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^{13}C NMR ANALYSIS OF SOME SIMPLE TETRAHYDROISOQUINOLINES*

RACHEL MATA†, CHING-JER CHANG and JERRY L. MCLAUGHLIN

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907, U S A ; † Laboratorio de Productos Naturales, Facultad de Farmacia, Apartado 40109, Universidad Central de Venezuela, Caracas 1040-A, Venezuela

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Key Word Index—^{13}C NMR spectra; cactus alkaloids; simple tetrahydroisoquinolines, carnegine; heliamine; lemaireocereine; longimammatine, lophophorine, *N*-methylanhalinine; *O*-methylcorypalline; *O*-methyluberine; nortehuanine; tehuanine; weberidine.

Abstract—^{13}C NMR resonances of 15 simple tetrahydroisoquinolines have been assigned on the basis of chemical shift theory, ^{13}C–^{1}H coupling constants and deuterium labelling at specific positions. The chemical shifts of both aliphatic and aromatic protons were correlated with substituent effects.

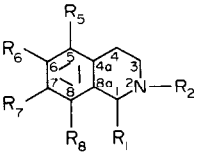
INTRODUCTION

In our previous work with cactus alkaloids, ^{13}C NMR was helpful in the structural elucidation of pterocereine (1-hydroxymethyl-2-methyl-5-β-D-glucopyranosyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) [1] and deglucopterocereine *N*-oxide [2]. However, more data is needed regarding the systematic ^{13}C NMR evaluations of simple tetrahydroisoquinolines [3, 4]. Singh *et al.* [5] have reported the ^{13}C chemical shift assignments of 1,2,3,4-tetrahydroisoquinoline (**15**) and salsolidine (1-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline); and Hughes *et al.* [6] have reported chemical shifts for *O*-methylcorypalline (**5**), lemaireocereine (**7**), tetrahydroisoquinoline (**15**) and salsolidine. Since such compounds are often encountered in the Cactaceae [7], as well as in other plant families [3, 4], a systematic analysis of the ^{13}C NMR spectral patterns of variously substituted simple tetrahydroisoquinolines was initiated to establish precedents for future structural elucidations.

RESULTS AND DISCUSSION

The structures (**1**–**15**) for the 15 simple tetrahydroisoquinolines studied are illustrated in Fig. 1. In Table 1 are listed the carbon chemical shifts and ^{13}C–^{1}H coupling constants for all of these compounds as the free bases The ^{13}C chemical shifts for seven of the oxygenated compounds, studied as the hydrochlorides, are listed in Table 2

*Part 54 in the series "Cactus Alkaloids". For Part 53 see Meyer, B N, Helfrich, J S, Nichols, D E, Davis, D V, Cooks, R G and McLaughlin, J L (1983) *J Nat Prod* **22** (submitted)



Compound	Trivial name	R_1	R_2	R_5	R_6	R_7	R_8
1	—	H	Me	OMe	H	H	H
2	Longimammatine	H	H	H	OMe	H	H
3	Weberidine	H	H	H	H	OMe	H
4	Heliamine	H	H	H	OMe	OMe	H
5	*O*-Methylcorypalline	H	Me	H	OMe	OMe	H
6	Carnegine	Me	Me	H	OMe	OMe	H
7	Lemaireocereine	H	H	H	H	OMe	OMe
8	*O*-Methyluberine	H	Me	OMe	H	OMe	H
9	—	H	H	OMe	OMe	H	H
10	—	H	H	H	OMe	H	OMe
11	Nortehuanine	H	H	OMe	OMe	OMe	H
12	Tehuanine	H	Me	OMe	OMe	OMe	H
13	*N*-Methylanhalinine	H	Me	H	OMe	OMe	OMe
14	Lophophorine	Me	Me	H	OMe	O–CH_2–O	
15	Tetrahydroisoquinoline	H	H	H	H	H	H

Fig 1 Structures of the simple tetrahydroisoquinolines studied

Table 1 ^{13}C NMR chemical shifts and ^{13}C ^{1}H coupling constants (H_z) of simple tetrahydroisoquinolines

Compound	Carbon No															
	1	3	4	4a	5	6	7	8	8a	1′	2′	5	6′	7′	8	7 8
1	57 5	52 3	23 4	122 4	156 7	106 9	125 7	118 5	135 7		45 7	54 6	–	–	–	–
	t hp	*to*	*tt*	*m*	*d sx*	*dd*	*d*	*ddt*	*m*		*qp*	*q*	—	—		–
	133 7	133	129 2	—	7 4	158	159 3	158 8			133 1	143 4	–	–		—
	(H-1)	(H-3)	(H-4)		(H-7)	(H-6)	(H-7)	(H-8)			(H-2′)	(H-5′)				
								7 3								
	5 7	4 8	3 1	—	3 7	8 5	-	(H-6)		-	2 2					—
								3 1								
	(H-2 , H-3, H-8)	(H-1, H-2′, H-4)	(H-3)		(H-4, H-5′)	(H-8)		(H-1)			(H-3 H-1)					
2	47 4	43 5	29 2	135 5	113 4	157 4	111 7	126 7	127 8	—	—	-	54 8	-	—	
	tq	*tp*	*tq*	*m*	*dq*	*m*	*dd*	*dt*	*m*	—	—	--	*q*		—	
	134 8	135 8	128 5	–	155 6	—	159 6	155 6	—	—	—	—	143 4	—	-	-
	(H-1)	(H-3)	(H-4)		(H-5)		(H-7)	(H-8)					(H-6′)			
	5 6	4 9	3 5	—	3 5	—	5 2	2 7	—	—	—	-	—	—		-
	(H-3, H-8)	(H-1, H-4)	(H-5 H-3)		(H-4, H-7)		(H-5)	(H-1)								
3	48	43 6	27 9	126 4	129 7	112	157 2	110 4	136 4	—	—	–	—	54 8		—
	tq	*tp*	*tq*	*m*	*dt*	*dd*	*d sx*	*br d*	*m*	—	—	—	–	—		–
	135 2	136 1	127 5	—	156 2	159 3	7 4	158 1	—	—	—	—	—	143		—
	(H-1)	(H-3)	(H-4)		(H-5)	(H-6)	(H-5)	(H-8)						(H-6′)		
	5 5	4 6	3 8	-	2 7	4 9	3 7	—	-	-	-	—	—	—		—
	(H-3, H-8)	(H-1, H-4)	(H-3, H-8)		(H-4)	(H-8)	(H-6, H-7′, H-8)									
4	47 3	43 3	28	125 2	111 5	146 7	146 5	108 5	127 2	—	—	—	55 2	55 2	—	—
	tq	*tp*	*tq*	*m*	*dt*	*dp*	*dp*	*dt*	*dp*	-	—	—	*q*	*q*	—	—
	135 5	135 7	127 9	—	154 8	7 6	7 6	154 3	7 8	-	–	—	147	147	—	—
	(H-1)	(H-3)	(H-4)		(H-5)	(H-8)	(H-6)	(H-8)	(H-5)				(H-6′)	(H-7′)		
	5 6	4 8	3 7	—	3 4	3 8	3 8	2 8	3 9	—	—	—	—	—	--	—
	(H-3, H-8)	(H-1, H-4),	(H-3, H-5)		(H-4)	(H-5, H-6′)	(H-8, H-7′)	(H-1)	(H-1, H-4)							
5	57	52 4	28	125 2	111	147 1	146 8	109	125 9	—	45 4	—	55 4	55 4	–	—
	t hp	*to*	*tq*	*m*	*dt*	*dp*	*dp*	*dt*	*m*	–	*qp*	—	*q*	*q*	–	—
	133 7	134 5	128 5	—	155	7 6	7 6	154 4	—	—	133	—	144	144		—
	(H-1)	(H-3)	(H-4)		(H-5)	(H-8)	(H-6)	(H-8)			(H-2′)		(H-6′)	(H-7′)		
	5 5	5 5	3 7		3 1	3 8	3 8	3 1	—	—	2 2	—	--	—	—	
	(H-2′, H-3, H-8)	(H-1, H-2′, H-4)	(H-3, H-5)		(H-4)	(H-5 H-6′)	(H-8, H-7′)	(H-1)			(H-1, H-3)					
6	58 4	48 7	27 4	125 7	111	147	147	109 7	131 4	19 5	42 7	—	55 7	55 7	--	-
	d dc	*th*	*tq*	*dp*	*dt*	*p*	*p*	*dd*	*d hp*	*dq*	*qq*	—	*q*	*q*	—	–
	133 7	134 6	128 5	9 2	155	7 8	7 8	156 1	7 8	126 6	133		55 5	55 5	-	-
	(H-1)	(H-3)	(H-4)	(H-8)	(H-5)	(H-8)	(H-5)	(H-8)	(H-5)	(H-1′)	(H-2′)					
	4 2	4 5	3 7	4 6	3 1	3 9	3 9	2 4	3 9	2 9	2 6		144	144	-	--
	(H-1′ H-2 H-3, H-8)	(H-1, H-2′ H-4)	(H-5, H-3)	(H-1, H-4, H-3)	(H-4)	(H-6 , H-5)	(H-7′, H-6)	(H-1)	(H-1 , H-1, H-4)	(H-1)	(H-1, H-3)		(H-6′)	(H-7′)		
7	43 2	43 2	28 1	129 2	123 9	110 3	144 9	149 8	127 5		--		—	55 3	59 7	—
	tt	*tm*	*br t*	*m*	*dt*	*d*	*m*	*hp*	*m*			—	—	*q*	*q*	–
	136 7	136 7	127 6	—	157 5	158 7	—	3 8	—	—	—	—	—	144	44	-
	(H-1)	(H-3)	(H-4)		(H-5)	(H-6)								(H-7′)	(H-8′)	
	5 5	—			3 8	—		-	—	—	—	—	—	—	--	
	(H-3)				(H-4)											
8	57 9	52 5	23	114 8	157 8	95 8	158 2	101 5	136 1		45 6	54 9	-	54 9		
	tm	*to*	*tt*	*m*	*m*	*dd*	*m*	*dq*	*p*	—	*qp*	*q*	--	*q*	—	
	133 7	133 3	129 1		—	157		157 5	3 7	—	133	143 4	—	143 3	—	
	(H-1)	(H-3)	(H-4)			(H-6)		(H-8)	(H-1, H-4)		(H-2′)	(H-5′)		(H-7′)		
	—	4 9	3 1		—	5 5	-	3 1	—	—	2 1		—	-	—	
		(H-1, H-2′ H-4)	(H-3)			(H-8)		(H-1 H-6)			(H-3, H-1)					

9	47 8	43 5	23 7	129	150 5	146 7	110 2	121 3	129	—	—	59 8	55 8	—	—	—
	tm	*tp*	*tm*	*m*	*m*	*dq*	*d*	*dt*	*m*	—	—	*q*	*q*	—	—	—
	134 9	135 1	127 5	—	—	7 8	158 7	156 9	—	—	—	143 8	143 8	—	—	—
	(H-1)	(H-3)	(H-4)			(H-8)	(H-7)	(H-8)	—	—	—	—	—	—	—	—
	—	3 7	—	—	—	3 9	—	3 3								
		(H-1, H-4)				(H-6')		(H-1)								
10	43 2	42 8	29 5	136 3	104 3	158 4*	95 8	156 8*	116 9	—	—	—	55 1	—	55 1	—
	t	*t*	*t*	*m*	*dq*	*m*	*m*	*m*	*m*	—	—	—	*q*	—	*q*	—
	133	133 4	127	—	157 5	—	158	—	—	—	—	—	55	—	55	—
	(H-1)	(H-3)	(H-4)		(H-5)		(H-7)									
	—	—	—	—	3 4	—	5 5	—	—	—	—	—	143 4	—	143 4	—
					(H-4, H-7)		(H-5)						(H-6')		(H-8')	
11	48	43 4	23	120 7	151 2	140	151 3	104 7	131 2	—	—	60 1	60 1	55 7	—	—
												60 6	60 6			
	tp	*tp*	*tt*	*ddp*	*q*	*dq*	*p*	*dt*	*p*	—	—	*q*	*q*	*q*	—	—
	135 4	136	129 4	10	4 1	7	4 1	155 8	4 4	—	—	144	144	144	—	—
	(H-1)	(H-3)	(H-4)	(H-8)	(H-5')	(H-8)	(H-7', H-8)	(H-8)	(H-1, H-4)			(H-5')	(H-6')	(H-7')		
				6 8												
	5 8	4 9	3	(H-3)	—	3 5	—	2 9	—	—	—	—	—	—	—	—
				3 4												
	(H-3, H-8)	(H-1, H-4)	(H-3)	(H-1, H-3)		(H-6')		(H-1)								
12	57 6	52 4	23 4	119 8	150 9	140	151 3	104 9	130 2	—	45 7	60	60	55 7	—	—
												60 5	60 5			
	tm	*to*	*tt*	*m*	*q*	*dq*	*p*	*dt*	*m*	—	*qp*	*q*	*q*	*q*	—	—
	135 5	133 7	128 8	—	3 7	7	3 7	155 6	—	—	133 1	144 4	144 2	144 4	—	—
	(H-1)	(H-3)	(H-4)		(H-5')	(H-8)	(H-7', H-8)	(H-8)			(H-2')	(H-5')	(H-6')	(H-5')		
	—	5 5	3 4	—	—	3 5	—	3 1	—	—	2 3	—	—	—	—	—
		(H-1, H-2', H-4)	(H-3)			(H-6')		(H-1)			(H-1, H-3)					
13	52 7	57 5	29 3	129 7	107	149 7	139 7	151 6	120 8	—	46 1	—	55 8	60 7	60 7	—
														60 3	60 3	
	tm	*tm*	*tq*	*m*	*dt*	*p*	*dq*	*sx*	*dp*	—	*qp*	—	*q*	*q*	*q*	—
	134 9	134 9	127 6	—	156 3	3 5	7 4	3 1	7 2	—	132 7	—	144	144	144	—
	(H-1)	(H-3)	(H-4)		(H-5)	(H-6', H-5)	(H-5)	(H-8', H-1)	(H-5)		(H-2')					
	—	—	3 9	—	2 8	—	3 7	—	3 6	—	2 2	—	—	—	—	—
			(H-3, H-8)		(H-4)		(H-7')		(H-1, H-4)		(H-1, H-3)					
14	55	43 9	28 3	129 1	107 4	142 8	133 8	145 8	116 2	17 8	43 2	—	57 1	—	—	101 8
	tn	*t hp*	*tq*	*tq*	*dt*	*p*	*dt*	*q*	—	*dq*	*tm*	—	*q*	—	—	*t*
	135 5	134 9	128 4	6	157 5	3 8	8 5	2 1	—	127 1	133 7	—	144 2	—	—	172 7
	(H-1)	(H-3)	(H-4)	(H-3)	(H-5)	(H-5, H-6')	(H-5)	(H-1, H-9')		(H-1')	(H-2')					(H-9)
	4 1	4 5	3 7	3	3 1	—	2 1	—	—	3 1	—	—	—	—	—	—
	(H-1', H-2', H-3)	(H-1, H-2', H-4)	(H-1, H-3)	(H-1, H-4)	(H-4)		(H-9')			(H-1)						
15	46 6	42 2	27 5	133 2	127 5	124 1	123 8	124 4	134 5	—	—	—	—	—	—	—
	tq	*tp*	*tq*	*m*	*ddt*	*dd*	*dd*	*dm*	*m*	—	—	—	—	—	—	—
	134 4	135	127 4	—	154 8	159 2	158 9	157	—	—	—	—	—	—	—	—
	(H-1)	(H-3)	(H-4)		(H-5)	(H-6)	(H-7)	(H-8)								
					7 8											
	5 6	4 9	3 8	—	(H-7)	7 3	6 1	—	—	—	—	—	—	—	—	—
					3 8											
	(H-3, H-8)	(H-1, H-4)	(H-3, H-5)		(H-4)	(H-8)	(H-5)									

dc, = 10 lines, *n* = 9 lines, * may be interchanged. *br d*, broad doublet, *br t*, broad triplet, *sx*, sextet, *hp*, heptet, *s*, singlet, *d*, doublet, *t*, *triplet* *q*, quartet, 7'–8', dioxymethylene carbon

Table 2 ^{13}C NMR chemical shifts of tetrahydroisoquinoline hydrochlorides

Compound	Carbon No 1	3	4	4a	5	6	7	8	8a	2′	5′	6′	7′	8′
1	54 3	51 1	20	119	156.4	110	128 1	118.6	128 2	42	55 6	—	—	—
2	44	41 4	24 6	132 8	113 3	158.2	113 3	128	120	—	—	55 3	—	—
3	44 2	40 7	23 6	123 5	129 9	114 2	157 3	111	128 4	—	—	—	55 2	—
7	41 4	40 5	23 8	124 5	125	113	144 6	150 2	121 8	—	—	—	60.5	55 9
8	54 3	51 2	19 4	111 7	151 6	98	159	102 3	128 8	42	55 5 55 6	—	55 5 55 6	—
9	44	41 3	19 6	125 7	151 2	145.2	112	123 1	120.8	—	55 8	60 3	—	—
12	54 1	51	19 7	117 1	150	140.7	152	106 2	123 5	42	61 60 8	56	61 60 8	—

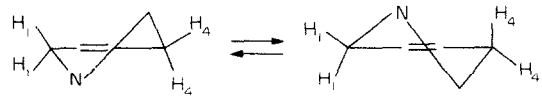
Aliphatic carbon assignments

The shift assignments for all of the aliphatic carbons were made by standard chemical shift theory [8]; these are in agreement with those previously reported by Hughes *et al* [6]; however, the C-1 and C-3 assignments of Singh *et al.* [5] must be reversed [4]. In the case of the *N*-methylated compounds (**1, 5–7, 12–14**), the *N*-methyl carbon (C-2′) absorptions were identified as such by a characteristic quartet centered in the range of δ 42 7–46.1 with J_{C-H} values ranging from 132.7 to 133.7 Hz. The C-1′ methyl absorptions of **6** and **14** were readily recognized by their low chemical shift values (δ 17.8 and 19.5, respectively) and their multiplicity in the proton coupled spectra For compounds bearing substituents at C-5 or C-8 (**1, 7–14**), a shielding effect was observed at C-1 and at C-4, respectively. This shielding effect can be attributed to a steric perturbation (γ-gauche effect) at C-1 or C-4 by the respective substituents at C-8 or C-5 [9]; the shielding factors in δ values (ppm) observed for **1** and **7–13** are summarized in Table 3

Table 3 γ-Effect on the ^{13}C chemical shifts in C-5 or C-8 substituted tetrahydroisoquinolines [δ values (ppm)]

Compound	Carbon No 1	4	2′
1	—	−4 1	—
8	—	−4 5	—
9	—	3 8	—
11	—	−4 5	—
12	—	−4.1	—
7	−3.4	—	—
10	−3 4	—	—
13	−3 6	—	—
6	—	—	−3.0
14	—	—	−2 5

As can be seen from the summarized data, the shielding effect is more pronounced at C-4 than at C-1; this may be attributed to the difference of the conformational equilibration (**A** → **B**) of the aliphatic ring as shown below The interaction between the R-5′ and the quasi-equatorial H-4 is probably stronger than that between the R-8′ and the quasi-equatorial H-1 for compounds bearing *N*-methyl groups (**5, 12**) A downfield β-shift (*ca* $\Delta\delta$ 9 3) of C-1 and C-3 was observed.



A **B**

According to the data reported by Singh *et al* [5], introduction of a methyl group at C-1 causes a downfield shift at C-1 (α-effect) of $\Delta\delta$ 5.6 and an upfield shift at C-3 (γ-effect) of $\Delta\delta$ −3.8 Introduction of both an *N*-methyl and a C-1 methyl group (**6**) resulted in a total downfield shift for C-1 of $\Delta\delta$ 11 8, a total downfield shift of $\Delta\delta$ 6 5 for C-3 and an upfield shift (*ca* $\Delta\delta$ 2.8) of the *N*-methyl carbon. This observation indicated, thus, that both the α- and the β-effect at C-1, and both the β- and the γ-effect at C-3 are not additive, a plausible explanation would be the reduction of the β-effect on both carbons because of the resulting steric crowding upon introduction of both methyl groups.

The three-bond spin-spin splittings for C-1 with H-8, H-3, and H-2′ ranged from 5.5 to 5 8 Hz. The exceptions were the observed values for **6** and **14** (i e 4.1 Hz). This can be attributed to a slight variation of the dihedral angle because of the steric congestion upon introduction of substituents at C-1 and C-3. In the case of C-4, the small splitting with H-5 ($^3J_{C-4-H-5}$) ranged from 3 5 to 3 9 Hz, finally, the splitting attributed to C-3 with H-1 and/or H-2′ ranged from 3 to 3.9 Hz

Aromatic carbon assignments

The assignments of the individual resonances of the aromatic carbons (unsubstituted, oxygenated, and those at the ring junctions) were made by a combination of chemical shift theory [8, 10], $^{13}C-^1H$ one-bond and long-range coupling patterns [8, 11–13] and deuterium labelling at specific positions [8, 14]

Monosubstituted compounds With the monosubstituted compounds (**1–3**), the oxygen-bearing carbons were assigned as such on the basis of chemical shift theory with these carbons displaying the lowest shifts of the spectra, i.e δ 156.7, 157.4, and 157 2, respectively The two quaternary carbons at the ring junctions (C-4a and C-8a) were also easily assigned on the basis of their *ortho*, *meta*, or *para* relationships with the oxygen-bearing carbons

The unsubstituted aromatic carbons were assigned using a combination of their known relative positions with the single methoxy group and long-range coupling

patterns, e.g. an analysis is given for **2**. With **2**, the most downfield signal of the three unsubstituted carbons was easily assigned to C-8 because of its *meta* relationship with the methoxy group and because of the observed small coupling with H-1 ($^3J_{C\text{-}8\text{-}H\text{-}1}$ = 2.7 Hz). The distinction between C-5 and C-7 was made by analysis of the long-range coupling patterns, i.e. the δ 111 7 peak was the only one with a single three bond coupling ($^3J_{C\text{-}7\text{-}H\text{-}5}$ = 5.2 Hz) On the other hand, the peak at δ 113.4 displayed three bond coupling with H-4 and with H-7 ($^3J_{C\text{-}5\text{-}H\text{-}7}$ = $^3J_{C\text{-}5\text{-}H4}$ = 3 5 Hz) (see Fig. 2).

Disubstituted compounds. The two methine signals of **5**, attributable to C-5 and C-8, showed resonances at δ 111 and 109. The most downfield signals at δ 147.1 and 146.8 were designated to the two oxygenated carbons (C-7 and C-6). The two non-oxygenated quaternary carbon signals at δ 125.2 and 125.9 could be assigned to C-4a and C-8a.

The differentiation of the two oxygen-bearing carbons was accomplished by replacement of the hydrogens on the C-7 methoxy group by deuterium. Spectral analysis of the deuterium labelled compound indicated a reduction of the relative intensity of the signal at δ 146.8, which was thus assigned to C-7 [14] with the signal at δ 147 1 being unequivocally assigned to C-6.

In order to discriminate between C-4a and C-8a, one of the protons at C-1 was replaced by deuterium. The proton noise decoupled spectrum of this second deuterated compound showed a reduction of the intensity of the signal at δ 125.9 due to the inefficient ^{13}C–^{2}H relaxation. This signal was then identified as C-8a because this carbon is closer to the deuterated C-1 than C-4a. Furthermore, a careful analysis of the long-range coupling pattern of the δ 109 signal of both deuterated and non-deuterated **5**, revealed the unique coupling between the C-8 and H-1 ($^3J_{C\text{-}8\text{-}H\text{-}1}$ = 1 8 Hz). As shown in Fig. 3, the triplet becomes a doublet where the H-1 is monodeuterated. This experimental evidence allowed unambiguous assignment of this signal to C-8 and that at δ 111 to C-5 The assignments for **4** and **6** came readily from **5**.

The assignments of C-8 and C-5, and C-6 and C-7 are in agreement with those previously reported by Hughes *et al.* [6] However, their assignments for C-4a and C-8a are incorrect and must be reversed.

With **7** and **9**, the higher field aromatic resonances were assigned to C-6 and C-7, respectively, based on the absence of three-bond coupling and/or chemical shift calculations. The other methine carbons were easily assigned in view of the small three-bond coupling with H-4 in the case of **7** ($^3J_{C\text{-}5\text{-}H\text{-}4}$ = 3.8 Hz) and with H-1 in the case of **9** ($^3J_{C\text{-}8\text{-}H\text{-}1}$ = 3.3 Hz) Of the two oxygen-bearing carbons in **7**, the signal at δ 149.8 was attributed to C-8 because of observed coupling with H-1 and H-6 ($^3J_{C\text{-}8\text{-}H\text{-}1}$ = $^3J_{C\text{-}8\text{-}H\text{-}6}$ = $^3J_{C\text{-}8\text{-}H\text{-}8'}$ = 3 8 Hz). The signal at δ 144 9 was then assigned to C-7 Of the two signals for oxygenated carbons in **9**, the one at δ 146.7 was attributed to C-6 due to the observed three-bond couplings with H-8 and H-6′ ($^3J_{C\text{-}6\text{-}H\text{-}8}$ = 7 8 Hz, $^3J_{C\text{-}6\text{-}H\text{-}6'}$ = 3.9 Hz). The other signal at δ 150 5 was then attributed to C-5. The carbons at the ring junctions for **7** and **9** were assigned on the basis of their *ortho* relationship with the methoxy groups and, for **7**, these assignments are in agreement with those reported by Hughes *et al* [6].

With **8**, the hydrogen bearing ring carbons exhibited absorptions at δ 95.8 and 101.5. The first value was attributed to C-6 because it is *ortho* to two methoxy groups. This assignment was also confirmed by observing the unique three-bond coupling with H-8 ($^3J_{C\text{-}6\text{-}H\text{-}8}$ = 5.5 Hz). The signal at δ 101.5 displayed three-bond

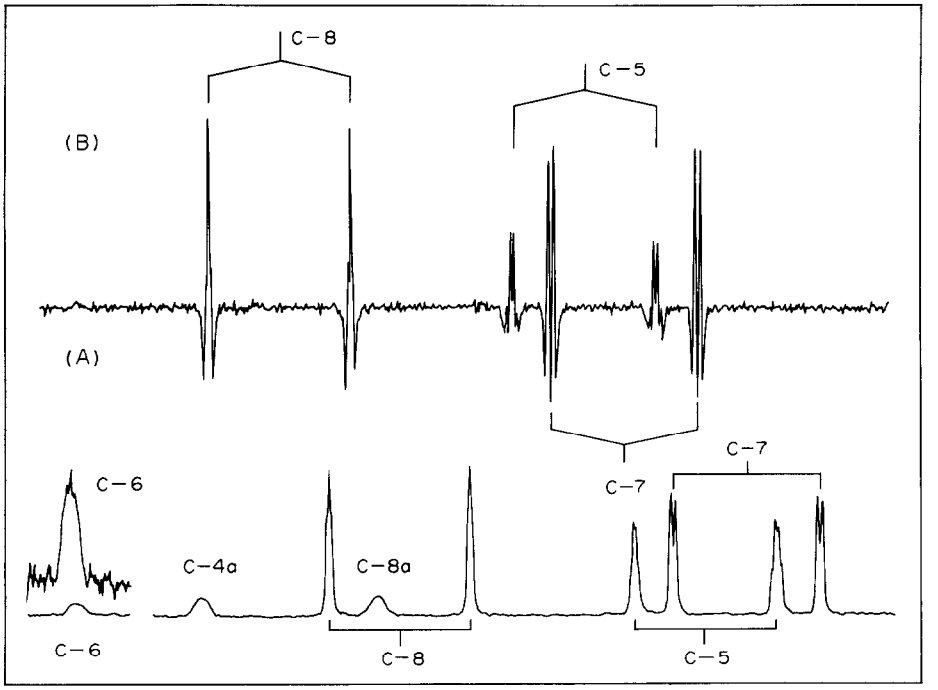


Fig. 2 (A) Aromatic region of the proton coupled spectrum of **2** (B) C-5, C-7 and C-8 signals using a narrow exponential (−3) window (50–100 Hz) for resolution enhancement

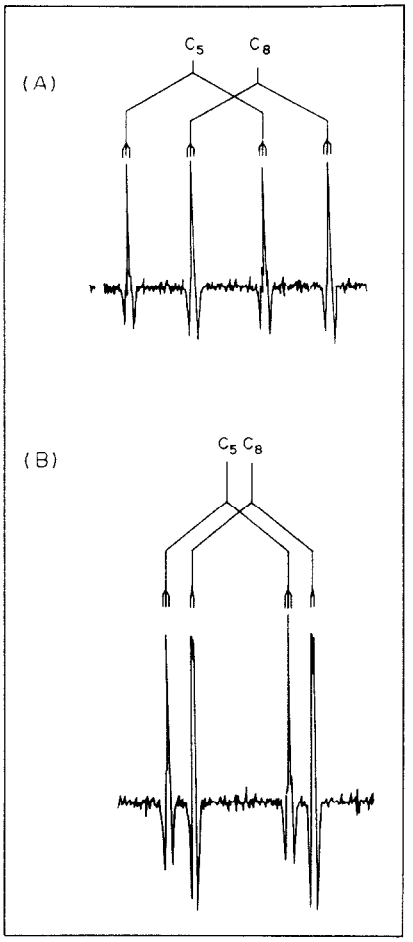


Fig 3 Change in coupling pattern of C-8 upon monodeuteration at C-1 in **5** using a narrow exponential (−3) window (50–100 Hz) for resolution enhancement. (A) Before deuteration, (B) after deuteration

coupling with both H-1 and H-6 ($^3J_{C\text{-}8\text{-}H\text{-}1} = {}^3J_{C\text{-}8\text{-}H\text{-}6} = 3.1$ Hz) and was then easily assigned to C-8 Of the two resonances due to the ring junction carbons of **8**, the upper field signal (δ 114 8) was identified as C-4a because of its position, both *ortho* and *para*, to the methoxy groups The lower field signal (δ 136 1) was thus assigned to C-8a The two oxygen bearing carbons of **8** were identified as C-5 (δ 157 8) and C-7 (δ 158 2), assuming addition of **1** and **3** to the reported [3] spectra of tetrahydroisoquinoline, however, because of the small difference in chemical shifts, these assignments may well be reversed

The spectrum of **10** showed similar resonances and coupling patterns as those of **8** Using the assignments presented for **8**, the ^{13}C chemical shift assignments could be readily accomplished except that the two very close signals (C-6 and C-8) were not unequivocally distinguished.

Trisubstituted compounds. In all these cases (**11**–**14**), the single methine carbons were easily recognized Of the three oxygen bearing carbons, the lower chemical shift was assigned to C-6 in **11** and **12** and C-7 in **13** and **14**, because of their *ortho* positions to two methoxy groups Also, the carbons at the ring junction were readily assigned on the basis of their *ortho* or *meta* relationships with the outer methoxy groups.

With **11**, the distinction between C-5 and C-7 was accomplished on the basis of the observed splitting pattern. The signal at δ 151 3 was assigned to C-7 because of the coupling with H-8 and H-7' The remaining signal at δ 151.2 was then assigned to C-5

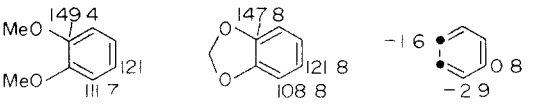
The analysis of **12** was essentially identical to that of **11** With **13**, the discrimination between C-6 and C-8 could again be accomplished by analysis of the coupling patterns The peak at δ 149 7 was assigned to C-6 due to the coupling with H-5 and H-6' ($^2J_{C\text{-}6\ H\text{-}5} = {}^3J_{C\text{-}6\ H\text{-}6'} = 3.5$ Hz)

With **14**, the signal corresponding to C-6 and C-8 showed absorptions at δ 142.8 and 145 8. The latter was assigned to C-8 because of the observed coupling with H-9' and H-1 ($^3J_{C\text{-}8\text{-}H\text{-}1} = {}^3J_{C\text{-}8\ H\text{-}9'} = 2\,1$ Hz) The remaining signal was thus attributed to C-7

Summary of aromatic assignments The discussed analysis of the aromatic carbons, as well as additional data summarized in Table 1, permit the following observations regarding chemical shift assignments and coupling constants (a) Comparison of the observed chemical shift of the three monosubstituted compounds with those of tetrahydroisoquinoline [6] permitted the substituent chemical shift values shown in Table 4 to be developed This data indicated that the substituent effect produced by C-7 and C-6 substitution is similar The C-5 methoxy substituent effect is unique due to the *peri* interactions with H-4 This is consistent with the fact that in 6,7-disubstituted compounds (**4**–**6**) the difference between chemical shifts of C-5 and C-8 carbons lead to the same order of differences as those in tetrahydroisoquinoline (**15**) Furthermore, comparison of the chemical shift of C-5 in **10**, **13** and **14** with C-8 of **8**, **11** and **12** indicated that probably the C-5 and C-8 substitution effects are also similar (b) Replacement of methoxy groups by a methylene dioxy group (**14**), resulted in shielding effects at both the *ipso* carbons and *ortho* carbons Comparison of shift parameters of **13** and **14** indicated a shielding factor of δ −5 9 for C-7 and −5 8 for C-8 (*ipso* carbons), and a shielding effect of δ −6 9 for C-6 and of −4 6 for C-8a (*ortho* carbons) Comparison with the chemical shift values of veratrole and methylene-dioxy benzene [6, 8, 10] indicates that there is a small symmetrical change at the

Table 4 Chemical shift values [$\Delta\delta$ (ppm)] of **1**–**3**

	Compounds		
	1	**2**	**3**
C-4a	−10 8	2 3	−6 8
C-5	29 2	−14 1	2 2
C-6	−16 9	33 6	−11 8
C-7	1 6	−12 4	33 1
C-8	−5 9	2 3	−14 0
C-8a	1 2	−6 7	1 6



ipso (δ −1.6) carbons upon substitution of the two methoxy groups by the 1,3-dioxole ring. Therefore, the higher shielding effects observed in the case of **14** might be related to the sterically crowded environment caused by the extra *ortho* substituents (c) One bond coupling ranged from 154.8 to 159.6 Hz which represents typical values for aromatic compounds. (d) In general, the inter-ring three-bond splittings of C-5 with H-4 ranged from 2.7 to 3.8 Hz That of C-8 with H-1 ranged from 2.1 to 3.8 Hz. Those of C-4a with H-1 ranged from 3 to 4.6 Hz, C-4a with H-3 from 4.6 to 6.8 Hz and C-8a with H-4 from 3.6 to 4.4 Hz. (e) Three-bond coupling, through carbons bearing no oxygen, ranged from 6.1 to 10 Hz. In most of the cases three-bond coupling across oxygen substituted carbons ranged from 3 5 to 7.6 Hz.

Assignment of sp^3 *oxygen bearing carbons*

In most cases, the assignments of the methoxy carbons were straightforward. They were readily recognized by their typical chemical shifts [8, 10] and by their characteristic quartet in the coupled spectra

In **7** and **9**, assignment of the two methoxy groups was based on the fact that in di-*ortho* (2,6-disubstituted) substituted anisoles, there is a considerable shielding of the methoxy group [3, 15]; whereas, the substituents at positions 2 and 6 are not affected to a large extent. Therefore, the lower field resonance of the methoxy groups in **7** and **9** was assigned to C-8′ and C-5′, respectively.

In the case of the trisubstituted compounds (**11–13**), the upper field signal was readily assigned to the more sterically crowded methoxy group (i.e C-7′, C-7′ and C-6′, respectively) [6]

In the case of the methoxy groups of **6** and the peripheral ones in **11–13**, the nearly identical chemical shifts precluded any unambiguous assignments.

The methylene dioxy carbon of **14** was readily recognized by its typical chemical shift value (*ca* δ 100), the ^{13}C–^{1}H coupling constant (*ca* 170 Hz) and multiplicity in the coupled spectra.

Protonation effects

^{13}C chemical shift effects upon protonation of seven oxygenated tetrahydroisoquinolines (Table 2) are summarized in Table 5. The data clearly indicates that protonation induces a significant shielding effect on carbons that are two or three bonds from the positively charged nitrogen (i.e. on C-8a, C-4, C-4a and C-8). The same effect has been previously observed in piperidine and other aliphatic amines [10]; it has been attributed to local electric fields generated at the nitrogen by protonation [16]. The observed changes in chemical shift in the other aromatic carbons as well as those in the β carbons were smaller. These slight variations in chemical shifts in the case of the aromatic carbons (C-5–C-7) are probably due to the change of molecular association

EXPERIMENTAL

Reference materials Compounds **1–8**, **10**, **11** and **13** were prepared by previously reported procedures [17–25] Compound **2** and corypalline hydrochloride (2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline) were kindly provided by Dr. S. Teitel from Hoffman–LaRoche Compound **12** was isolated from *Pachycereus weberi* (Coult) Backbg [17] Compound **14** was obtained from S B Penick & Co and **15** was purchased from Aldrich Chemicals

Methods. ^{13}C NMR spectra were recorded at 23 kgauss, using a Fourier-transform computer with 20K memory. The spectra were measured at room temp using a deuterium lock, the chemical shifts were measured at 4000 Hz (**4** and **11**) and 5000 Hz (all other compounds) sweep width The pulse width was 23 msec (90° pulse), and the repetition time between pulses was 4 sec The proton decoupled ^{13}C NMR spectra were recorded while the protons were decoupled using broad band (2 5 kHz) incoherent radio-frequency scores (99 99 MHz). Coupling constants or splittings were measured from proton coupled spectra. Samples, in the case of the tetrahydroisoquinoline bases, were prepared in 1 5 ml $CDCl_3$ using TMS as int ref Those of the tetrahydroisoquinoline hydrochlorides were prepared in D_2O (1 5 ml) using MeOH as int ref Sample tubes had o.d s of 10 mm

^{1}H NMR spectra were recorded at 60 MHz using $CDCl_3$ or D_2O as solvents and TMS or DOS as int ref, respectively

MS were determined on low resolution instruments

Synthesis of 1-*monodeuterio*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* [8, 9] 3,4-Dimethoxy-β-phenethyl formamide 4.97 g (0 0237 mol), prepared from the amine (Aldrich Chemical Co) and HCO_2H was used as the starting material Bischler–Napieralski reaction of the amide afforded 3 15 g 6,7-dimethoxy-3,4-dihydroisoquinoline [^{1}H NMR (60 MHz, $CDCl_3$, δ). 8 4 (1H, *d*, H–C=N), 6 95 (1H, *s*, =CH-8), 6 8 (1H, *s*, =CH-5), 4.84 (2H, *t*, CH_2-3), 4.05 (6H, *s*, OMe), 2 70 (3H, *t*,

Table 5 Protonation effect on the ^{13}C NMR chemical shifts in various tetrahydroisoquinolines [δ values (ppm)]

Compound	Carbon No. 1	3	4	4a	5	6	7	8	8a	2′	5′	6′	7′	8′
1	−3.2	−1 2	−3 4	−2.8	−0 3	3.1	2 4	0.1	−7.5	−3.7	1	—	—	—
2	−3.4	−2.1	−4.6	−2.7	−0.1	0.8	1.6	1.3	−7.8	—	—	0.5	—	—
3	−3.8	−2 9	−4 3	−2.9	0.2	2.2	0.1	0.6	−6.7	—	—	—	0.4	—
7	−1.8	−2 7	−4 3	−4.7	1 1	2.7	−0 3	0 4	−5 7	—	—	—	0 8	0.8
8	−3.6	−1 3	−3 6	−3.1	−0.2	2.2	0.8	0.8	−7.3	−3 6	−0 6 −0 7	—	−0 6 −0 7	—
9	−3.8	−1.1	−4.1	−3.3	0.6	−1.5	1.8	1.8	−8	—	0	0.7	—	—
12	−3.5	−1.4	−3.7	−2.7	−0 9	0.7	0.7	1.3	−6.7	−3 7	1 0.5 0.8 0.3	0.3	1 0 5 0 8 0 3	—

CH_2-4)] Methylation of 2 15 g dihydroisoquinoline with excess MeI afforded 3 g of the corresponding methiodide mp 205°, [^{1}H NMR (60 MHz, $CDCl_3$, δ) 9 9 (1H, *m*, H-C=N), 7 7 (1H, *s*, =CH-8), 7 (1H, *s*, =CH-6), 4 15 (2H, *t*, CH_2-3), 4 1 (6H, *s*, OMe), 4 (3H, *s*, N-Me), 3 35 (2H, *t*, CH_2-4)] Reduction of 0 6 g methiodide with 1 g $NaBD_4$ afforded 0 357 g (22 % yield from the amide) 1-monodeutero-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline free base That the compound was monodeuterated at position 1 was verified by ^{1}H NMR of the resulting base (the singlet at δ 3 55 corresponding to CH_2-1 had half of the intensity of that of the compound bearing no deuterium at position 1) MS analysis indicated the following isotopic composition in the M^+ region $d_0 = 47\,75\%$, $d_1 = 52\,24\%$

Synthesis of 2-methyl-6-methoxy-7-deuteromethoxy-1,2,3,4-tetrahydroisoquinoline This compound was prepared via *O*-methylation of 2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (corypalline) with CD_2N_2 Corypalline hydrochloride (0 24 g, 0 001 mol) was repeatedly dissolved in D_2O and CD_3OD, and then concd until complete exchange of the proton on the OH group had taken place, the complete exchange was verified by ^{1}H NMR in $CDCl_3$ The resulting 2-methyl-6-methoxy-7-deuteroxy-1,2,3,4-tetrahydroisoquinoline was dissolved in 10 ml CD_3OD and then 20 ml of an Et_2O soln of CD_2N_2 (containing 0 01 mol) was added The soln was left at −5° for 48 hr and then the solvent removed *in vacuo* The crude product was purified by means of anion exchange chromatography (IRA-401S, Mallinckrodt Chemicals) to separate the desired non-phenolic product from unreacted corypalline The MeOH eluates yielded 160 mg (73 % yield relative to oxymethylcorypalline HCl) of the base, mp 60° That the compound had incorporated a trideuteromethoxyl group was verified by the ^{1}H NMR of the base in $CDCl_3$ (the sharp singlet at δ 3 85 had half of the normal intensity) MS analysis indicated the following isotopic composition in the M^+ region $d_0 = 1\,26\%$, $d_1 = 5\,06\%$, $d_2 = 50\,63\%$, $d_3 = 43\,03\%$

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