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^{13}C NMR SPECTRAL ANALYSIS OF SOME ISOQUINOLINE ALKALOIDS

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Key Word Index—^{13}C NMR spectra; benzylisoquinoline alkaloids; papaverine; 1-(*p*-methoxybenzyl)-6,7-dimethoxyisoquinoline; 1-(*p*-methoxybenzyl)-6,7-methylenedioxyisoquinoline; 1-(*p*-methoxybenzyl)-6,7-dimethoxytetrahydroisoquinoline; 1-(*p*-methoxybenzyl)-6,7-methylenedioxytetrahydroisoquinoline; *N*-methylpapaverine; *N*-methyllaudanosine; bisbenzylisoquinoline alkaloids; isochondodendrine.

Abstract—The ^{13}C NMR spectra of some isoquinoline and tetrahydroisoquinoline alkaloids and their corresponding *N*-methosalts and of the bisbenzylisoquinoline alkaloid isochondodendrine were recorded and the signals assigned. The substituent shielding effects and the ^{13}C–^{1}H long range couplings were analysed and utilized in the spectral interpretation.

INTRODUCTION

In recent years effort has been devoted to the ^{13}C NMR spectral analysis of isoquinoline alkaloids and valuable information regarding their structural features has been obtained [1–3]. In this connection, and as part of a project on the ^{13}C NMR spectroscopy of natural products [4], and in order to facilitate the shift assignments of related alkaloids, the analysis of the ^{13}C NMR spectra of some benzylisoquinoline, benzyltetrahydroisoquinoline alkaloids, their corresponding *N*-methosalts and the *bis*benzylisoquinoline alkaloid isochondodendrine was carried out. To the best of our knowledge this is the first ^{13}C NMR spectral analysis of a *bis*benzylisoquinoline alkaloid.

RESULTS AND DISCUSSION

Table 1 lists the carbon shifts of papaverine **1**, 1-(*p*-methoxybenzyl)-6,7-dimethoxyisoquinoline **2** and 1-(*p*-methoxybenzyl)-6,7-methylenedioxyisoquinoline **3** [5], assigned by standard chemical shift theory, comparison with reference compounds and mainly, by analysis of the SFORD and the fully coupled ^{13}C NMR spectra.

Amongst the proton-bearing carbons of **1**, clearly assigned from a SFORD spectrum, C-3 and C-4 show shifts at 140.6 and 118.3 ppm respectively, in agreement with reported values for isoquinoline and further, confirmed by analysis of their fine structure from a ^{1}H-coupled ^{13}C spectrum [$^{2}J(C_4\text{-}H_3) = 8$ Hz, $^{3}J(C_4\text{-}H_5) = 4.9$ Hz, $^{2}J(C_3\text{-}H_4) = 3.1$ Hz] [6]. Of the remaining 5 methines, the lowest field signal at 120.1 ppm can be assigned to C-6, by its chemical shift and its complex coupling pattern due to a $^{3}J_{CH}$ and two angle dependent couplings with the benzylic protons [7]. The distinction of the methines *ortho* to methoxyl groups is founded again on the analysis of their fine structure, the signal at 104.9 ppm showing a $^{3}J_{CH} = 4.9$ Hz was assigned to C-5 while the one at 103.8 ppm, with no long-range splittings to C-8. Carbon-5′ at 110.5 ppm appears as a clean doublet with no discernible $^{2}J_{CH}$ or $^{3}J_{CH'}$ and C-2, at 111.5 ppm shows a very complex fine structure.

The signals corresponding to the oxygenated quaternary carbons at 152.0 and 149.7 ppm were assigned to C-6 and C-7 respectively, by comparison with related carbons of 6,7-dimethoxyisoquinoline **5** and the remaining ones at 148.6 and 147.0 ppm, to C-3, and C-4, respectively, by comparison with the benzyl moiety of laudanosine, **9** [1].

Based on their multiplicities, the non-oxygenated quaternary carbon signals at 133.0 and 122.5 ppm were assigned to C-4a and C-8a respectively, C-4a shows a clear triplet [$^{3}J(C_4\text{-}H_{8,3}) = 7.0$ Hz] while C-8a appears as a complex multiplet, difficult to analyze because of

Table 1. ^{13}C NMR spectral data for compounds **1**–**4**, **7** and **8***

Carbon	**1**	**2**	**3**	**4**	**7**	**8**
1	157.4	157.7	158.0	155.4	64.4	65.0
3	140.6	140.8	141.0	140.2	46.3	46.6
4	118.3	118.4	119.1	118.3	25.0	25.6
4a	133.0	133.2	134.8	132.6	125.3	127.3
5	104.9	105.1	102.9	104.9	113.0	108.0
6	152.0	152.1	150.0	152.5	146.6	145.0
7	149.7	149.5	148.0	149.8	145.7	145.4
8	103.8	104.0	101.7	102.8	110.7	107.0
8a	122.5	122.6	124.6	122.4	128.6	130.4
α	42.0	41.7	41.4	37.9	39.7	40.5
1′	131.9	131.5	131.3	128.7	131.3	131.6
2′	111.5	129.2	129.2	113.4	130.1	130.1
3′	148.6	113.7	113.7	152.2	113.0	113.2
4′	147.0	157.7	157.7	146.9	157.3	157.5
5′	110.5	113.7	113.7	107.7	113.0	113.2
6′	120.1	129.2	129.1	141.0	130.1	130.1
—OMe	55.5	55.2	55.1	55.6	54.6	54.9
		55.7		55.7	55.0	
		55.8			55.2	
—OCH_2O—			101.3			100.2
—NME					42.1	42.4

* The spectra were obtained at 25.2 MHz in Fourier transform mode in $CDCl_3$ solutions. The data for each carbon are shown in ppm downfield from TMS.

the overlap of signals. The remaining two signals at 157.4 and 131.9 ppm, which are, as expected, essentially unaffected in compounds **1**, **2** and **3**, were assigned to C-1 and C-1′, respectively. Further, the δ values of **6**, used as model for ring B of these compounds, support the above assignments [8]. The nonaromatic carbons of **1**, **2** and **3** were readily assigned on the basis of standard chemical shift theory and analysis of the SFORD spectrum.

Comparison of the shifts of C-5 and C-8 of **1** and **2** with the reported values for related carbons of 6,7-dimethoxyisoquinoline **5** [2], shows some interesting results. In **1** and **2** the mentioned carbons are clearly shielded and, at least on C-5, this is probably due to an electronic effect of the substituent on C-1, apparently the observed shielding effect is independent of the electron releasing capacity of the substituents on ring C, since the introduction of a nitro group, **4**, does not affect the chemical shift of C-5. On C-8 however, a γ effect produced by C_α, similar to that observed on a similar carbon in the conversion of naphthalene to 1-methylnaphthalene [9], could be invoked to explain its chemical shift.

The replacement of the 6,7-dimethoxyisoquinoline in **1** and **2** by a methylenedioxyisoquinoline system in **3** causes the expected changes on the benzenoid carbons; C-5, C-6, C-7 and C-8 are shielded while C-4a and C-8a are deshielded [1]. The transformation of **1** into **4**, affects the carbons of ring C in a predictable way confirming the above assignment.

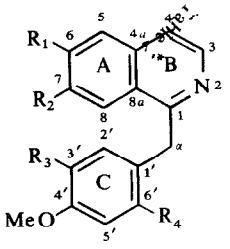
The analysis of **7** and **8** was greatly simplified by previous work [1] and their shifts are also listed in Table 1. As expected, the resonances due to the nonaromatic carbons and those of ring C of **7** and **8** are in good agreement with the reported values for laudanosine **9** and for compounds **2** and **3** respectively; they were readily assigned and further confirmed by analysis of their multiplicities. Comparison of the carbon signals of the tetrahydroisoquinoline system of **9** with the corresponding ones of **7**, shows agreement for all except for the shift of 132.2 ppm assigned to C-8a, which should be reversed with the 129.0 ppm signal previously assigned to C-1 [10]. The replacement of the 6,7-dimethoxy groups of **7** by the methylenedioxy unit of **8**, produces again the expected changes confirming the above assignments.

The transformation of compounds **1**, **2** and **3** into their corresponding *N*-methosalts **10**, **11** and **12** respectively, produces similar changes on A and B rings to the ones observed on isoquinoline by protonation [11]. Carbon-1 and C-3 are shielded while C-4, C-6 and C-7 are deshielded. The remaining aromatic carbons of **10**, **11** and **12**, except C-1′, which suffers a strong shielding effect, are

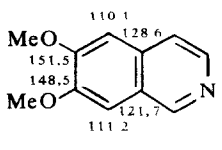
Table 2. ^{13}C NMR spectral data for compounds **10**–**15***

Carbon	10†	11	12	13†	14	15
1	152.7	151.7	151.7	71.3	71.7	71.9
3	135.6	134.3	136.1	54.7	54.8	54.4
4	122.5	121.5	123.1	23.1	23.1	23.3
4a	135.4	134.7	137.5	120.6	120.6	122.0
5	106.1	105.4	103.5	111.0	111.1	107.8
6	156.7	155.7	155.0	148.9	148.5	147.5
7	154.2	153.6	154.7	146.6	146.1	145.5
8	104.6	104.0	102.5	110.5	110.2	107.5
8a	123.9	123.0	125.6	119.1	119.2	120.9
α	34.8	33.6	34.6	37.4	37.1	37.0
1′	125.4	124.1	124.4	126.3	125.8	125.5
2′	111.5	127.8	128.6	113.1	131.1	130.5
3′	149.0	113.4	114.3	148.9	113.4	113.4
4′	147.9	157.3	158.3	147.9	158.2	158.1
5′	111.1	113.4	114.3	110.1	113.4	113.4
6′	118.9	127.8	128.6	122.3	131.1	130.5
OMe	56.6	56.6	54.9	56.4	55.4	54.6
	56.5	56.0		55.4	54.7	
	56.0	55.1		54.9		
	55.8			54.7		
$^+$NMe	46.9	45.8	46.8	52.3	52.4	52.2
				50.3	50.5	50.6
$-OCH_2O-$			102.5			100.8

* The spectra were obtained at 25.2 MHz in Fourier transform mode in $CDCl_3$ solutions. The data for each carbon are shown in ppm downfield from TMS.† Some methanol was added for better dissolution of the compound.



1, $R_1 = R_2 = R_3 = -OMe$; $R_4 = H$
2, $R_1 = R_2 = -OMe$, $R_3 = R_4 = H$
3, $R_1 = R_2 = -OCH_2O-$; $R_3 = R_4 = H$
4, $R_1 = R_2 = R_3 = -OMe$; $R_4 = -NO_2$



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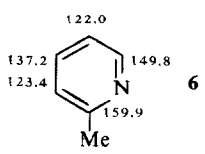

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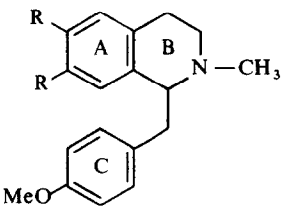

7, $R_1 = R_2 = -OMe$
8, $R_1 = R_2 = -OCH_2O-$

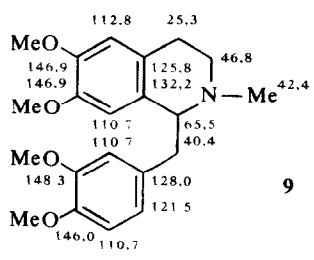

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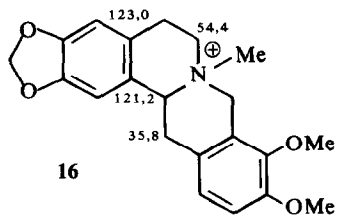
Table 3. ^{13}C NMR spectral data for compounds **17–19***

Carbon	17†	18	19‡
¶ 1(1′)	58.0	59.2	59.4
3(3′)	44.0	44.4	44.2
4(4′)	25.8	24.6	24.5
4a(4a′)	122.9	129.4	132.6
5(5′)	107.3	108.9	108.7
6(6′)	149.9	151.4	150.5
7(7′)	135.7	138.5	129.3
8(8′)	139.4	143.3	142.8
8(8a′)	124.8	125.2	124.8
9(9′)	129.0	130.1	130.8
10(10′)	127.2§	127.7§	128.0§
11(11′)	114.3‖	113.6‖	113.9‖
12(12′)	153.3	153.7	153.5
13(13′)	117.4‖	117.0‖	117.3§
14(14′)	128.6§	128.3§	128.2‖
15(15′)	33.8	37.6	39.1
OMe	55.2	59.7	55.8
		55.7	
NMe	40.5	42.1	42.1

* The spectra were obtained at 25.2 MHz in the Fourier transform mode in $CDCl_3$ solutions. The δ values are in ppm downfield from TMS. † Some methanol was added for better solution of the compound. ‡ The acetyl C=O and Me shifts are 166.9 and 19.6 ppm, respectively.§, ‖ Signals within the vertical columns may be reversed¶ The numbering system follows the rules reported in C.A. 1967–71.



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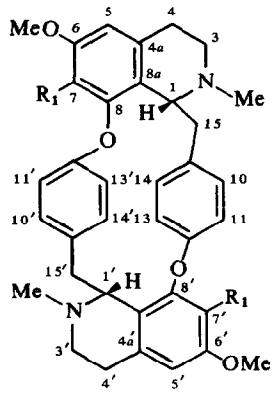


17, R_1 = OH
18, R_1 = OMe
19, R_1 = OC—Me

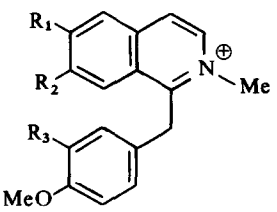
essentially unaffected. Carbon-α is also shielded in comparison with the related carbon of **1**, **2** or **3** due to a γ effect imposed by the *N*-Me group.

In view of the relatively wide distribution of quaternary alkaloids derived from tetrahydroisoquinoline, the *N*-methosalts **13**, **14** and **15** were also analyzed. As expected, the most affected carbons are the ones at ring B; C-1 and C-3 are deshielded while C-4, C-4a and C-8a are shielded comparing with the related carbons of the tertiary alkaloids. As was observed above, the N atom carrying a positive charge induces a shielding effect on C-1. The δ values for all carbons of compounds **10–15** are listed in Table 2.

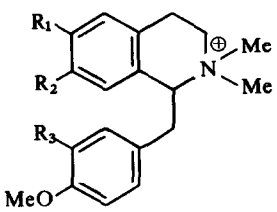
In an attempt to explain the shifts of the carbons of ring B of **13**, **14** and **15**, a comparison with like carbons of the α and β forms of quaternary protoberberine alkaloids was carried out [12]. The striking similarity of the δ values of C-3, C-4a, C-8a and C_α of **13**, **14** and **15** with the corresponding ones of **16** could be explained assuming that ring B with a rigid half-chair conformation has the benzylic carbon C_α at a quasi-axial position [13].

The shifts of the bisbenzylisoquinoline alkaloid isochondodendrine **17**, its Me and acetyl derivatives **18** and **19** respectively, greatly simplified by the symmetry of these molecules, are listed in Table 3. The nonaromatic carbons of **17** were assigned by analysis of a SFORD spectrum, standard chemical shift theory and comparison with related carbons of **7** and **8**. The introduction of a third oxygenated function on C-8 of the tetrahydroisoquinoline system produces a shielding effect on C-1 and C-15, similar to that observed on the protoberberine alkaloids [2].

The quaternary aromatic carbons, distinguished on the basis of the SFORD spectrum, show signals at 129.0 and 153.8 ppm which remain unchanged in the transformation of **17** into **18** and **19**. Based on this result and on the similarity of their shifts with C-1′ and C-4′, of **7** and **8** they were assigned to C-9 and C-12 respectively, The assignment of the remaining quaternary carbons is founded on the known fact that in a 1,3-dimethoxy-2-hydroxy substituted benzene ring, the methylation of the OH group induces deshielding on ipso, *ortho* and *para* carbons, while the *meta* positions are much less affected [14]. Further support for the assignment of signals at 122.0 and 124.8 ppm to the nonoxygenated quaternary carbons C-4a and C-8a respectively, and



10, $R_1 = R_2 = R_3$ = —OMe
11, $R_1 = R_2$ = —OMe; R_3 = H
12, $R_1 = R_2$ = —OCH_2O—; R_3 = H



13, $R_1 = R_2 = R_3$ = —OMe
14, $R_1 = R_2$ = —OMe; R_3 = H
15, $R_1 = R_2$ = —OCH_2O—; R_3 = H

the signals at 149.9, 135.7 and 139.7 ppm to the oxygenated ones C-6, C-7 and C-8, was obtained by acetylation. As expected, C-7 suffers a shielding effect, C-6, C-8 and C-4a, *ortho* and *para* to the acetoxy group respectively, are deshielded, while C-5 and C-8a are unaffected [15].

Of the aromatic methine shifts, the assignment of the 107.3 ppm signal to C-5 is simple. The remaining 4 signals are split into two pairs of similar chemical shifts. Although the higher field pair, 114.3 and 117.4 ppm, can be assigned to carbons *ortho* to the oxygenated function of the *p*-substituted benzene ring, specific assignments become difficult. The non-equivalence of the protons attached to these carbons, previously observed in the PMR spectrum of **17**, has been attributed to restricted rotation of both benzene rings [16].

EXPERIMENTAL

Papaverine was a commercial sample and compounds **2** and **3** were isolated from an *Ocotea* sp. kindly provided by Dr. U. M. F. Meirelles, according to ref. [17]. Compound **4** was prepared according to ref. [18]. The *N*-methosalts were prepared by refluxing with CH_3I in MeOH, their reductions were carried out with $NaBH_4$ in MeOH solns. Methylation and acetylation of **17** was carried out under usual conditions; treatment with CH_2N_2 in $CHCl_3$–MeOH soln and Ac_2O-Py, yielded **18** and **19**, respectively.

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15. The fine structure of C_7[$^3J(C_7\text{-}H_5) = 7.4$ Hz] of **17**, which becomes a multiplet in **18** and again a doublet [$^3J(C_7\text{-}H_5) = 8.0$ Hz] in **19**, confirms the previous assignment. Methylation of **17** produces a crowded system in which the *o*-methyl group of C_7 resonates, as expected, at lower field.
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