

Spectral Assignments and Reference Data

Complete structural and spectral assignment of oxoisoaporphines by HMQC and HMBC experiments

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The oxoisoaporphines 2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one, 2,3-dihydro-5-methoxy-7H-dibenzo[de,h]quinolin-7-one, 5-methoxy-6-hydroxy-2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one, 5,6-dimethoxy-2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one and 5,6-methylenedioxy-2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one were prepared by cyclization of phenylethylaminophthalides with polyphosphoric acid or by treating 1-(2-carboxyphenyl)-3,4-dihydroisoquinoline hydrochloride with sulfuric acid at 0 °C. The structures were confirmed and ¹H and ¹³C NMR spectra were completely assigned using a combination of one- and two-dimensional NMR techniques. Copyright © 2003 John Wiley & Sons, Ltd.

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INTRODUCTION

The oxoisoaporphine alkaloids isolated since the early 1980s from the rhizomes of *Menispermum dauricum* DC (Menispermaceae) are an unusual type of isoquinoline structure with a dubious biogenesis having a 7H-dibenzo[de,h]quinolin-7-one skeleton confirmed through total synthesis and spectroscopic assignment.^{1–4} Some 2,3-dihydrooxoisoaporphines have been synthesized previously, together with a number of side-products, by cyclization of phenylethylaminophthalides with polyphosphoric acid, although their spectral characterization is poor by present-day standards.⁵ The unsubstituted 2,3-dihydrooxoisoaporphine had been synthesized by a different route by heating 1-(2-carboxyphenyl)-3,4-dihydroisoquinoline hydrochloride in sulfuric acid, and the relevant spectroscopic information is also incomplete.⁶

In this paper, we describe the structure confirmation, conducted entirely by the use of NMR spectroscopy, and the complete chemical shift assignments of the ¹H and ¹³C NMR spectra of several 2,3-dihydrooxoisoaporphine derivatives. This was achieved through the concerted application of a variety of one- and two-dimensional techniques such as COSY⁷, HMQC⁸ and HMBC⁹ and the incorporation of the well-documented¹⁰ pulsed field gradients (PFG).¹¹

These compounds have a structure consisting of two four-spin ¹H systems (two methylenes and four aromatic protons) and an

additional three- or two-spin system or a singlet depending on the substitution pattern on ring B. These signals can be assigned unequivocally on the basis of the ¹H–¹H COSY spectra. The isolation of these systems by a nitrogen heteroatom and the carbonyl group makes the assignment of the ¹H and ¹³C RMN spectra relatively straightforward.

RESULTS AND DISCUSSION

The dihydrooxoisoaporphines 4–7 were obtained starting from the condensation products of 3,4-dimethoxyphenylethylamine (homoveratrylamine) (1) or 3,4-methylenedioxyphenylethylamine (homopiperonylamine) (2) with phthalaldehydic acid (3). The intermediates were subsequently treated with polyphosphoric acid to give the final products. On the other hand, 11 was obtained via *N*-phenethylphthalimide (8), which was partially reduced and cyclized to 5,6,8,12b-tetrahydro-8-isoindolo[1,2-a]isoquinolone (9) and this converted into 1-(2-carboxyphenyl)-3,4-dihydroisoquinoline (10), which was finally cyclized with sulfuric acid. The synthetic routes and the molecular structures of the different 2,3-dihydro-7H-dibenzo[de,h]quinolin-7-ones are shown in Scheme 1.

The ¹H NMR spectra of 4–7 and 11 (Table 1), analyzed with the aid of ¹H–¹H COSY and HMQC, displayed signals of aliphatic protons coupled mutually at δ 4.05–4.20 (t, J = 7.5–7.9 Hz) and 2.78–2.96 (t, J = 7.7–8.3 Hz) assigned to C-2 and C-3, respectively, the former strongly deshielded by the neighboring imine group, and four aromatic protons at δ 8.22–8.32 (d, J = 7.5–7.6 Hz), 7.59 (ddd, J = 7.3–8.5, 1.1 Hz), 7.6–7.7 (ddd, J = 7.2–7.4, 1.3 Hz) and 8.31–8.41 (d, J = 7.1–7.3 Hz) attributed to C-8, C-9, C-10 and C-11, respectively, in the D ring. Also, analyzing the ¹H, ¹H–¹H COSY and HMQC NMR spectra of 4, the methoxyl group at C-5 can be easily assigned. The strong deshielding of the proton at C-11, which resonates at δ 8.31–8.41 in all the studied oxoisoaporphines due to the anisotropic effect of the attached quinolone unit, was the starting point for the assignments of the quinoline system. The ¹³C NMR spectra of all five dihydrooxoisoaporphines showed 13 common carbon resonances corresponding to two methylenes, four methines and seven quaternary carbon atoms. The remaining resonances for ring B varied according to the substitution level, from three methines for 11, to two methines and an additional quaternary carbon for 4, and one methine and two additional quaternary carbons for 5, 6 and 7. Important correlations revealed by the HMBC experiment are shown in Table 2. The imine carbon atom, C-11b, and the carbonyl C-7 were the starting points for assignment of the protons of the methine carbon atoms C-8 and C-11, similarly affected by the deshielding moieties, C=N and C=O. For the former, the carbon resonates at almost the same frequency in all five dihydrooxoisoaporphines, between δ 154.8 and 156.1 ppm. However, C-7 resonates close to 184 ppm in 4, 6, 7 and 11, but at 189 ppm in 5 owing to hydrogen bonding of the carbonyl oxygen, evidenced by the chelated OH-6 proton resonance at δ 12.94 ppm.

EXPERIMENTAL

Synthesis of alkoxy-substituted 2,3-dihydro-7H-dibenzo[de,h]quinolin-7-ones (4–7)

A solution of phthalaldehydic acid in toluene was treated with homoveratrylamine or homopiperonylamine and refluxed with stirring under a Dean–Stark trap for 2 h. Each resulting mixture was treated with polyphosphoric acid and kept at 100 °C for 10 min. The red mixtures were taken up in water, neutralized with aqueous ammonia and extracted with CHCl₃. The chloroform extracts were then dried over anhydrous Na₂SO₄, concentrated and the residues subjected to silica gel flash chromatography, eluting with hexane–ethyl acetate (95:5, v/v) to give, among other side-products, the 2,3-dihydro-7H-dibenzo[de,h]quinolin-7-ones 4–7. Their yields and melting-points are reported in Table 3.

Synthesis of 2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one (11)
N-Phenethylphthalimide (8) was reduced partially with sodium borohydride in MeOH at room temperature and cyclized with

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Table 1. ¹H chemical shifts δ [H–X, multiplicity, J (H,H) (Hz)]^a of 2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one (**1**), and 5-methoxy-2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one (**4**), 5-methoxy-6-hydroxy-2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one (**5**), 5,6-dimethoxy-2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one (**6**) and 5,6-methylenedioxy-7H-dibenzo[de,h]quinolin-7-one (**7**)

Position	11	4	5	6	7
2	4.20 [H-2 α /H-2 β , t, <i>J</i> (2 α ,2 β) = 7.5]	4.15 [H-2 α /H-2 β , t, <i>J</i> (2 α ,2 β) = 7.9]	4.11 [H-2 α /H-2 β , t, <i>J</i> (2 α ,2 β) = 8.1]	4.07 [H-2 α /H-2 β , t, <i>J</i> (2 α ,2 β) = 7.7]	4.05 [H-2 α /H-2 β , t, <i>J</i> (2 α ,2 β) = 8.0]
3	2.96 [H-3 α /H-3 β , t, <i>J</i> (3 α ,3 β) = 7.7]	2.90 [H-3 α /H-3 β , t, <i>J</i> (3 α ,3 β) = 7.7]	2.81 [H-3 α /H-3 β , t, <i>J</i> (3 α ,3 β) = 8.5]	2.86 [H-3 α /H-3 β , t, <i>J</i> (3 α ,3 β) = 8.1]	2.78 [H-3 α /H-3 β , t, <i>J</i> (3 α ,3 β) = 8.3]
3a					
3b					
4	7.50 [H-4, d, <i>J</i> (4,5) = 7.4]	7.59 [H-4, dd, <i>J</i> (4,6) = 2.3]	6.94	7.01	6.85
5	7.58 [H-5, dd, <i>J</i> (6,5,4) = 7.6]				
6	8.18 [H-6, d, <i>J</i> (6,5) = 7.5]	6.99 [H-6, dd, <i>J</i> (6,4) = 2.1]			
6a					
7					
7a					
8	8.32 [H-8, d, <i>J</i> (8,9) = 7.6]	8.28 [H-8, d, <i>J</i> (8,9) = 7.5]	8.29 [H-8, dd, <i>J</i> (8,9) = 9.1, <i>J</i> (9,10) = 1.3]	8.22 [H-8, d, <i>J</i> (8,9) = 7.6]	8.25 [H-8, dd, <i>J</i> (8,9) = 9.1, <i>J</i> (9,10) = 1.4]
9	7.65 [H-9, dd, <i>J</i> (8,9,10) = 6.4]	7.61 [H-9, dd, <i>J</i> (8,9,10) = 7.4]	7.63 [H-9, ddd, <i>J</i> (8,9) = <i>J</i> (9,10) = 7.5, <i>J</i> (9,11) = 1.4]	7.59 [H-9, ddd, <i>J</i> (8,9) = <i>J</i> (9,10) = 7.3, <i>J</i> (9,11) = 1.1]	7.59 [H-9, ddd, <i>J</i> (8,9) = <i>J</i> (9,10) = 8.5, <i>J</i> (9,11) = 1.2]
10	7.73 [H-10, dd, <i>J</i> (9,10,11) = 7.5]	7.70 [H-10, dd, <i>J</i> (9,10,11) = 6.6]	7.72 [H-10, ddd, <i>J</i> (9,10) = <i>J</i> (10,11) = 7.5, <i>J</i> (10,8) = 1.2]	7.66 [H-10, ddd, <i>J</i> (9,10) = <i>J</i> (10,11) = 7.3, <i>J</i> (10,8) = 1.3]	7.67 [H-10, ddd, <i>J</i> (9,10) = <i>J</i> (10,11) = 8.9, <i>J</i> (10,8) = 1.4]
11	8.41 [H-11, d, <i>J</i> (11,10) = 7.4]	8.39 [H-11, d, <i>J</i> (11,10) = 7.8]	8.39 [H-11, d, <i>J</i> (11,10) = 7.8]	8.31 [H-11, d, <i>J</i> (11,10) = 7.1]	8.38 [H-11, d, <i>J</i> (11,10) = 7.5]
11a					
11b					
O-5-CH ₃	—	3.93	3.98	3.96	—
O-6-CH ₃	—	—	—	3.98	—
O-CH ₂ -O	—	—	—	—	6.20
OH-6	—	—	12.94	—	—

^a In ppm from TMS.

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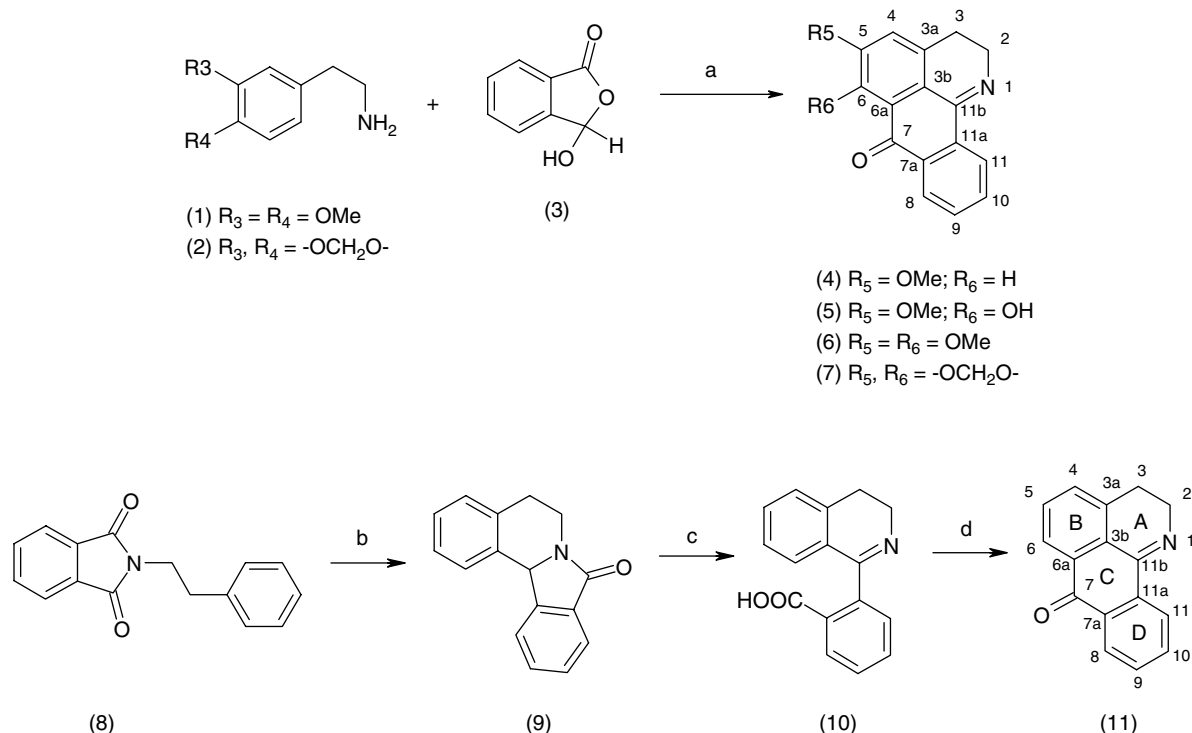
Table 2. ^{13}C chemical shifts δ (^{13}C)^a of 2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one (**11**), 5-methoxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one (**4**), 5-methoxy-6-hydroxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one (**5**), 5,6-dimethoxy-2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-one (**6**) and 5,6-methylenedioxy-7*H*-dibenzo[*de,h*]quinolin-7-one (**7**)

Position	11		4		5		6		7	
	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	48.59	3	48.54	3	48.04	3	47.98	3	47.75	3
3	25.40	2	25.86	2	24.53	2, 4	26.07	2, 4	25.28	2, 4
3a	127.9		138.7	2, 3	127.7	2, 3	133.6	4	130.5	
3b	126.2	2, 3, 6	120.3		117.7	3, 4	120.2	2, 3, 4	119.4	3, 4
4	133.1	3, 6	108.1	3, 6	116.1	3	116.3	3	112.2	3
5	131.8		162.3	3, O-5-CH ₃	150.8	4, O-5-CH ₃ , OH-6	156.6	4, O-5-CH ₃	146.4	4, O-CH ₂ -O
6	125.8	4	120.4	3, 4	151.3	4, OH-6	148.8	4, O-6-CH ₃	150.9	O-CH ₂ -O
6a	129.9	5	131.8		113.4	OH-6	124.3	4	120.5	
7	184.3	8, 11	184.3		189.5	8	184.1	8	182.6	8
7a	132.2	9, 11	132.3	9, 11	131.3	9, 11	133.8		131.4	9
8	127.3	10	127.3	10	126.5	10	127.2	10	126.6	10
9	131.1	11	131.0	11	130.6	11	131.0	11	129.7	11
10	133.9	8	133.9	8	134.2	8	133.4	8	133.4	8
11	125.0	9	124.9	9	124.7	9	124.6	9	124.7	9
11a	136.3	8, 10	136.3	8, 10	136.3	8, 10	135.6	8, 10	135.9	2, 8, 10
11b	156.1	11	155.7	2, 11	154.8	2, 11	156.0	2, 11	155.1	2, 11
O-5-CH ₃	—	—	56.10		56.25		56.64		—	—
O-6-CH ₃	—	—	—	—	—	—	61.79		—	—
O-CH ₂ -O	—	—	—	—	—	—	—	—	103.0	

^a In ppm from TMS.

^b $^{\text{C,H}}$ HMBC connectivities.

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a = APF/100°C/10 min., b = $\text{NaBH}_4/\text{MeOH-HCl}$ reflux, c = air/MeOH-dimethyl sulphate/heating, d = $\text{H}_2\text{SO}_4/\text{SO}_3$

Scheme 1. Syntheses of 2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one (**11**) and derivatives (**4-7**).

Table 3. Yields and melting-points of the 2,3-dihydrooxoisoaporphine derivatives

Compound	Melting-point (°C)	Yield (%)
4	164–165	30
5	156–157	9
6	154–155	4
7	175 (d) ^a	7
11	163–164	69

^a Decomposition.

hydrochloric acid to give 5,6,8,12b-tetrahydro-8-isoindolo[1,2-*a*]isoquinolone (**9**) (90%). Compound **9** was then oxidized with air in the presence of NaOH-MeOH and dimethyl sulfate to afford by heating 1-(2-methoxycarbonylphenyl)-3,4-dihydroisoquinoline, which was not isolated, but directly hydrolyzed to (**10**) with hydrochloric acid. Using fuming sulfuric acid at 0–5°C, **11** was obtained as yellowish needles crystallized from MeOH.

NMR studies

Proton 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 **4**, **5**, **6**, **7** and **11** in CDCl_3 containing tetramethylsilane (TMS) as an internal standard. All one- and two-dimensional spectra were acquired with a Bruker inverse 5 mm Z gradient probe. ^1H spectra were obtained with a spectral width of 5000 Hz, 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 17 000 Hz with 3 s between transients and the

90° pulse was 10 μs . The homonuclear $^1\text{H}-^1\text{H}$ shift-correlated 2D spectra were obtained using standard Bruker software (cosygs). The spectral widths were 5000 Hz. The spectra were collected as 512×512 blocks of data and were processed by sinusoidal multiplication in each 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 512×512 data points, a data acquisition of four scans $\times F_2$ and 256 increments in t_1 . Spectral widths of 5000 and 15 000 Hz 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 inv4gslprnd pulse sequence in the Bruker software and collected with 512×512 data points, a data acquisition of 10 scans $\times F_2$ 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 $\text{lb} = 0.3$ Hz and Qsine window in F_1 .

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