THE NATURAL OCCURRENCE AND PARTIAL SYNTHESIS OF 1α,4(S),6β,14α,16β-19,20-DIDEHYDRO-1,6,14,16-TETRAMETHOXY-4-[[[2-(3-METHYL-2,5-DIOXOPYRROLIDINYL)BENZOYL]OXY]METHYL]ACONITANE-7,8-DIOL; CONCERNING ANHWEIDELPHININE

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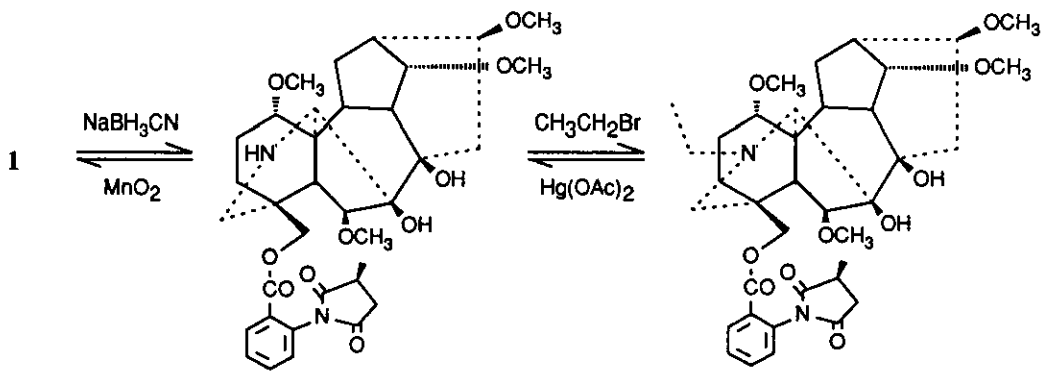
Abstract - The title compound, alkaloid-Y, which is probably identical with anhweidelphinine, was isolated from *Delphinium nuttalianum* and its structure was proven by its conversion into methyllycaconitine, and also by its preparation from that alkaloid.

During an investigation of the alkaloids of *D. nuttallianum*[1] small amounts of an alkaloid were isolated which was identified as the norditerpenoid (***1***) on the basis of ms, ^{1}H and ^{13}C-nmr data. At the time we thought that this was a previously unknown alkaloid, which we designated alkaloid-Y, but just before we presented our results we found its structure given in a review[2] of the alkaloids of Chinese medicinal plants. It was identified as anhweidelphinine, with a reference to its isolation by Jin[3] from *D. anhweiense*. The Chemical Abstracts citation[4] of that paper shows a formula for the alkaloid which lacks the N,19-double bond and also shows the stereochemistry at C-1 as α: indeed anhweidelphinine was indexed as 1α,4(S),6β,14α,16β-19,20-didehydro-1,6,14,16-tetramethoxy-4-[[[2-(3-methyl-2,5-dioxopyrrolidinyl)benzoyl]oxy]methyl]aconitane-7,8-diol, and this name is retained in the 1990 Index Guide to Chemical Abstracts, while structure ***1*** also appears for anhweidelphinine in a recent authoritative Dictionary of Alkaloids[5] (with an accompanying note warning of the defective structure presented in the Chemical Abstracts citation). Only an inspection of the original article[3] reveals that Jin and Zhong had assigned the 1β-configuration to the A-ring methoxyl functionality i.e. ascribed structure ***2*** to their alkaloid. This is unusual: when oxygenated at C-1 the vast majority of the norditerpenoid alkaloids have this substituent in an α-configuration, and Joshi and Pelletier[6] have pointed out that the ^{13}C-resonance (δ 84.5) ascribed to C-1 of anhweidelphinine by Jin and Zhong is in accord with what is expected of 1α rather than 1β-methoxylation, and they therefore revised the structure of the alkaloid to that ***1*** given in the various misrepresentations of ***2***. However, we think that Jin and Zhong mis-assigned among others

the resonances for C-1 and C-14 i.e. that at δ 82.6 ppm corresponds to C-1, while the δ 84.5 ppm absorption is due to C-14. This is certainly the case for alkaloid-Y where we could establish the relationship between H-14, a triplet-like double-doublet at δ 3.67, $J_{9,14} = J_{13,14} = 4.5$ Hz, and the C-14 resonance at δ 84.2 ppm. The "anomolous" shift for C-1, which we observed at δ 82.2, we attribute to the proximity of the N,19-double bond. The characteristic H-14 resonance served as a reference point from which, by means of ^{1}H,^{1}H-COSY and ^{13}C,^{1}H-XHCORR nmr spectra, we were able to identify H- and C- 9, 10, 12 and 13. Conversely the ^{13}C shifts of C-1 and 16 enabled us to identify H-1 and 16, overlapped at δ ca. 3.3, from whence we located (COSY) H-2, 3, and 15 and so (XHCORR) C-2, -3 and 15. The resonance for C-5 was identified on the basis of being the only otherwise unassigned one in the range 40-50 ppm in which it normally falls. Finally, some minor reassignments for ***2-4*** of the 3′, 5′ and 6′ aryl protons followed from XHCORR spectra, while COLOC spectra showed that the resonances ascribed to the methoxyl groups at C-6 and 14 should be interchanged.

We now report chemical evidence which proves that our isolate from *D. nuttallianum* has the structure ***1***.

Reduction of alkaloid-Y with sodium cyanoborohydride, followed by treatment with bromoethane gave a base which was identical with the known alkaloid methyllycaconitine (***4***) whose stereochemistry has been firmly established[7] i.e. we carried out the correlation ***1*** → ***3*** → ***4***.



3 4

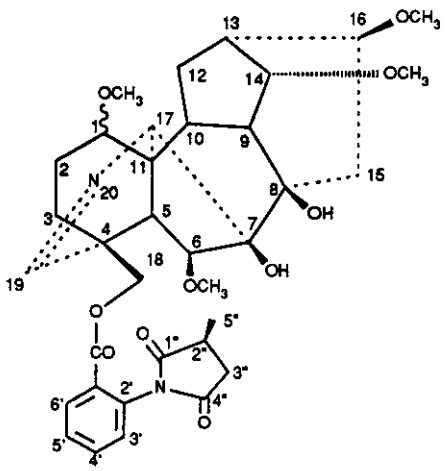
We were also able to achieve the reverse sequence of reactions by de-N-ethylation of methyllycaconitine with mercury(II) acetate in aqueous acetic acid to give ***3***, followed by manganese(IV) oxide oxidation of the desethyl alkaloid to yield ***1***. The product of this sequence of reactions had spectroscopic properties (^{1}H, ^{13}C nmr, ms) identical with those of our natural product, the presumed anhweidelphinine.

Although we have not carried out a direct comparison of alkaloid-Y with an authentic specimen of anhweidelphinine and, as shown in Table 1, there are some discrepancies in the ^{13}C-nmr data reported by Jin

and Zhong and that which we collected, we strongly suspect that the two alkaloids are identical i.e. anhweidelphinine is correctly represented as *1*.

Table 1. ^{13}C Nmr chemical shift data for alkaloid-Y (*1*), anhweidelphinine (*2*), des-N-ethylmethyllycaconitine (*3*), and methyllycaconitine (*4*).

Carbon	*1*	*2*[3]	*3*	*4*
1	82.2	84.5	84.2	84.0
2	21.0	25.4	25.0	26.1
3	24.6	21.8	29.4	32.1
4	46.9	44.1	37.3	37.5
5	45.5	43.3	48.2	50.9
6	91.6	92.0	91.1	90.9
7	86.5	86.7	84.1	88.5
8	77.3	77.3	77.9	77.6
9	43.0	50.4	43.6	43.2
10	43.5	38.6	45.1	46.1
11	50.5	47.5	48.7	49.1
12	30.3	30.4	28.9	28.7
13	38.4	47.1	38.6	38.2
14	84.2	82.6	84.1	84.0
15	33.1	33.7	33.4	33.7
16	81.4	81.8	82.5	82.6
17	64.5	65.0	60.4	64.5
18	66.7	67.2	69.4	69.6
19	162.9	163.8	48.6	52.4
1-OCH_3	56.3	56.2	55.8	55.7
6-OCH_3	58.7	58.9	58.1	58.2
14-OCH_3	57.8	57.7	57.8	57.8
16-OCH_3	56.3	56.3	56.3	56.3
CO	164.0	164.3	164.1	164.1
1′	127.0	127.2	127.0	127.1
2′	133.1	133.4	133.1	133.1
3′	130.1	130.2	130.1	130.0
4′	133.9	133.7	133.6	133.6
5′	129.4	129.4	129.3	129.3
6′	130.9	130.9	131.0	131.0
1″	175.8	175.5	175.8	175.8
2″	35.3	35.4	35.2	35.0
3″	36.9	37.2	36.9	37.0
4″	179.8	179.6	179.8	179.8
5″	16.4	16.4	16.4	16.4



1 1α-OCH_3

2 1β-OCH_3

EXPERIMENTAL

General: - The ^1H and ^{13}C nmr spectra were determined in $CDCl_3$ with residual $CHCl_3$ (δ 7.27 ppm) and $^{13}CDCl_3$ (δ 77.0) as internal references on Bruker ACE-200 and AM-400 MHz spectrometers, δ values are in

ppm, J in Hz.. The ir spectra were recorded with a Mattson FT-IR spectrophotometer model-4030 of samples dispersed in KBr discs. The ms data were obtained with a VG-7070 mass spectrometer. All tlc were carried out on silica gel 60 F254 (Merck 5715). Methyllycaconitine (*4*) and *1* were isolated[1] from *D. nuttallianum*.

Alkaloid-Y, the presumed anhweidelphinine (*1*): $C_{35}H_{44}N_2O_{10}$ (652), ms (EI): 652 (M+), 637, 621, 436, 420, 370, 216. IR (KBr): 3465, 1714, 1602, 1456, 1390 and 1089 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) (based on COSY and XHCORR): 8.05 (1H, d, J=7.7, H-6′), 7.71 (1H, dt, J=1.5 and 7.7, H-4′), 7.55 (1H, dt, J=1.5 and 7.7, H-5′), 7.48 (1H, br s, H-19), 7.31 (1H, d, J=7.7, H-3′), 4.38 (2H, br s, H-18), 3.88 (1H, s, H-17), 3.78 (1H, s, H-6), 3.67 (1H, t, J=4.4, H-14), 3.43 (3H, s, CH_3O-14), 3.36 (3H, CH_3O-16), 3.31 (3H, s, CH_3O-6), 3.18 (3H, s, CH_3O-1), 3.29 (1H, m, H-16), 3.21 (1H, m, H-1), 3.10 and 2.55 (each ^{1}H, m, H-3″), 3.10 (1H, m, H-2″), 2.85 and 1.78 (each 1H, m, H-15), 2.85 (1H, br s, H-9), 2.42 (1H, m, H-13), 2.04 (1H, m, H-10), 2.01 and 1.55 (each 1H, m, H-12), 1.85 and 1.50 (each 1H, m, H-3), 1.80 (2H, m, H-2), 1.75 (1H, br, H-5) and 1.45 (3H, d, J=7.0, H-5″); ^{13}C nmr data see table 1.

Preparation of Des-N-ethylmethyllycaconitine (*3*):

(a) Reduction of *1* - To alkaloid-Y (4.5 mg, 0.0069 mmol) in dry methanol (2 ml) was added sodium cyanoborohydride (0.46 mg, 3 mmol). After 1 h, silica gel (100 mg) was added, the reaction mixture was stirred, filtered and the filter cake was washed with chloroform:methanol (9:1) to give des-N-ethylmethyllycaconitine (*3*) (4.8 mg) after removal of solvent, homogeneous by tlc analysis, and with spectroscopic properties as for *3* prepared by the next procedure. (b) Oxidation of methyllycaconitine (*4*)[8] - A solution of methyllycaconitine iodide (404 mg, 0.5 mmol) and mercuric acetate (810 mg, 5 mmol) in 2.5% acetic acid (25 ml) was refluxed for 1 h. The reaction mixture was then stirred at room temperature overnight and filtered. The filtrate was made alkaline with 28% aqueous ammonia (2 ml). Extraction with chloroform (4 × 20 ml) afforded des-N-ethylmethyllycaconitine (*3*) (237 mg) (yield 73%) after chromatography on silica gel (60-200 mesh, 50 g, chloroform:methanol (9:1)). Spectroscopic data: Ms (EI): 654, 637(15%), 623(82%), 592(23%), 372(18%), 216(77%). ^{1}H-Nmr ($CDCl_3$) (based on COSY and XHCORR): 8.02 (1H, dd, J=1.5, 7.6, H-6′), 7.69 (1H, dt, J=1.5, 7.6, H-4′), 7.53 (1H, dt, J=1.5, 7.6, H-5′), 7.29 (1H, d, J=7.6, H-3′), 4.02 and 4.07 (each 1H, d, J=11.1, H-18), 3.94 (1H, s, H-6), 3.41 (3H, s, OCH_3-14), 3.35 (3H, s, OCH_3-6), 3.32 (3H, s, OCH_3-16), 3.28 (3H, s, OCH_3-1), 3.19 (1H, t, J=6.3, H-1), 3.10 (1H, s, H-9), 3.06 (1H, t, J=5, H-16), 2.88 (1H, d, J=2.1, H-17), 2.64 and 2.78 (each 1H, d, J=13.3, H-19), 2.50 and 3.18 (each 1H, br m, H-3″), 2.10 (1H, H-10), 2.00 (1H, m, H-5), 1.80-2.10 (2H, m, H-3), 1.70-2.00 (2H, m, H-2), 1.44 (3H, br d, H-5″). ^{13}C Nmr data see table 1.

Oxidation of Des-N-ethylmethyllycaconitine (*3*) to *1*[9]: - Des-N-ethylmethyllycaconitine (37 mg, 0.057 mmol) and manganese dioxide (100 mg) in chloroform (7 ml) were stirred at room temperature overnight. The reaction mixture was filtered, evaporated and the residue was separated by ptlc on silica gel (20 × 20 cm × 0.25 mm, 3 plates, chloroform:methanol (9:1)) to give *1* (12.2 mg, yield 33%). The spectroscopic data of this product were identical with those of alkaloid-Y isolated from *D. nuttalianum* (ms, tlc, ^{1}H and ^{13}C nmr).

Ethylation of Des-N-ethylmethyllycaconitine (*3*) to *4*: - To des-N-ethylmethyllycaconitine (4.5 mg from reaction a) and potassium carbonate (5 mg) in dry DMF (2ml), was added ethyl bromide (2 ml) and the reaction mixture was stirred at room temperature for 3 days. The solvent was evaporated and the residue was extracted with chloroform (3 × 6 ml) and the solvent was removed to give after removal of solvent a product (4.6 mg), homogeneous by tlc. The spectroscopic data of this product were identical(ms, tlc, ^{1}H and ^{13}C nmr) with authentic methyllycaconitine (4).

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