, co-t.l.c., ir, ^1H and ^{13}C nmr spectra with those of an authentic sample of dictyocarpine showed them to be identical.

Isolation of cammaconine (12) — Fraction E_2 (1 g) was chromatographed by v.l.c. on a short column of alumina (65 g). Elution was carried out successively with mixtures of hexane, toluene, chloroform and methanol. Fractions (200 ml each) were collected. Fraction 35 ($CHCl_3$:5% MeOH) (216 mg) when crystallized from a mixture of methylene chloride-methanol afforded cammaconine (120 mg), mp 135-137°C; MS: m/z 407. Found: C, 64.83; H, 9.26; N, 3.27. Calc. for $C_{23}H_{37}NO_5$-H_2O: C, 64.94; H, 9.17; N, 3.29%. Comparison of the m.mp, co-t.l.c. and ir spectrum with those of an authentic sample of cammaconine showed them to be identical. ^1H nmr (90 MHz, $CDCl_3$, TMS): δ 1.06 (3H, t, N-CH_2-CH_3); 3.21 and 3.29 (each 3H, s, -OCH_3) and 4.08 ppm (1H, t, C(14)-β-H). For the ^{13}C nmr spectrum see Table 1.

Dealkylation of columbidine to talatizamine — Columbidine (**4**, 12 mg) was heated under reflux with 3M H_2SO_4 (4 ml) for 60 h. The solution was cooled, basified with aqueous Na_2CO_3 (pH 9) and extracted with $CHCl_3$ to afford an amorphous product (10 mg) which showed two spots on t.l.c. (Al_2O_3; $CHCl_3$:MeOH; 98.5:1.5). This product was separated by preparative t.l.c. on Al_2O_3 (0.5 mm) and eluted with $CHCl_3$:MeOH (98:2). The band (Rf 0.4) was extracted with $CHCl_3$:10% MeOH to afford a crystalline solid (2 mg), mp 145°C. Comparison of the m.mp and co-t.l.c. with those of an authentic sample of talatizamine showed them to be identical.

14-Acetyl-8-O-methyltalatizamine (8) — 8,14-Di-*O*-acetyltalatizamine (100 mg) and methanol (5 ml) were heated in a sealed tube at 100°C. After 4 h, methanol was removed and the residue (95 mg) was chromatographed on a short v.l.c. column to give 60 mg of **8** as a homogeneous amorphous product. IR (nujol): 1750 cm^{-1}; ^1H nmr ($CDCl_3$, TMS): δ 1.05 (3H, t, J=7Hz, N-CH_2-CH_3), 2.00 (3H, s, -OCOCH_3), 3.07, 3.22, 3.24 and 3.26 (each 3H, s, -OCH_3), 4.64 (1H, t, C(14)-β-H). For the ^{13}C nmr spectrum refer to Table 1.

8-O-Methyltalatizamine (7) — Fifty-five mg of 14-acetyl-8-*O*-methyltalatizamine (8) was refluxed with a solution of 5% methanolic potassium hydroxide. After 2 h the solvent was removed, ice water added, and the mixture was extracted with chloroform to give 40 mg of (7), identical with 8-methoxytalatizamine isolated from *A. columbianum*, as shown by its ^{13}C nmr spectrum.

14-O-acetylcolumbidine (5) — A mixture of columbidine (42 mg), acetic anhydride (0.2 ml) and pyridine (0.2 ml) was left at room temperature for 24 h after which the reaction mixture was poured over crushed ice. This was basified with K_2CO_3 (pH 9) and extracted with $CHCl_3$ to afford an amorphous product (50 mg) that was purified by chromatography on alumina. ^1H nmr: δ 1.06 (3H, t, J = 7 Hz, -N-CH_2-CH_3), 2.00 (3H, s, -OCOCH_3), 3.20 (6H, s, -OCH_3), 3.28 (3H, s, -OCH_3), 4.68 ppm (1H, t, J = 7 Hz, C(14)-β-H). For the ^{13}C nmr spectrum refer to Table 1.

ACKNOWLEDGEMENT

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