

# Spectral Assignments and Reference Data

## Complete $^1\text{H}$ and $^{13}\text{C}$ NMR spectral assignment of hydrogenated oxoisoaporphine derivatives

Eduardo Sobarzo-Sánchez,<sup>1\*</sup> Bruce K. Cassels<sup>1</sup> and Luis Castedo<sup>2</sup>

<sup>1</sup> Department of Chemistry, Faculty of Sciences, and Millennium Institute for Advanced Studies in Cell Biology and Biotechnology, University of Chile, Casilla 653, Santiago, Chile

<sup>2</sup> Department of Organic Chemistry and CSIC Associated Unit, Faculty of Chemistry, University of Santiago, 15706 Santiago de Compostela, Spain

Received 13 January 2003; accepted 10 March 2003

2,3,8,9,10,11-Hexahydro-7*H*-dibenzo[*de,h*]quinolin-7-one, 5-methoxy-2,3,8,9,10,11-hexahydro-7*H*-dibenzo[*de,h*]quinolin-7-one, 5-methoxy-6-hydroxy-1,2,3,7*a*,8,9,10,11,11*a*,11*b*-decahydro-7*H*-dibenzo[*de,h*]quinolin-7-one, 5-methoxy-5,6,8,9,10,11-hexahydro-4*H*-dibenzo[*de,h*]quinolin-7-ol, 5,6,8,9,10,11-hexahydro-4*H*-dibenzo[*de,h*]quinolin-7-ol and 5,6-dihydro-4*H*-dibenzo[*de,h*]quinolin-7-ol were prepared by catalytic hydrogenation of oxoisoaporphines or their 2,3-dihydro derivatives over  $\text{PtO}_2$  in acetic acid under mild conditions. Their structures were confirmed and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were completely assigned using a combination of one- and two-dimensional NMR techniques. Copyright © 2003 John Wiley & Sons, Ltd.

**KEYWORDS:** NMR;  $^1\text{H}$  NMR;  $^{13}\text{C}$  NMR;  $^1\text{H}$ - $^1\text{H}$  COSY; HMBC; HMQC; 7*H*-dibenzo[*de,h*]quinolin-7-one; 4*H*-dibenzo[*de,h*]quinolin-7-ol

## INTRODUCTION

'Oxoisoaporphines' is the generic name given to a series of unusual natural products with the 7*H*-dibenzo[*de,h*]quinolin-7-one skeleton,<sup>1</sup> because of their isomeric relationship to the better known oxoaporphines or 7*H*-dibenzo[*de,g*]quinolin-7-ones, which are formed by oxidation of the relatively abundant (nor)aporphine alkaloids.<sup>2</sup> The fact that aporphines usually co-exist with oxoaporphines suggests the possibility of finding 'isoaporphines' together with oxoaporphines. However, 'isoaporphines' have never been found in nature, and do not seem to have been described as synthetic products. This situation prompted us to study the reduction chemistry of oxoisoaporphines as a possible route to 'isoaporphines.'

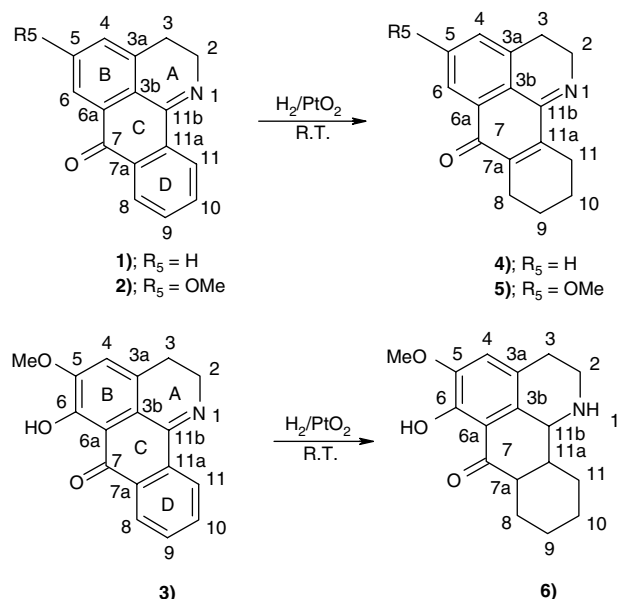
We have previously reported the complete  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral assignments of a series of 2,3-dihydrooxoisoaporphines.<sup>3</sup> In this paper, we describe the structure determination, conducted entirely by the use of NMR spectroscopy, and the complete chemical shift assignments of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the hydrogenation products of several oxoaporphines and 2,3-dihydrooxoisoaporphines. This was achieved through the concerted application of a variety of one- and two-dimensional techniques such as COSY,<sup>4</sup> and gradient-enhanced<sup>5</sup> HMQC and HMBC,<sup>6,7</sup> experiments.

These new and novel compounds were separated into two groups: (i) two 2,3,8,9,10,11-hexahydrooxoisoaporphines (4, 5) consisting of one two-spin (two *meta* aromatic protons), one four-spin and one eight-spin  $^1\text{H}$  systems (two and four methylenes, respectively), and a 1,2,3,7*a*,8,9,10,11,11*a*,11*b*-decahydrooxoisoaporphine

(6) with one four-spin and one 11-spin  $^1\text{H}$  systems (two methylenes, separated by the nitrogen atom from four methylenes and three methines); and (ii) three annelated quinolin-7-ols, one (9) with a two-spin (quinoline  $\alpha$ - and  $\beta$ -H), a four-spin vicinal aromatic and a six-spin (three methylene)  $^1\text{H}$  systems, and two (10, 11) incorporating one five- or six-spin  $^1\text{H}$  system on the B ring (two methylenes separated by a methine, or three methylenes), one two-spin (quinoline  $\alpha$ - and  $\beta$ -H), and one eight-spin (four methylene)  $^1\text{H}$  systems. All  $^1\text{H}$  signals could be assigned unequivocally on the basis of the  $^1\text{H}$ - $^1\text{H}$  COSY spectra. However, the complexity of the coupling patterns in the  $^1\text{H}$  NMR spectra due to the presence of several neighboring methylenes and methines made it necessary to apply HMQC and HMBC techniques for the direct unequivocal assignment of the heteronuclear correlations.

## RESULTS AND DISCUSSION

Several previously described 2,3-dihydrooxoisoaporphine and oxoisoaporphine derivatives were catalytically hydrogenated over  $\text{PtO}_2$  at room temperature and at 60–70 psi in acetic acid. Thus, when 2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one (1)<sup>8</sup> and 5-methoxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one (2)<sup>9</sup> were used as starting materials, they afforded in good yields 2,3,8,9,10,11-hexahydro-7*H*-dibenzo[*de,h*]quinolin-7-one (4) and 5-methoxy-2,3,8,9,10,11-hexahydro-7*H*-dibenzo[*de,h*]quinolin-7-one (5), respectively, in which only ring D is saturated.<sup>10</sup> However, 5-methoxy-6-hydroxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one (3)<sup>9</sup> gave the more highly reduced 1,2,3,7*a*,8,9,10,11,11*a*,11*b*-decahydro-7*H*-dibenzo[*de,h*]quinolin-7-one (6).<sup>10</sup> This difference could be attributed to the presence of the OH group at C-6 forming a hydrogen bond with the carbonyl at C-7 and affecting the reactivity of the conjugated C-7a=C-11a and C-11b=N bonds. On the other hand, reduction of the 7*H*-dibenzo[*de,h*]quinolin-7-ones 7 and 8 afforded annelated quinolin-7-ols.<sup>10</sup> Thus, 7 gave the ring B-saturated 5,6-dihydro-4*H*-dibenzo[*de,h*]quinolin-7-ol (9) in good yield as the only isolated product. Catalytic hydrogenation of the oxoisoaporphine 8 generated two more highly reduced products with saturation of rings B and D: 5-methoxy-5,6,8,9,10,11-hexahydro-4*H*-dibenzo[*de,h*]quinolin-7-ol (10) and 5,6,8,9,10,11-hexahydro-4*H*-dibenzo[*de,h*]quinolin-7-ol (11), the latter with hydrogenolytic loss of the methoxy group. The reactions leading to these new products and their structures are summarized in Schemes 1 and 2. The complete assignments of the NMR spectra of 4, 5, 6, 9, 10 and 11 are summarized in Tables 1–3.



**Scheme 1.** Preparation of new saturated 7*H*-dibenzo[*de,h*]quinolin-7-one derivatives (4–6).

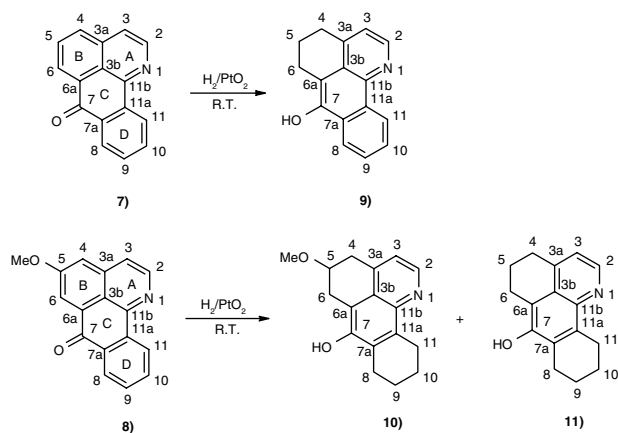
\*Correspondence to: Eduardo Sobarzo-Sánchez, Department of Chemistry, Faculty of Sciences, and Millennium Institute for Advanced Studies in Cell Biology and Biotechnology, University of Chile, Casilla 653, Santiago, Chile. E-mail: esobarzo@usc.es

Contract/grant sponsor: FONDECYT; Contract/grant number: 2010056.

## Spectral Assignments and Reference Data

**Table 1.**  $^1\text{H}$  chemical shifts  $\delta$  (ppm from TMS), signal multiplicity and  $J(\text{H,H})$  (Hz) of **4–6**

	<b>4</b>	<b>5</b>	<b>6</b>
$2\alpha/2\beta$	4.11; t, $J = 7.8$	4.08; t, $J = 7.7$	3.11 [H-2 $\alpha$ , dd, $J_{\text{gem}} = 12.2$ , $J(2\alpha, 3\beta) = 4.6^\circ$ ] 3.44; m
$3\alpha/3\beta$	2.85; t, $J = 7.8$	2.82; t, $J = 7.7$	2.62–2.96; m
3a			
3b			
4	7.37; d, $J(4,6) = 7.8$	6.89; d, $J(4,6) = 2.2$	6.78
5	7.47; dd, $J(4,5,6) = 7.6$		
6	7.94; d, $J(6,4) = 7.8$	7.40; d, $J(6,4) = 2.5$	
6a			
7			
7a			2.37; m
$8\alpha/8\beta$	2.57; bs <sup>a</sup>	2.56; bs <sup>a</sup>	1.40–2.64; m
$9\alpha/9\beta$	1.75; m	1.75; m	1.0–1.25; m
$10\alpha/10\beta$	1.75; m	1.75; m	1.60–1.70; m
$11\alpha/11\beta$	2.74; bs <sup>a</sup>	2.73; bs <sup>a</sup>	1.25–1.70; m
11a			2.81; bs <sup>a</sup>
11b			4.11; bs <sup>a</sup>
O-5-CH <sub>3</sub>	—	3.89	3.87
OH-6	—	—	12.93

<sup>a</sup> bs = Broad singlet.**Scheme 2.** Preparation of saturated 4H-dibenzo[de,h]quinolin-7-ol derivatives (**9–11**).

The  $^1\text{H}$  NMR spectra of **4** and **5** displayed signals of aliphatic protons coupled mutually at  $\delta$  4.08–4.11 ppm ( $t$ ,  $J = 7.7$ –7.8 Hz) and 2.82–2.85 ppm ( $t$ ,  $J = 7.7$ –7.8 Hz) assigned to C-2 and C-3 respectively, the former strongly deshielded by the neighboring imine group. However, the aliphatic protons bonded to C-8 and C-11 appear as broad singlets at 2.56–2.74 ppm. These were determined mainly in the  $^{13}\text{C}$  NMR spectrum due to the deshielding afforded by the C7a–C11a bond conjugated with the C=N bond. The HMBC spectrum of **5** showed the coupling of the protons bonded to C-8 at  $\delta$  2.56 ppm with C-9 and C-10, which in turn helped to assign the C-11 signals in **4** and **5**. In the case of **6**, the complete reduction of ring D led to the appearance of three additional  $\text{sp}^3$  carbons. The corresponding protons resonate at 2.37, 2.81 and 4.11 ppm, being easily assigned to C-7a, C-11a and C-11b, respectively, on the basis of the HMQC and HMBC spectra. The last two methylene groups appear in the  $^1\text{H}$  NMR spectrum as broad singlets, like the protons bonded to C-8 and C-11.

The  $^1\text{H}$  NMR spectra **9**, **10** and **11**, do not show clear multiplicities for the protons bonded to C-4, C-5 and C-6. These were identified fully by means of the couplings seen in the HMBC spectra. Unlike the cases of **4** and **5**, the C-9 and C-10 methylenes of ring D in **10** and **11** appear as broad singlets at 1.85 and 1.77 ppm, respectively. This is also true for all four methylenes forming ring D in **11**, indicating that the cyclohexene conformers are able to interconvert rapidly on the NMR time-scale, thus leading to equivalence of each pair of methylene protons.

## EXPERIMENTAL

## Representative general synthetic procedure

A yellow solution of **2** (0.5 g, 1.90 mmol) in AcOH (50 ml) was hydrogenated at 68 psi over  $\text{PtO}_2$  (0.3 g) for 24 h at room temperature. The resulting colorless solution was diluted with water (100 ml), neutralized with  $\text{NH}_3$  and extracted with  $\text{CHCl}_3$  (200 ml). The  $\text{CHCl}_3$  extract was dried over  $\text{Na}_2\text{SO}_4$  and concentrated to dryness, and the residue was subjected to flash column chromatography on silica gel, eluting with 9 : 1 (v/v) EtOAc–hexane to give **5** (0.390 g, 77% yield), which crystallized in MeOH as yellowish needles. The yields and melting points of **4**, **5**, **6**, **9**, **10** and **11** are reported in Table 4.

## Spectra

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were acquired using a Bruker Avance DRX 300 spectrometer operating at 300.13 and 75.47 MHz, respectively. All measurements were performed at a probe temperature of 300 K, using solutions of **4**, **5**, **6**, **7**, **9**, **10** and **11** in  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$  containing tetramethylsilane (TMS) as an internal standard. All one- and two-dimensional spectra were acquired with a Bruker inverse 5 mm Z-gradient probe.  $^1\text{H}$  spectra were obtained with a spectral width of 5 kHz, a  $90^\circ$  flip angle (10.1  $\mu\text{s}$ ) and 2 s relaxation delay in 32 scans. The one-dimensional carbon spectra were obtained with a spectral width of 18 000 Hz with 3 s between transients and the  $90^\circ$  pulse was 10  $\mu\text{s}$ . The homonuclear  $^1\text{H}$ – $^1\text{H}$  shift-correlated 2D spectra were obtained using standard Bruker software (cosygs). The spectral widths were 4 kHz. The spectra were collected as  $512 \times 512$  blocks of data and were processed by sinusoidal multiplication in each

## Spectral Assignments and Reference Data

**Table 2.**  $^1\text{H}$  chemical shifts  $\delta$  (ppm from TMS), signal multiplicity and  $J(\text{H,H})$  (Hz) of **9–11**

	9	10	11
2	8.58; d, $J(2,3) = 4.4$	8.64; d, $J(2,3) = 4.4$	8.49; d, $J(2,3) = 4.2$
3	7.26; d, $J(3,2) = 4.4$	7.09; d, $J(3,2) = 4.2$	7.08; d, $J(3,2) = 4.3$
3a			
3b			
4 $\alpha$ /4 $\beta$	2.96; m	3.10–3.25; m	2.91; m
5 $\alpha$ /5 $\beta$	1.90; m	3.91; m	1.90; m
6 $\alpha$ /6 $\beta$	2.99; m	3.02–3.26; m	2.91; m
6a			
7			
7a			
8	8.23; dd, $J(8, 9) = 7.48$ , $J(8, 10) = 1.5$	2.71; m	2.73; bs <sup>b</sup>
9	7.59; m	1.85; bs <sup>b</sup>	1.77; bs <sup>b</sup>
10	7.64; m	1.85; bs <sup>b</sup>	1.77; bs <sup>b</sup>
11	9.06; dd, $J(11,10) = 7.4$ , $J(11, 9) = 1.2$	3.28; m	3.14; bs <sup>b</sup>
11a			
11b			
OH-7	9.28		8.62
O-5-CH <sub>3</sub>	—	3.45	—

<sup>a</sup> bs = Broad singlet.**Table 3.**  $^{13}\text{C}$  chemical shifts  $\delta$  ( $^{13}\text{C}$ ) (ppm from TMS) of **4–6** and **9–11**

	4	5	6	9	10	11
2	48.85	48.44	45.18	145.5	146.4	145.3
3	24.93	25.00	29.36	121.0	119.5	118.2
3a	135.2	137.2	125.3	141.6	142.1	143.7
3b	125.0	118.7	131.0	124.8	124.1	123.8
4	132.1	118.7	119.9	29.59	35.02	29.30
5	131.3	161.5	148.6	21.48	74.13	21.52
6	124.7	107.0	153.0	24.04	28.77	23.50
6a	129.1	130.6	116.1	112.6	110.4	113.7
7	185.8	185.4	207.6	145.6	148.7	148.5
7a	139.0	138.5	44.07	130.7	128.4	129.6
8	23.58	23.26	27.38	122.0	23.95	24.23
9	22.09	21.72	24.15	126.2	22.31	22.09
10	22.01	21.65	24.07	127.9	22.36	22.17
11	24.72	24.26	26.49	124.1	25.02	24.60
11a	146.7	146.3	49.74	127.9	134.2	132.5
11b	158.5	157.8	58.61	144.2	141.9	141.5
O-5-CH <sub>3</sub>	—	55.65	57.65	—	56.16	—

dimension. Other parameters were as follows: number of increments in  $t_1$ , 256; number of scans, 4; and relaxation delay, 2 s.

The HMQC spectra were recorded using standard Bruker software (inv4gstp). These spectra were collected with  $512 \times 512$  data points, a data acquisition of four scans  $\times F_2$  and 256 increments in  $t_1$ . Spectral widths of 4 and 15 kHz were employed in the  $F_2$  ( $^1\text{H}$ ) and  $F_1$  ( $^{13}\text{C}$ ) domains, respectively. Data were processed using Qsine functions for weighting in both dimensions. The HMBC spectra were obtained using the inv4gslprnd pulse sequence in the Bruker software and collected with  $512 \times 512$  data points, a data acquisition

**Table 4.** Yields and melting points of the partially saturated oxoisoaporphine and quinolin-7-ol derivatives

Compound	Melting point (°C)	Yield (%)
4	149–150	53
5	157–158	77
6	213 (d) <sup>a</sup>	90
9	200 (d) <sup>a</sup>	81
10	181–182	58
11	160–161	41

<sup>a</sup> d = Decomposition.

of 10 scans  $\times F_2$  and 256 increments in  $t_1$ . The spectral widths were 4 kHz ( $F_2$ ) and 18 kHz ( $F_1$ ) and the delays  $\Delta_1$  and  $\Delta_2$  were set to 3.45 and 65 ms, respectively. Data were processed using an exponential window in  $F_2$  with lb = 0.3 Hz and Qsine window in  $F_1$ .

**Acknowledgements**

E.S.-S. thanks Fundación Andes for a scholarship. This work was supported in part by FONDECYT Grant No. 2010056.

**REFERENCES**

1. Yu B-W, Meng L-H, Chen J-Y, Zhou T-X, Cheng K-F, Ding J, Quin G-W. *J. Nat. Prod.* 2001; **64**: 968, and references cited therein.
2. Guinaudeau H, Leboeuf M, Cavé A. *J. Nat. Prod.* 1994; **57**: 1033, and references cited therein.
3. Sobarzo-Sánchez E, Cassels BK, Jullian C, Castedo L. *Magn. Reson. Chem.* 2003; **41**: 296.
4. Nagayama K, Kumar A, Wüthrich K, Ernst RR. *J. Magn. Reson.* 1980; **40**: 321.

## Spectral Assignments and Reference Data

5. Hurd RE. *J. Magn. Reson.* 1990; **87**: 422.
6. Bax A, Subramanian S. *J. Magn. Reson.* 1986; **65**: 565.
7. Bax A, Summers MF. *J. Am. Chem. Soc.* 1986; **108**: 2093.
8. Fabre J-L, Farge D, James C. US Patent 4 128 650, 1978.
9. Walker GN, Kempton RJ. *J. Org. Chem.* 1971; **36**: 1413.
10. Sobarzo-Sánchez E, Cassels BK, Castedo L. *Synlett.* submitted.