Synthesis and total assignment of ^{1}H and ^{13}C NMR spectra of new oxoisoaporphines by long-range heteronuclear correlations

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The new oxoisoaporphines 7*H*-dibenzo[*de,h*]quinolin-7-one, 5-methoxy-7*H*-dibenzo[*de,h*]quinolin-7-one, 5-methoxy-6-hydroxy-7*H*-dibenzo[*de,h*]quinolin-7-one, 5-hydroxy-7*H*-dibenzo[*de,h*]quinolin-7-one and 5-methoxy-6*H*-dibenzo[*de,h*]quinolin-6-one were prepared either by oxidation of their 2,3-dihydro derivatives or by heating (2′-(3,4-dihydro-6,7-dimethoxyisoquinolin-1′-yl)phenyl)methylbenzoate with an acetic acid/sulfuric acid mixture at 100 °C. The structures were confirmed and ^{1}H and ^{13}C NMR spectra were completely assigned using two-dimensional NMR techniques.

KEYWORDS: ^{1}H NMR; ^{13}C NMR; HMQC; HMBC; oxoisoaporphines; 7*H*-dibenzo[*de,h*]quinolin-7-ones; 6*H*-dibenzo[*de,h*]quinolin-6-one

INTRODUCTION

The not very well-known isoquinolinic alkaloids designated as 'oxoisoaporphines' have been isolated from *Menispermum dauricum* DC (Menispermaceae) more than three decades ago and whose 7*H*-dibenzo[*de,h*]quinolin-7-one skeleton was assigned partially.[1] Later on, synthetic studies afforded them some unusual derivatives[2] that have been starting material for a photoreduction study by tertiary amines.[3] Thus, we have previously reported the complete ^{1}H and ^{13}C NMR spectral assignments of a series of 2,3-dihydrooxoisoaporphines.[4] 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}H and ^{13}C NMR spectra of new oxoisoaporphine derivatives of the oxidation with Pd/C and the presence of a new isoquinoline skeleton, 6*H*-dibenzo[*de,h*]quinolin-6-one. This was achieved through the concerted application of gradient-enhanced[5] experiments such as HMQC and HMBC.[6,7]

These compounds have a structure consisting of six-spin ^{1}H systems (six aromatic protons) and an additional three- or two-spin system or a singlet, depending on the substitution pattern on ring B. For the case of (**9**), the presence of a phenanthrene pattern with a seven-spin ^{1}H system with an additional singlet is due to the substitution of the B aromatic ring by the carbonyl and methoxyl groups. Thus, the application of HMQC and HMBC techniques to contribute to a direct unequivocal assignment of the heteronuclear correlations.

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Contract/grant sponsor: FONDECYT; Contract/grant number: 1030963.

RESULTS AND DISCUSSION

The 2,3-dihydrooxoisoaporphines generated by cyclization of 3,4-dimethoxyphenylethylamine or homoveratrylamine (HV) and phthalaldehydic acid (PA) were used as starting material to generate, by means of the oxidation with 10% Pd on charcoal over benzene, oxoisoaporphines in high yields. However, exploring new routes of formation of these new heterocycles, it was generated through the Bischler–Napierlaski condensation (B–N) with HV and 2-(benzylbenzoate)chloride, a compound characterized as (2′-(3,4-dihydro-6,7-dimethoxyisoquinolin-1′-yl)phenyl)methylbenzoate (**8**) that, when it was made to react with an $AcOH/H_2SO_4$ mixture at 100 °C, surprisingly afforded only compound 5-methoxy-6*H*-dibenzo[*de,h*]quinolin-6-one (**9**) in moderate yield. The complete assignments of the NMR spectra of **4**, **5**, **6**, **7** and **9** are summarized in Tables 1, 2 and 3. The synthetic routes and the molecular structures of the different 6- and 7-oxoisoaporphines are shown in Schemes 1 and 2.

The ^{1}H NMR spectra of compounds **4–7**, analyzed with the aid of HMQC, displayed signals of aromatic protons coupled at δ 8.56–8.74 (d, J = 5.3–5.7 Hz) and 7.49–7.71 (d, J = 5.2–5.6 Hz) assigned to C-2 and C-3 respectively. However, **9** which is the isomer compound of **5**, has an aromatic proton at C-2 strongly deshielded by the neighboring carbonyl group at δ 9.01 (d, J = 4.6 Hz). On the other hand, **5** and **7** have two aromatic protons at δ 7.25–7.48 (d, J = 2.3 Hz) and 8.10–8.25 (d, J = 2.4 Hz), attributed to C-4 and C-6, respectively, in the B ring. This is due to the shielding afforded by the electron-donating group at C-5. By contrast, **4** presents aromatic protons with a deshielding evident at δ 8.11 and 8.62 ppm respectively. Also, analyzing the HMQC NMR spectra of **9**, the strong deshielding of the proton at C-11, which resonates at δ 9.31 because of the anisotropic effect of the attached azaphenalenone unit, differs from the assignments of the D ring of **4–7**. The ^{13}C NMR spectra of the two isomers **5** and **9** showed an important difference at C-2 in this last isomer due to the neighboring carbonyl group at B ring. HMBC experiments in all the oxoisoaporphines revealed many correlations to long range, which were very useful and which are shown in Table 3. Thus, the nitrogen atom and the carbonyl at C-6 and C-7, together with the electron-donating group were the starting points for assignment of all the aromatic protons. For the quaternary carbons, these last ones resonate to a frequency very similar in all oxoisoaporphines, except at C-6a and C-11b in **6** with δ 108.5 and 143.4 ppm respectively. This could be due to a tautomeric form afforded by the enolization from the C═O group at C-7 and the OH group at C-6 to give a deshielding effect on these carbons. However, C-6 resonates in **9** at δ 4 ppm much lower than the other carbonyl groups at C-7 in **5–7**, probably by the electron-donating effect from the methoxyl group at C-5.

EXPERIMENTAL

Synthesis of 7*H*-dibenzo[*de,h*]quinolin-7-ones (4–6)

On a solution of the 2,3-dihydrooxoisoaporphine in benzene was added 10% Pd on charcoal and then refluxed with stirring for 2 h. Then, the mixture was filtered over celite and washed with small portions of hot benzene. The organic residues were concentrated in vacuum to only give 7*H*-dibenzo[*de,h*]quinolin-7-ones **4–6**. Their yields and melting points are reported in Table 4.

Synthesis of oxoisoaporphine (7)

5-methoxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one (**5**) was dissolved in 37% HCl and then dust zinc was added with stirring at 90 °C for 1 h. The mixture was taken up in water, neutralized with NH_4OH and extracted with CH_2Cl_2. The dichloromethane extracts were then dried over anhydrous Na_2SO_4, concentrated, and the residues subjected to silica gel flash chromatography, eluting with hexane-ethyl acetate 1 : 4 (v/v) to give (**7**) crystallized in hexane as brownish needles.

Synthesis of 6-oxoisoaporphine (9)

(2′-(3,4-dihydro-6,7-dimethoxyisoquinolin-1′-yl)phenyl) methylbenzoate (**8**) got by the B–N condensation between HV and 2-(benzylbenzoate)chloride, was dissolved over an $AcOH/H_2SO_4$ mixture and heated with stirring at 100 °C for 1 h. Later, the organic

Table 1. ^{1}H chemical shifts δ [H-X, multiplicity, J(H,H) (Hz)][a] of 7*H*-dibenzo[*de*,*h*]quinolin-7-one (**4**) and 5-methoxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (**5**)

Position	**4**	**5**
2	8.74 [H-2, d, $J(2, 3) = 5.6$]	8.56 [H-2, d, $J(2, 3) = 5.6$]
3	7.71 [H-3, d, $J(3, 2) = 5.6$]	7.49 [H-3, d, $J(3, 2) = 5.6$]
3a	–	–
3b	–	–
4	8.11 [H-4, dd, $J(4, 5) = 8.2$, $J(5, 6) = 1.1$]	7.25 [H-4, d, $J(4, 6) = 2.3$]
5	7.88 [H-5, dd, $J(5, 6) = 7.7$, $J(6, 4) = 0.9$]	–
6	8.62 [H-6, dd, $J(6, 5) = 7.3$, $J(6, 4) = 1.2$]	8.10 [H-6, d, $J(6, 4) = 2.4$]
6a	–	–
7	–	–
7a	–	–
8	8.40 [H-8, dd, $J(8, 9) = 7.8$, $J(9, 10) = 1.4$]	8.33 [H-8, d, $J(8, 9) = 7.7$]
9	7.64 [H-9, ddd, $J(8, 9) = J(9, 10) = 7.1$, $J(9, 11) = 1.3$]	7.60 [H-9, dd, $J(8, 9, 10) = 7.5$]
10	7.80 [H-10, ddd, $J(9, 10) = J(10, 11) = 7.2$, $J(10, 8) = 1.4$]	7.76 [H-10, dd, $J(9, 10, 11) = 7.5$]
11	8.86 [H-11, dd, $J(11, 10) = 8.0$, $J(10, 9) = 0.8$]	8.79 [H-11, d, $J(11, 10) = 7.9$]
11a	–	–
11b	–	–
O-5-CH_3	–	3.96

[a] In ppm from TMS.

Table 2. ^{1}H chemical shifts δ [H-X, multiplicity, J(H,H) (Hz)][a] of 5-methoxy-6-hydroxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (**6**), 5-hydroxy-7*H*-dibenzo[*de*,*h*]quinolin-7-one (**7**) and 5-methoxy-6*H*-dibenzo[*de*,*h*]quinolin-6-one (**9**)

Position	**6**	**7**	**9**
2	8.72 [H-2, d, $J(2, 3) = 5.3$]	8.63 [H-2, d, $J(2, 3) = 5.7$]	9.01 [H-2, d, $J(2, 3) = 4.6$]
3	7.56 [H-3, d, $J(3, 2) = 5.2$]	7.60 [H-3, d, $J(3, 2) = 5.6$]	7.51 [H-3, d, $J(3, 2) = 4.6$]
3a	–	–	–
3b	–	–	–
4	7.23	7.48 [H-4, d, $J(4, 6) = 2.3$]	6.81
5	–	–	–
6	–	8.25 [H-6, d, $J(6, 4) = 2.4$]	–
6a	–	–	–
7	–	–	9.03
7a	–	–	–
8	8.50 [H-8, dd, $J(8, 9) = 9.1$, $J(9, 10) = 1.1$]	8.50 [H-8, d, $J(8, 9) = 7.7$]	8.15 [H-8, d, $J(8, 9) = 7.7$]
9	7.70 [H-9, ddd, $J(8, 9) = J(9, 10) = 7.6$, $J(9, 11) = 1.1$]	7.63 [H-9, dd, $J(8, 9, 10) = 7.8$]	7.79 [H-9, ddd, $J(8, 9) = J(9, 10) = 7.5$, $J(9, 11) = 1.3$]
10	7.87 [H-10, ddd, $J(9, 10) = J(10, 11) = 7.6$, $J(10, 8) = 1.3$]	7.80 [H-10, dd, $J(9, 10, 11) = 8.1$]	7.92 [H-10, ddd, $J(9, 10) = J(10, 11) = 7.7$, $J(10, 8) = 1.2$]
11	9.00 [H-11, d, $J(11, 10) = 8.0$]	8.88 [H-11, d, $J(11, 10) = 7.9$]	9.31 [H-11, d, $J(11, 10) = 8.4$]
11a	–	–	–
11b	–	–	–
O-5-CH_3	4.07	–	4.00
OH-5	–	10.21	–
OH-6	15.92	–	–

[a] In ppm from TMS.

residue was diluted in water, neutralized with NH_4OH and extracted with CH_2Cl_2. The extracts were then dried with Na_2SO_4 and concentrated in vacuum to be subjected to silica gel flash chromatography with elution with hexane-ethyl acetate 1 : 4 (v/v), affording (**9**) as brownish-yellow needles.

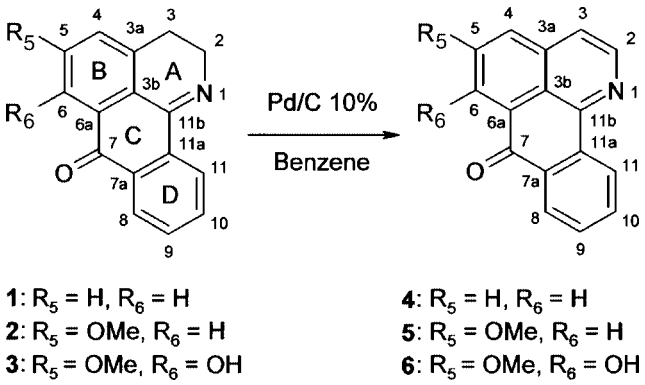
NMR studies

^{1}H and ^{13}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 compounds **4**, **5**, **6**, **7** and **9** in $CDCl_3$

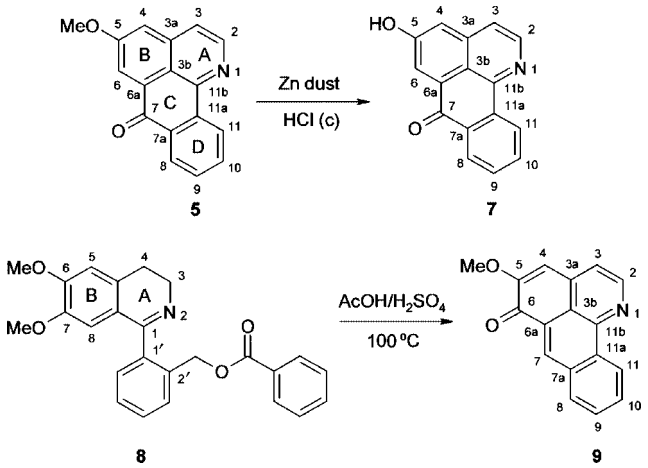
Table 3. ^{13}C chemical shifts δ (^{13}C)[a] of 7*H*-dibenzo[*de,h*]quinolin-7-one (**4**), 5-methoxy-7*H*-dibenzo[*de,h*]quinolin-7-one (**5**), 5-methoxy-6-hydroxy-7*H*-dibenzo[*de,h*]quinolin-7-one (**6**), 5-hydroxy-7*H*-dibenzo[*de,h*]quinolin-7-one (**7**) and 5-methoxy-6*H*-dibenzo[*de,h*]quinolin-6-one (**9**)

	4		**5**		**6**		**7**		**9**	
Position	δ(^{13}C)	HMBC[b]	δ(^{13}C)	HMBC[b]	δ(^{13}C)	HMBC[b]	δ(^{13}C)	HMBC[b]	δ(^{13}C)	HMBC[b]
2	143.9	3, 3a, 3b, 11b	144.3	3, 3a, 11b	144.0	3, 3a, 11b	144.3	3, 3a, 3b, 4, 11b	149.7	3, 3a, 3b, 11a, 11b
3	120.8	2, 3a, 3b, 4, 11b	120.0	2, 3b, 4	120.4	2, 3b, 4	120.7	2, 3b, 4, 7, 11b	120.5	2, 3b, 4
3a	135.0	2, 3, 4, 5	137.2	2	130.8	2	137.6	2, 4	135.5	2
3b	122.7	2, 3, 4, 6	118.6	3, 4, 6	117.1	3	117.7	2, 3, 4, 6	117.9	2, 3, 4, 7
4	133.3	3, 3a, 3b, 6	111.5	3, 3b, 5, 6	111.9	3, 3b, 5, 6	115.3	3a, 3b, 5, 6, 6a	110.5	3, 3b, 5, 6
5	130.4	3a, 6a	160.7	4, 6, *O*-5-CH_3	152.9	4, *O*-5-CH_3, OH-6	159.5	4, 6	156.0	*O*-5-CH_3
6	129.8	3b, 4, 7	121.0	3b, 5, 7	164.5	4, OH-6	121.2	3b, 4, 5, 7	179.3	4, 7
6a	128.9	5	130.6		108.5	OH-6	130.7	4	126.6	
7	183.3	6, 8	182.9	6, 8	184.7	8	182.5	6, 8, 11	134.4	3b, 6, 8, 11, 11a
7a	132.2	9, 11	132.1	9, 11	130.2	9, 11	132.0	9, 10, 11	132.5	9, 11
8	127.5	7, 10, 11a	127.4	7, 10, 11a	126.3	7, 10, 11a	127.3	7, 10, 11, 11a, 11b	131.0	7, 10, 11a
9	130.3	7a, 11	130.1	7a, 11	129.4	7a, 8, 11	130.7	7a, 8, 11, 11a	128.9	7a, 11
10	133.9	8, 11a	133.9	8, 11a	134.0	8, 11a	134.5	7a, 8, 11, 11a	130.8	7, 8, 11a
11	125.2	7a, 9, 11b	125.2	7a, 9, 11b	125.2	7a, 9, 11b	125.3	7, 7a, 8, 9, 10, 11b	124.8	2, 7, 7a, 9, 11a, 11b
11a	136.6	10	136.8	8, 10	137.2	8, 10	136.7	8, 9, 10	134.3	2, 7, 8, 10, 11
11b	148.6	2, 3	148.0	2, 11	143.4	2, 11	147.3	2, 3, 8, 11	144.8	2, 11
O-5-CH_3	–	–	55.80	–	56.30	–	–	–	56.00	–

[a] In ppm from TMS.
[b] C,H HMBC connectivities.



Scheme 1. Syntheses of 7*H*-dibenzo[*de,h*]quinolin-7-one (**4**) and derivatives (**5**–**6**).



Scheme 2. Synthesis of 5-hydroxy-7*H*-dibenzo[*de,h*]quinolin-7-one (**7**) and 5-methoxy−6*H*-dibenzo[*de,h*]quinolin-6-one (**9**).

Table 4. Yields and melting points of the oxoisoaporphine derivatives

Oxoisoaporphines	Melting point (°C)	Yield (%)
4	183–185	81
5	177–178	82
6	233–234	84
7	291 (d)	91
9	203 (d)	22

d = Decomposition.

containing tetramethylsilane (TMS) as an internal standard. All two-dimensional spectra were acquired with a Bruker inverse 5 mm Z gradient probe. ^1H spectra were obtained with a spectral width of 5 kHz, a 90° flip angle (10.1 μs) and 2 s relaxation delay in 32 scans. The one-dimensional carbon spectrum was obtained with a spectral width of 17 kHz with 3 s between transients and the 90° pulse was 10 μs.

The HMQC spectra were recorded using standard Bruker software (inv4gstp). These spectra were collected with 512 × 512 data points, a data acquisition of 4 scans × F_2 and 256 increments in t_1. Spectral widths of 5 and 15 kHz were employed in the F_2 (^1H) and F_1 (^{13}C) domains, respectively. Data were processed using Qsine functions for weighting in both dimensions. The HMBC spectra were obtained using the inv4gslplrnd pulse sequence in the Bruker software and collected with 512 × 512 data points, a data acquisition of 10 scans × F_2 and 256 increments in t_1. The spectral widths were 5000 Hz (F_2) and 18 000 Hz (F_1) and the delays Δ_1 and Δ_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 AECI-MAE for a postdoctoral fellowship and FONDECYT Grant N° 1030963 for financial support.

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