HETISINE 13-O-ACETATE, A NEW DITERPENOID ALKALOID FROM *DELPHINIUM NUTTALLIANUM* PRITZ.

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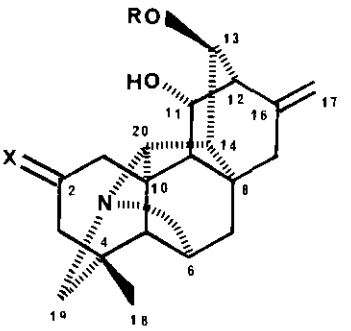
Abstract - Hetisine-13-O-acetate was isolated from D. nuttallianum and its structure was deduced by MS, ^1H and ^{13}C nmr and proven by X-ray crystallography of the perchlorate salt.

From Delphinium nuttallianum Pritz. we have isolated an alkaloid and identified it as the apparently previously unknown 13-O-acetyl derivative (1) of hetisine (2). We describe here our characterization of 1, and the evidence which enabled us to decide its structure. Conventional column chromatography of the alkaloids of D. nuttallianum over neutral alumina resulted in the isolation of 1 as an amorphous solid, homogeneous by tlc (silica gel 60, MeOH-$CHCl_3$, 4:1 v/v), which gave a crystalline salt with $HClO_4$, mp. 273-250°C. The ir spectrum of this salt had ν_{max} (KBr) 3480 (br, OH), 1709 (str, C=O), 1655 and 886 (m, $C=CH_2$). The 200 MHz ^1H nmr spectrum of 1 ($CDCl_3$, TMS = 0) contained absorptions at δ 0.97 (3H, s, quaternary-CH_3), 2.18 (3H, s, acetate-CH_3), 4.24 (2H, br s, 2 × CHOH) 4.75 and 4.92 (each 1H, br s, $>C=CH_2$) and 5.20 (1H, dt J = 10.5 and 2Hz, $>$CHOAc). Upon addition of a little methanol-d_4 the signal at δ 4.24 separated into two absorptions: δ 4.11 (1H, br s, $w_{1/2}$ ca. 10 Hz) and 4.20 (1H, d, J = 9 Hz). The genus Delphinium is a rich source of diterpenoid alkaloids which fall into two broad groups: those with C_{19}-skeletons, usually carrying an ethyl or methyl substituent on nitrogen[1]; and those with C_{20}-skeletons, which often lack such N-alkyl groups but usually possess an exocyclic methylene functionality[2]. The absence of absorptions in the ^1H nmr spectrum of our alkaloid which could be attributed to N-ethyl or N-methyl substituents, together with evidence for a $C=CH_2$ unit, accordingly suggested that it belonged to the C_{20}-diterpenoids. The ei-ms of 1 revealed m/s 371(15), 312(18) and 43(100), which was consistent with a molecular composition $C_{22}H_{29}NO_4$ and the presence of the acetate group previously inferred from the analysis of the ^1H nmr spectrum. We thus deduced our alkaloid to be a monoacetate of a heptacyclic C_{20}-diterpenoid-triol, such as

Table: ^{13}C nmr data[a] for 13-O-acetylhetisine (1), hetisine (2) and 13-O-acetylhetisinone (3)

1	2[b]	3[c]
21.3 q		21.1 q (C-18)[d]
29.8 q	30.3 q (C-18)	28.7 q (acetate $\underline{C}H_3$)[d]
33.7 t		
34.0 t	34.3 t	
36.2 t	36.6 t	
36.7 s	36.6 s (C-4)	
40.5 t	39.0 t	
43.7 s	43.5 s	
48.6 d	50.9 d	
50.4 d	50.7 s (C-10)	
50.7 s	52.5	
55.4 d	55.6 d	
61.6 d	61.6 d	
63.7 t	63.4 t	
64.4 d	64.2 d	
67.0 d	66.5 d	
68.8 d	68.1 d	
74.5 d	71.9 d	73.6 d
75.8 d	76.1 d	74.4 d
108.7 t	107.4 t (C-17)	106.3 t (C-17)
144.9 s	146.5 s (C-16)	144.5 s (C-16)
170.1 s		170.3 s (acetate $\underline{C}O$)



1 X = α-OH, β-H; R = Ac

2 X = α-OH, β-H; R = H

3 X = O, R = Ac

[a] At 200 Mz, in $CDCl_3$, relative to TMS = 0.

[b] From ref. 4 (19 signals reported). [c] From ref. 3.

[d] These assignments should be reversed.

hetisine (2). The ^{13}C nmr spectrum of 1 was in excellent accord with this idea (see Table), i.e. suggested that we were dealing with a hetisine monoacetate. While none of these acetates appear to have been described as natural products the closely related hetisinone 13-O-acetate (3) has been isolated from Delphinium cardiopetalum DC, and the data reported for it[3], in particular the ^1H nmr signals for H-13 (δ 5.12) and H-11 (δ 4.24, d, J = 9 Hz) induced us to tentatively identify our alkaloid as hetisine 13-O-acetate (1).

Paucity of material precluded chemical studies so in order to test our deductions we resorted to a X-ray crystallographic analysis of the perchlorate salt of the alkaloid[5]. The salt crystallized in the orthorhombic space group $P2_12_12_1$ with a = 11.835(1), b = 15.736(1), c = 11.342(1)A, V = 2112.4(4)Å^3, and 4 formula units in the cell. The structure refined to give agreement factors of R = 0.054 and R_w = 0.056. The absolute stereochemistry could not be determined but the skeletal framework of the cation confirms the proposed structure 1 for the free base: a compound which does not appear to have been described before.

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REFERENCES AND NOTES

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2. (a) S.W. Pelletier and N.V. Mody in "The Alkaloids: Chemistry and Physiology", vol. 18, ed. R.G.A. Rodrigo, Academic Press, New York, 1981, p. 99.
   (b) Further examples of C_{20}-diterpenoid alkaloids are presented in S.W. Pelletier and S.W. Page, Natural Products Reports, 1984, 1, 375, and references therein.
3. A.G. Gonzalez, G. de la Fuente, and M. Reina, An. Quim. Ser. C, 1981, 77, 171.
4. S.W. Pelletier, J.A. Glinski, B.S. Joshi, and S. Chen, Heterocycles, 1983, 20, 1347.
5. A full account of the X-ray structure determination will be submitted to Acta Cryst. Sec. C.

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