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^{13}C NMR SPECTROSCOPY OF SOME HETISINE SUBTYPE C_{20}-DITERPENOID ALKALOIDS AND THEIR DERIVATIVES

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Abstract—The ^{13}C NMR spectra of the diterpenoid alkaloids hetisine, hetisinone, 13-acetylhetisinone, cardiopetamine, and 15-acetylcardiopetamine, as well as certain of their derivatives, were obtained in the Fourier mode at 50.32 MHz. With the aid of proton decoupling techniques, SFORD and SFSD, and chemical shift comparisons, self-consistent assignments of nearly all the resonances have been made.

INTRODUCTION

Much attention has been devoted to the diterpenoid alkaloids because of their complex structures and wide range of biological activities [1]. Among them, the hetisine subtype C_{20}-diterpenoid alkaloids may be considered as derived from the atisine skeleton by formation of new bonds between C-14 and C-20 and between C-6 and the nitrogen atom [2]. While ^{13}C NMR studies of atisine and veatchine type C_{20}-diterpenoid alkaloids have been publishee [3] only a few carbon resonances have been assigned in paniculatine [4], hetisine (**1**) and hetisinone (**3**) [5] for the hetisine subtype. We have, therefore, carried out a ^{13}C NMR study of some hetisine subtype alkaloids and their derivatives, which should be of considerable value in solving structures of related compounds.

RESULTS AND DISCUSSION

The ^{13}C chemical shifts and assignments reported are noise-decoupled, single frequency off-resonance decoupled (SFORD) and, in some cases, single-frequency selective decoupled (SFSD). The assignments were also made taking into account known substituent effects [6] and comparison of spectra from compound to compound.

In general, the aromatic, carbonyl, double bond and methyl carbons, as well as the methylene carbon attached to the nitrogen atom, were readily assigned because they were distinguished by their SFDR spectrum and characteristic chemical shifts.

Quaternary carbons

The signals at δ44.3 in hetisinone (**3**) [7], 48.8 in the aminoalcohol (**8**) [8] and 55.8 in 15-ketocardiopetamine (**14**) [8] were assigned to C-8, due to the β-effect of 4.5 ppm or 11.5 ppm shifts observed on the introduction at C-15 of a β-hydroxy or carbonyl group, respectively. The comparison of the quaternary carbon resonances of hetisinone (**3**) and diketohetisine (**6**) [7] permitted the signals at 42.3 in **3** and 42.7 in **6** to be assigned to C-4, because of their minor change. Consequently, the C-8 signal in compound **6** and the C-10 signal in compounds **3**, **6**, **8** and **14** [8] were then assigned without difficulty. The C-4, C-8 and C-18 resonances in hetisine (**1**) were assigned by comparison with those of hetisinone (**3**), considering the γ-effects of 5.6 and 4.2 ppm on C-4 and C-10, respectively, produced by the introduction of a keto group at C-2.

The upfield quaternary carbon resonances for the remaining compounds [7, 8] in Table 1 were readily established by their comparison with those of some of the previously considered compounds.

Methine carbons

Resonances at δ58.7, 65.6 and 69.6 in compound **7** were unambiguously assigned to C-12, C-6 and C-13, respectively, with the aid of the selective decoupling (SFSD) technique [6]. The lowest field methine carbon resonance at δ70.7 was then assigned to C-20. The remaining methine carbon resonance at δ70.7 was assigned to C-20 and the remaining methine carbon resonances in **7** and those in compounds **3**–**6** were assigned on the basis of the α- and β-effects observed upon acetylation of the C-11α and C-13β hydroxyls and the β-effects produced by oxidation of the C-11α hydroxyl.

In hetisine (**1**) and diacetylhetisine (**2**), the methine resonances were determined by comparison with those of hetisinone (**3**) and diacetylhetisinone (**5**), respectively.

By means of SFSD experiments also, the methine carbon resonances at δ64.9, 69.0, 69.8 and 75.1 in cardiopetamine (**9**) were assigned to C-6, C-13, C-15 and C-11, respectively. The remainder of the methine resonances in **9**, as well as those of 15-acetylcardiopetamine (**10**) and their derivatives **8** and **11**–**15**, were established taking into account the previous assignment in compounds **3**–**7**, the γ-gauche effect of $\sim$4 ppm on C-9 produced by the substitution of H-15β by a hydroxyl or acetoxyl group

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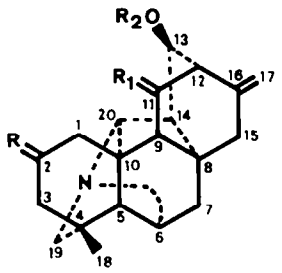
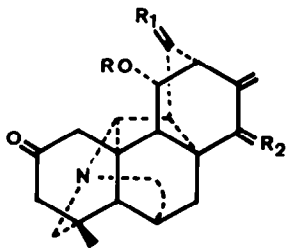
Table 1. ^{13}C Chemical shifts and assignments for alkaloids 1–15

Carbon	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	34.5	32.0	45.3	45.2	43.9	43.3	43.6	44.9	44.0	44.1	44.1	45.8	45.7	43.8	43.9
2	67.0	67.4	213.0	213.0	211.8	210.7	210.1	213.1	212.1	212.0	211.3	209.9	209.6	211.4	211.1
3	39.4	40.6	49.7	50.2	50.3	50.5	50.7	49.8	49.6	50.0	50.2	49.6	49.7	49.9	50.2
4	36.7	36.8	42.3	42.8	42.9	42.7	43.1	41.4	42.1	42.6	43.0	42.5	42.6	42.6	43.0
5	61.7	61.4	60.4	60.9	60.5	59.4	59.5	60.2	59.7	60.2	60.3	59.9	60.0	60.3	60.5
6	64.5	64.5	65.2	65.3	65.3	65.7	65.6	64.8	64.9	65.2	65.0	65.7	65.5	64.9	64.9
7	36.6	36.2	36.1	36.0	35.9	35.0	34.7	33.3	33.1	32.9	32.6	31.6	31.6	29.0	28.8
8	43.6	44.0	44.3	44.7	44.9	45.1	45.2	48.8	49.3	48.1	48.0	49.5	48.2	55.8	56.1
9	55.8	53.3	54.9	54.7	52.7	65.0	65.0	50.5*	48.7*	49.4*	49.4	49.1	49.8	53.0	52.9
10	51.2	50.6	55.4	55.5	55.4	52.5	50.5	54.6	54.5	55.0	55.1	54.4	54.5	55.7	55.7
11	76.7	76.1	75.8	74.4	75.4	209.3	208.0	72.2	75.1	75.1	74.7	71.9*	71.9	75.8	75.7
12	50.8	45.2	50.7	48.4	44.8	62.8	58.7	50.4*	47.7	47.8	44.2	57.7	57.7	47.5	44.3
13	72.4	73.2	71.6	73.6	72.5	68.0	69.6	70.1	69.0	69.6	71.7	205.6	204.9	69.1	70.9
14	52.9	50.4	52.4	49.9	49.9	51.9	49.8	49.6	48.9*	49.6*	47.3	58.6	58.8	51.1	49.0
15	34.5	34.1	33.8	33.7	33.7	33.3	33.2	69.8	69.8	72.0	71.8	71.3	71.7	199.3	199.3
16	146.4	143.9	145.2	144.5	142.9	139.7	138.2	152.4	150.5	144.7	143.2	143.4	138.7	142.5	141.4
17	107.7	109.8	108.2	109.9	110.5	113.0	114.5	110.4	112.1	116.5	118.0	117.9	121.3	119.1	120.6
18	30.3	29.8	28.8	28.7	28.7	28.5	28.5	28.4	28.3	28.6	28.6	28.6	28.7	28.6	28.6
19	63.7	63.9	64.3	64.7	64.8	65.1	65.1	65.0	65.0	64.6	64.7	64.2	64.2	64.4	64.5
20	68.4	68.7	70.4	70.7	70.5	69.9	70.7	69.8	69.8	70.1	70.1	71.7*	71.9	70.4	70.9
									165.8	166.6	166.4	166.0	166.2	166.4	166.4
									130.1	129.8	129.7	129.1	128.9	129.4	129.7
									129.6	129.8	129.6	129.9	129.9	129.9	129.7
									128.9	128.7	128.7	128.8	128.9	128.7	128.9
									133.5	133.3	133.5	133.7	133.9	133.5	133.8
CO		170.4		170.3	170.3		171.4			171.0	170.1		170.8		170.4
		170.8			170.7						170.8				
		21.3		21.1	21.1		20.8			21.3	21.1		21.3		21.1
Me		21.6			21.5						21.2				

Chemical shifts in δ(ppm) downfield from TMS.
*Values in any vertical column may be interchanged.





1 R = αOH, βH; R_1 = αOH,βH; R_2=H
2 R = αOH, βH; R_1 = αAc,βH; R_2=Ac
3 R = O; R_1 = αOH, βH; R_2=H
4 R = O; R_1 = αOH, βH; R_2=Ac
5 R = O; R_1 = αOAc,βH; R_2=Ac
6 R = R_1 = O; R_2=H
7 R = R_1 = O; R_2=Ac

8 R = H; R_1 = R_2 = βOH, αH
9 R = Bz; R_1 = R_2 = βOH, αH
10 R = Bz; R_1 = βOH, αH; R_2=βOAc αH
11 R = Bz; R_1 = R_2 = βOAc, αH
12 R = Bz; R_1 = O; R_2 = βOH, αH
13 R = Bz; R_1 = O; R_2 = βOAc, αH
14 R = Bz; R_1 = βOH, αH; R_2=O
15 R = Bz; R_1 = βOAc, αH; R_2=O

and the changes observed in the methine resonances among them, caused by acetylation of the C-13β hydroxyl and the oxidation of the C-15β and the C-13β hydroxyls. The C-6, C-11, C-15 and C-20 signals in **13** were also confirmed by their SFSD spectra.

Methylene carbons

The presence of a double doublet rather than a triplet in the SFORD spectra of compounds **2–15** in the upfield region enabled us to assign the C-1 resonances, assuming the magnetic non-equivalence of the attached protons to be induced by the C-11 functionality [9]. Consequently, the C-3 and C-7 signals in compounds **8–15** were assigned without difficulty. The C-3, C-7 and C-15 signals in compounds **3–7** were assigned by comparison with those of compounds **8–11**, considering the γ-gauche effects of ~ 3 ppm on C-7 produced by the replacement of H-15β by a hydroxyl or acetoxyl group. Finally, the highest field methylene carbon resonances in hetisine (**1**) and diacetylhetisine (**2**) were established by comparison with those of hetisinone (**3**) and diacetylhetisinone (**5**), respectively, taking into account the β-effects on C-1 and C-3 of the carbonyl group.

EXPERIMENTAL

^{13}C NMR spectra were recorded at 50.32 MHz Fourier mode on a spectrometer provided with a 48 K memory computer and a deuterium lock system. Spectra of the compounds were determined in $CDCl_3$ soln except for cardiopetamine (**9**) and amino alcohol (**8**) where DMSO-d_6 was used. The samples were contained in 10 mm o.d. tubes. A 12 μsec pulse, corresponding to tilt angle of 90°, was employed and for the spectral width of 10000 Hz or 15000 Hz the pulse interval was 2 or 3 sec. Acquisition time averaged 0.5–2 hr over 16 K data points for concns of the order of 0.03–0.17 M. In the SFORD expts this time was 4–8 hr and the decoupler frequency centred at 3 ppm upfield from TMS. The selective decoupled (SFSD) spectra were obtained by low-power irradiation (1000 Hz) at the resonance frequencies of the desired protons. ^{1}H NMR (200 MHz); **7**: δ2.96 (*d*, J = 2.5 Hz, H-12), 3.35 (*br s*, $W_{1/2}$ = 6.5 Hz, H-6) and 5.18 (*dd*, J_1 = 10.0 Hz, J_2 = 2.5 Hz); **9**: 3.22 (*br s*, $W_{1/2}$ = 6.5 Hz, H-6), 3.73 (*br s*, $W_{1/2}$ = 5 Hz, H-15), 3.90 (*br d*, J = 10.8 Hz, $W_{1/2}$ = 6.5 Hz, H-13) and 5.48 (*d*, J = 8.5 Hz, H-11); **13**: 3.13 (*s*, H-20), 3.37 (*br s*, $W_{1/2}$ = 6.0 Hz, H-6), 5.47 (*br s*, $W_{1/2}$ = 5 Hz, H-15) and 5.65 (*d*, J = 8.0 Hz, H-11).

Hetisine (**1**) was obtained by $NaBH_4$ reduction of hetisinone (**3**) [10], diacetylhetisine (**2**) by acetylation of hetisine and compound **15** by treatment of **14** with Ac_2O–pyridine. The other alkaloids and their derivatives used here were isolated or synthesized by procedures given in refs [7, 8].

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