Synthesis and ^{1}H-, ^{13}C-NMR Analysis of some Substituted 1,2,3,4-Tetrahydroisoquinolines

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Synthesis and ^{1}H-, ^{13}C-nmr analysis of some substituted 3-phenyl-1,2,3,4-tetrahydroisoquinolines are reported. Spectroscopy assignments of hydrogen and carbon resonances were made on the basis of standard chemical shift theory, comparison with reference compounds, attached proton test and fully coupled ^{13}C-nmr spectra. Data showed that at room temperature two conformers predominated for the 1,3-disubstituted and 1,2,3-trisubstituted isoquinolines.

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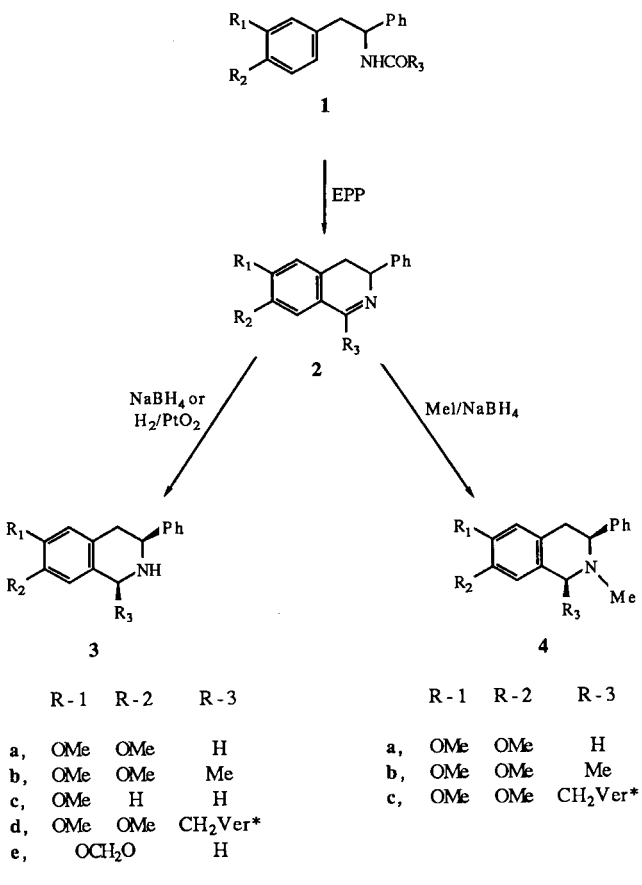
Standard isoquinoline ring syntheses [1] are satisfactory for derivatives with electron donor groups at the future C-6 position and for 1- and 4-substituted compounds, but isoquinolines substituted at C-3 may prove most troublesome to prepare, particularly when a 3-arylisoquinoline is required. However, the amides **1** have been converted into **2** in very high yields when treated with EPP [2]. By analogy with the results obtained by Gal *et al* [3], reduction of **2** with hydrogen/platinum oxide invariably afforded the 1,3-*cis*-isomers (Scheme 1).

Scheme 1



	R-1	R-2	R-3
a,	OMe	OMe	H
b,	OMe	OMe	Me
c,	OMe	H	H
d,	OMe	OMe	CH_2Ver*
e,	OCH_2O		H

	R-1	R-2	R-3
a,	OMe	OMe	H
b,	OMe	OMe	Me
c,	OMe	OMe	CH_2Ver*

* Ver = 3,4-dimethoxyphenyl-

In recent years, ^{13}C-nmr spectra of isoquinoline alkaloids have been determined and many of their structural features described [4,5]. In order to facilitate shift assignments of related and other unknown alkaloids of this group, ^{1}H- and ^{13}C-nmr spectra analyses of some 3-phenyl, 1-methyl-3-phenyl and 1-benzyl-3-phenyl-1,2,3,4-tetrahydroisoquinolines, as well as their corresponding *N*-methyl derivatives, were carried out.

Spectroscopy assignments of hydrogen and carbon resonances were made on the basis of standard chemical shift theory [6-9], comparison with reference compounds, attached proton test and fully coupled ^{13}C-nmr spectra.

Predictably enough, the introduction of a phenyl group at C-3 of the tetrahydroisoquinoline systems produced several interesting effects. Table 1 lists the carbon chemical shifts for the compounds studied.

Accordingly, a phenyl group at C-3 caused a downfield shift of $\Delta\delta$ = 14.93 ±0.07 ppm at C-3 (α effect), of $\Delta\delta$ = 9.17 ±0.37 ppm at C-4 (β effect) and of $\Delta\delta$ = 1.20 ±0.30 ppm at C-1 (γ effect). The magnitude of such shifts, particularly that due to the γ effect, is attributable to the preferential equatorial position taken up by the phenyl group [6-9,10].

Scheme 2

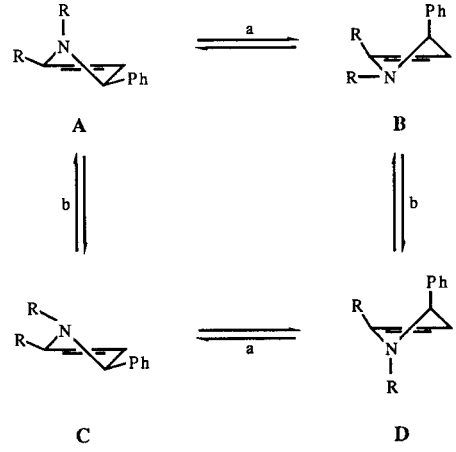
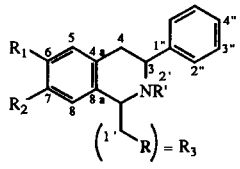
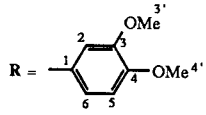


Table 1

^{13}C-NMR of 1,2,3,4-Tetrahydroisoquinolines [a]





C	3a	3b	3c	3d	3e	4a	4b	4c	6
1	48.53	52.83	48.21	57.82	48.80	57.75	60.65	66.03	47.30
3	58.30	58.48	58.16	57.97	58.26	65.95	65.77	67.00	43.30
4	36.80	38.00	37.53	38.47	37.30	37.29	38.05	38.91	28.00
4a	126.69	126.31	135.50	126.88	126.60	125.76	126.19	128.77	125.20
5	111.67	111.50	113.39	113.84	110.37	110.21	112.34	108.56	111.50
6	147.26	147.26	143.79	147.26	145.90	147.12	147.13	147.32	146.70
7	147.37	147.26	112.91	148.42	145.90	146.87	146.83	148.06	146.50
8	108.99	108.46	126.76	108.33	105.95	108.54	109.29	110.39	108.50
8a	126.26	131.58	126.93	130.61	126.34	125.87	131.23	131.57	127.20
1'		22.26		42.11			23.04	44.42	
2'						42.76	40.46	42.35	
1"	143.96	144.09	143.79	144.05	143.70	142.26	144.14	145.20	55.20
6 OCH_3	55.70	56.65	54.80	55.39		55.34	55.44	55.72	55.20
7 OCH_3	55.70	55.82		55.64		55.34	55.64	55.52	
OCH_2O					100.50				
2"	127.05	126.06	127.12	127.61	127.24	127.40	127.28	127.23	
3"	128.29	128.29	128.34	128.10	128.10	128.00	128.04	128.04	
4"	126.26	126.31	126.26	126.70	126.80	126.85	126.57	126.69	

^{13}C-NMR of R substituent

	C1	C2	C3	C4	C5	C6	C3'	C4'
3d	129.41	110.95	146.91	147.15	111.31	121.08	55.39	55.39
4c	129.62	110.62	147.08	147.20	110.76	122.42	55.72	55.72

[a] Deuteriochloroform and TMS as internal standard.

Owing to the ring inversion (a) jointly with the nitrogen inversion (b) (Scheme 2), four conformations are possible for the tetrahydroisoquinoline ring. At room temperature and in simple systems, these inversions are too fast for nmr detection [6,7], but in polysubstituted systems the various substituents influence the equilibrium position, so that conformers are not equally populated [7,15,16]. Data show that at room temperature conformers **A** and **C** predominated for the 1,3-disubstituted (**3b** and **3d**) and 1,2,3-trisubstituted isoquinolines (**4b** and **4c**).

For **3b** and **3d**, the quasi-equatorial conformation for the substituent as C-1 and the equatorial position for the substituent at C-3 are supported by the γ effect at C-3 and C-1, respectively. Thus, for compound **3a** the methyl group at C-1 caused a downfield shift of $\Delta\delta$ = 0.18 ppm at C-3 (γ effect) and one of $\Delta\delta$ = 4.3 ppm at C-1 (α effect). Likewise, for the benzyl group the γ effect was $\Delta\delta$ = 1.67 ppm and the α effect was $\Delta\delta$ = 9.29 ppm.

That the same **A-C** equilibrium is predominant for compounds **4b** and **4c** is also supported by the γ effect at C-3. Furthermore, the introduction of a methyl or benzyl group at C-1 in compound **4a** resulted in an upfield shift of $\Delta\delta$ = -0.18 ppm or a downfield shift of $\Delta\delta$ = 1.05 ppm for C-3 (γ effects), respectively. Introduction of an *N*-methyl group in compound **3a** caused β effects of $\Delta\delta$ = 9.20 ppm at C-1 and of $\Delta\delta$ = 7.65 ppm at C-3.

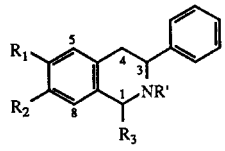
Introduction of both an *N*-methyl and a C-1 methyl group resulted in a downfield shift of $\Delta\delta$ = 12.12 ppm for C-1 and of $\Delta\delta$ = 7.47 ppm for C-3.

Calculated effects for C-1 and C-3 are 13.50 ppm (4.3 + 9.20 ppm) and 7.83 ppm (0.18 + 7.65 ppm). Therefore, both the α and β effects at C-1 and both the β and γ effects at C-3 are roughly additive.

In order to calculate α and γ effects, (±)-Salsolidine **5** [11,12] (Figure 1) was not used, since previous results had shown that they were not additive [5]. Perhaps the dis-

Table 2

^{1}H-NMR of 1,2,3,4-Tetrahydroisoquinoline [a]



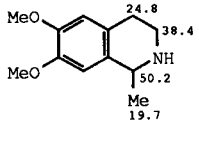
R' = -H o'-Me

	6 OCH_3	7 OCH_3	H1	NH or NCH_3	H3	H4	H5	H8	Other [b]
3 a	3.85 (s) [c]	3.85 (s)	4.15 (s)	2.20 (s)	4.00 (t)	2.90 (d)	6.50 (s)	6.50 (s)	
3 b	3.80 (s)	3.85 (s)	4.15 (m)	1.70 (s)	3.90 (m)	2.85 (m)	6.50 (s)	6.65 (s)	CH_3 1.50 (d)
3 c	3.65 (s)		4.00 (s)	2.15 (s)	3.85 (t)	2.80 (d)	6.50 (s)		
3 d	3.75 (s)	3.80 (s)	4.35 (m)	3.35 (s)	3.90 (m)	2.80 (m)	6.50 (s)	6.75 (s)	CH_2 2.80 (d)
3 e			4.02 (s)	2.55 (s)	3.80 (t)	2.80 (d)	6.45 (s)	6.45 (s)	OCH_2O 5.85 (s)
4 a	3.85 (s)	3.87 (s)	3.60 (s)	2.15 (s)	2.60-3.50 (m)		6.55 (s)	6.55 (s)	
4 b	3.85 (s)	3.90 (s)	2.5-3.65 (m)	2.15 (s)	2.50-3.65 (m)		6.50 (s)	6.65 (s)	CH_3 1.55 (d)
4 c	3.70 (s)	3.75 (s)	3.37 (t)	2.25 (s)	3.80 (m)	2.97 (d)	6.45 (s)	6.65 (s)	CH_2 2.43 (d)

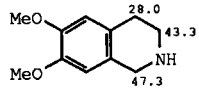
[a] Deuteriochloroform and TMS as internal standard. [b] All compounds exhibit aromatic protons in the region 7.2-7.8 ppm. [c] (Multiplicity).

crepancy found could be ascribed to the methyl group at C-1 conformation. Thus, the introduction of a methyl group at C-1 of the (±)-Heliamine **6** [5,12] (Figure 1) producing an α, a β and γ effect ($\Delta\delta$ = 2.90, $\Delta\delta$ = -4.90 and $\Delta\delta$ = -3.20 ppm, respectively), assigns the methyl group to a quasi-axial position, which would tend to minimize steric interaction between C-1 and C-8 substituents [13]. In our compounds, the quasi-equatorial position is more likely, as steric interaction between C-1 and C-3 substituents seems more significant.

Figure 1



5 (±)-Salsolidine [11]



6 (±)-Heliamine [5,12]

Table 2 summarizes ^{1}H-nmr data for these tetrahydroisoquinolines. The 80 MHz ^{1}H-nmr spectra of **3a**, **3c**, and **3e** display a singlet for H-1, a doublet for H-4 ($J_{H-4,H-3}$ = 7.5 ±0.5 Hz) and a broad triplet with the same J for H-3. Such data agree with rapid equilibration among the four conformers (Scheme 2).

For the *N*-methyl derivatives **4a-c**, the parameters observed showed an upfield shielding for H-1 and H-3 (0.5 ± 0.05 ppm) consistent with a quasi-equatorial *N*-methyl group [8]. Signals corresponding to H-1, H-3 and H-4 are now more complex.

The compound **3b** displays an H-1 signal as a broad quartet ($\Delta\delta$ = 4.15 ppm; $J_{H-1,H-1'}$ = 5.50 Hz) in close agreement with the value predicted for an H in quasi-axial position [14]. H-3 shows a complex signal at $\Delta\delta$ = 3.90 ppm, a value which remains practically constant for all the derivatives. As expected, H-4 displays an ABX pattern and

the methyl group at C-1 a doublet ($\Delta\delta$ = 1.50 ppm; $J_{H\text{-}1,H\text{-}1'}$ = 5.5 Hz). Lastly, there is a downfield shift for NH.

Spectra of the 1-alkyl derivatives, **3a**, **4b**, **3d** and **4c**, show the difference between H-8 and H-5. Inspection of models **7** [17] and **8** [18] (Figure 2) indicates that the alkyl group at C-1 at a quasi-equatorial position is the only one compatible with deshielding at H-8.

Other findings would assign a 3-phenyl group to an equatorial position, since H-3 appears more shielded than an equatorial proton in these systems [14] ($\Delta\delta$ = 5.60 ppm) and there was no significant shielding for H-1 due to a C-3 phenyl group at an axial position [14].

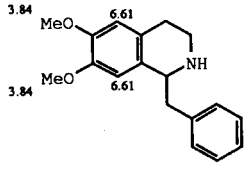
Finally, Table 3 summarizes the $^1J_{C\text{-}H}$ value obtained for **4a**.

Table 3

Coupling Constants ($^1J_{C\text{-}H}$) of **4a**

C-H	Hz (multiplicity)	C-H	Hz (multiplicity)
1	134.40 (t)	8	154.20 (d)
3	133.65 (d)	2'	133.30 (q)
4	128.84 (t)	6'	144.10 (q)

Figure 2



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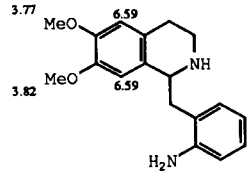

8

EXPERIMENTAL

All melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian FT 80 A spectrometer or on a Bruker WO 80 SYFT. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS). Elemental analyses were performed on a Coleman analyzer.

General Procedure for the preparation of 3-Phenyl-3,4-dihydroisoquinolines **2**.

Ethyl polyphosphate (EPP) (2.64 g) in chloroform solution, prepared by a published procedure [2] and the respective amide prepared also by a published procedure [2] were intimely mixed and heated at 80° for 8 hours, then the solvent was removed. The crude product was stirred with water 2 hours to give a precipitate. Recrystallization of the precipitate afforded **2**. The melting point, recrystallization solvent, ^{1}H-nmr data and elemental analysis for the following 3-phenyl-3,4-dihydroisoquinolines were previously performed and published [2]: these are the 6,7-dimethoxy, 6,7-dimethoxy-1-methyl, 6-methoxy and 6,7-methylenedioxy derivatives.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-3-phenyl-3,4-dihydroisoquinoline.

This compound was obtained as colorless crystals (ethanol), mp 102-104°, in 89% yield; ^{1}H nmr: δ 2.80 (m, 2H, CH_2), 3.75, 3.83, 3.90 (s, 9H, OCH_3), 4.07 (d, 2H, CH_2), 4.65 (broad q, 1H, CH), 6.60-7.55 (m, 8H, Ar).

Anal. Calcd. for $C_{26}H_{27}NO_4$ (417.48): C, 74.77; H, 6.52; N, 3.36. Found: C, 74.70; H, 6.51; N, 3.38.

General Procedure for the Preparation of 3-Phenyl-1,2,3,4-tetrahydroisoquinolines **3**.

To a solution of **2** (1.2 mmoles) in methanol (10 ml) was added, with stirring, sodium borohydride (200 mg). After stirring for 10 minutes the solvent was evaporated and the residue treated with water and extracted with ether (2 x 20 ml). The combined extracts were dried with sodium sulfate and concentrated *in vacuo* to give **3**. The melting point, recrystallization solvent, and elemental analysis of 6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**3a**) were previously performed and published [2]. For spectroscopic data of compounds **3a-3e** *cf.* Tables 1 and 2.

6,7-Dimethoxy-1-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**3b**).

This compound was obtained as colorless crystals (ethanol), mp 68-69°, in 75% yield.

Anal. Calcd. for $C_{18}H_{21}NO_2$ (283.35): C, 76.29; H, 7.47; N, 4.94. Found: C, 76.23; H, 7.49; N, 4.94.

6-Methoxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**3c**).

This compound was obtained as an oil in 56% yield.

Anal. Calcd. for $C_{16}H_{17}NO$ (239.30): C, 80.30; H, 7.16; N, 5.85. Found: C, 80.38; H, 7.13; N, 5.80.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**3d**).

This compound was obtained as an oil in 90% yield.

Anal. Calcd. for $C_{26}H_{29}NO_4$ (419.5): C, 74.44; H, 6.97; N, 3.34. Found: C, 74.40; H, 6.95; N, 3.41.

6,7-Methylenedioxy-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**3e**).

This compound was obtained as colorless crystals (ethanol), mp 147-148°, in 89% yield.

Anal. Calcd. for $C_{16}H_{15}NO_2$ (253.29): C, 75.86; H, 5.97; N, 5.53. Found: C, 75.90; H, 6.01; N, 5.51.

General Procedure for the Preparation of 2-Methyl-3-phenyl-1,2,3,4-tetrahydroisoquinolines (**4**).

A solution of **2** (1.5 mmoles) in dry methanol (10 ml) and methyl iodide (1.5 ml) was refluxed with stirring under a nitrogen atmosphere for 1.5 hours. After evaporation the residue was dissolved in methanol (10 ml) and sodium borohydride (300 mg) was added slowly (30 minutes) with stirring. The reaction mixture was heated at 40° during 40 minutes and then was evaporated to an oily residue. The residue was treated with water (15 ml) and

then with ammonium hydroxide (0.5 ml) and extracted with ether (2 x 15 ml). The combined extracts were dried with sodium sulfate and evaporated *in vacuo* to afford **4**. For spectroscopic data of compounds **4a-4c** *cf.* Tables 1 and 2.

6,7-Dimethoxy-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**4a**).

This compound was obtained as colorless crystals (ethanol), mp 98-99°, in 85% yield.

Anal. Calcd. for $C_{18}H_{21}NO_2$ (283.35): C, 76.29; H, 7.47; N, 4.94. Found: C, 76.32; H, 7.45; N, 5.00.

6,7-Dimethoxy-1,2-dimethyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**4b**).

This compound was obtained as colorless crystals (ethanol), mp 128-129°, in 73% yield.

Anal. Calcd. for $C_{19}H_{23}NO_2$ (297.38): C, 76.73; H, 7.80; N, 4.71. Found: C, 76.70; H, 7.83; N, 4.74.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**4c**).

This compound was obtained as an oil in 95% yield.

Anal. Calcd. for $C_{27}H_{31}NO_4$ (433.53): C, 74.80; H, 7.21; N, 3.23. Found: C, 74.89; H, 7.17; N, 3.19.

Acknowledgements.

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