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An Expedient Synthesis of Unusual Oxoisoaporphine and Annelated Quinoline Derivatives

Eduardo Sobarzo-Sánchez,*[a] Bruce K. Cassels,[a] Luis Castedo[b]

[a] 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

[b] Department of Organic Chemistry and C.S.I.C. Associated Unit, Faculty of Chemistry, University of Santiago, 15782 Santiago de Compostela, Spain

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Abstract: Several 2,3-dihydro-7*H*-dibenzo[*de,h*]quinolin-7-ones and 7*H*-dibenzo[*de,h*]quinolin-7-ones were catalytically hydrogenated over PtO_2 in acetic acid to afford 7-hydroxyquinoline and quinolone derivatives with reduced benzene rings.

Key words: 7*H*-dibenzo[*de,h*]quinolin-7-ones, oxoisoaporphines, catalytic hydrogenation, reductions, chemoselectivity

A limited number of compounds with the 7*H*-dibenzo[*de,h*]quinoline skeleton, known as 1-azabenzanthrones, were synthesized three decades ago as intermediates for the formation of dyes,[1] and due to their possible photo- and electrochemical properties.[2] About the same time, the synthesis of 7*H*-dibenzo[*de,h*]quinolin-7-one derivatives via *N*-phenethylphthalimides was reported in connection with their possible antiviral activity,[3] and the synthesis of some 2,3-dihydro derivatives by cyclization of 3-(β-dialkoxyarylethylamino)phthalides was also reported.[4] In the case of the 5-methoxy-2,3-dihydro analogue (**2**), this compound was obtained in large enough quantities to subject it to some preliminary reduction studies, affording a basic carbinol whose structure, however, was not adequately confirmed. Since the 1980's, a small group of alkaloids possessing the 7*H*-dibenzo[*de,h*]quinoline skeleton and bearing different substitution patterns have been isolated from *Menispermum dauricum* DC. (Menispermaceae) and designated as oxoisoaporphines.[5] Some of them have exhibited cytotoxic activities against a small panel of cancer cell lines.[6] In the structurally similar oxoaporphines (7*H*-dibenzo[*de,g*]quinolin-7-ones), which might also be called 6-azabenzanthrones, the reduction of the carbonyl group had been carried out under mild conditions, affording aporphines,[7] but no similar results have been recorded for the oxoisoaporphines. In this connection it is interesting that, unlike the oxoaporphines, the oxoisoaporphines are not accompanied in plants by their reduced (or unoxidized) congeners.

Due to the lack of information on the reactivity of these compounds under reductive conditions, we have now studied the catalytic hydrogenation of several 2,3-dihydrooxoisoaporphines over Adams' catalyst. This method is useful for the preparation of new and unusual oxoisoaporphine and quinoline derivatives, due to its simplicity and efficiency.

The dihydro- and oxoisoaporphines used in this work and the generated products are summarized in Table 1. In all cases, hydrogenation was carried out for 24 hours at room temperature at pressures between 60–70 psi.[8] Under these conditions, complete or partial reduction of aromatic ring D and of the C-N imine bond of the dihydrooxoisoaporphines resulted (Scheme 1). However, in the case of the oxoisoaporphines, aromatic rings B and D were reduced (Scheme 2). Thus, the chemoreduction shown by these compounds would seem to depend mainly on the substitution at C-6 and on the degree of unsaturation of the isoquinoline skeleton. When Pd/C was used as catalyst, the unchanged starting material was recovered.

As can be seen in Scheme 1, the 2,3-dihydrooxoisoaporphines **1** and **2**, lacking a hydroxyl group at C-6, are partially reduced in ring D without affecting the C=N bond, affording **4** and **5** respectively. Hydrogenation of compound **3**, with an OH group at C-6, under identical conditions, led to complete reduction of ring D and the C=N bond to give **6**.

Table 1 Formation of Partially Hydrogenated Oxoisoaporphines **4**–**6**, 6-Oxoisoaporphine **13** and 7-Hydroxyquinolines **8**, **10** and **11** by Catalytic Hydrogenation[a]

Substrate	R^5	R^6	Product	Yield [%]
1	H	H	**4**	53
2	OMe	H	**5**	77
3	OMe	OH	**6**	90
7	H	H	**8**	81
9	OMe	H	**10**	58
			11	41
12	OMe	OH	**13**	32

[a] Conditions: Hydrogenation over PtO_2 in AcOH with stirring for 24 hours at room temperature (20–22 °C).

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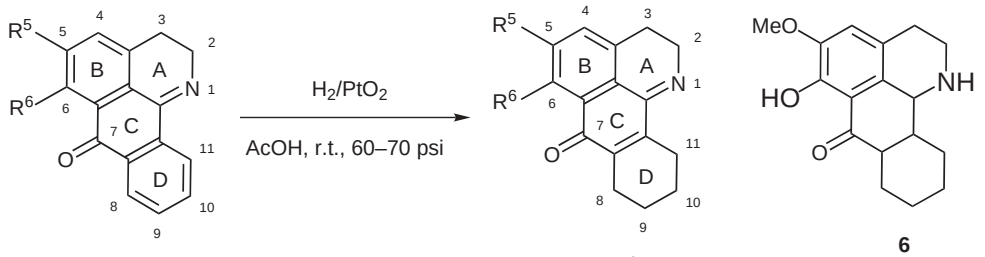

1. R^5 = H; R^6 = H
2. R^5 = OMe; R^6 = H
3. R^5 = OMe; R^6 = OH

4. R^5 = H; R^6 = H
5. R^5 = OMe; R^6 = H

6

Scheme 1 Synthesis of oxoisoaporphine derivatives **4**–**6** by catalytic hydrogenation over Adams' catalyst

This unusual reactivity shown by the 2,3-dihydrooxoisoaporphines is drastically altered when the isoquinoline A/B rings are fully aromatic. Thus, in **7** benzene ring B is reduced with concomitant enolization of the carbonyl group to give **8** as the final product. However, **9** afforded **10** and **11**, with reduction of both rings B and D and partial hydrogenolysis of the methoxyl group (Scheme 2). The structures of all these reduction products were established unambiguously using HMQC and HMBC experiments.[9] As the reactivity of these completely aromatized oxoisoaporphines appeared to be sensitive to substitution on ring B, the hydrogenation of **12** was also checked. Surprisingly, **12** afforded **13** as the only isolated product, which could be rationalized as a consequence of reduction of the carbonyl group at C-7 with subsequent elimination of water to afford the enone tautomer of the C-6 phenol function. An analogous mechanism has been proposed for the reduction of the natural product menisporphine (**14**) to bianfugecine (**15**) under similar conditions (Scheme 3).[10]

In conclusion, we report a short, practical method to afford new reduced oxoisoaporphines and other annelated quinolines which have not been reported as natural products. Our present efforts are directed to the synthesis and the exploration of the reactivity of oxoisoaporphines with different reduction agents in order to improve our understanding of their biogenesis.

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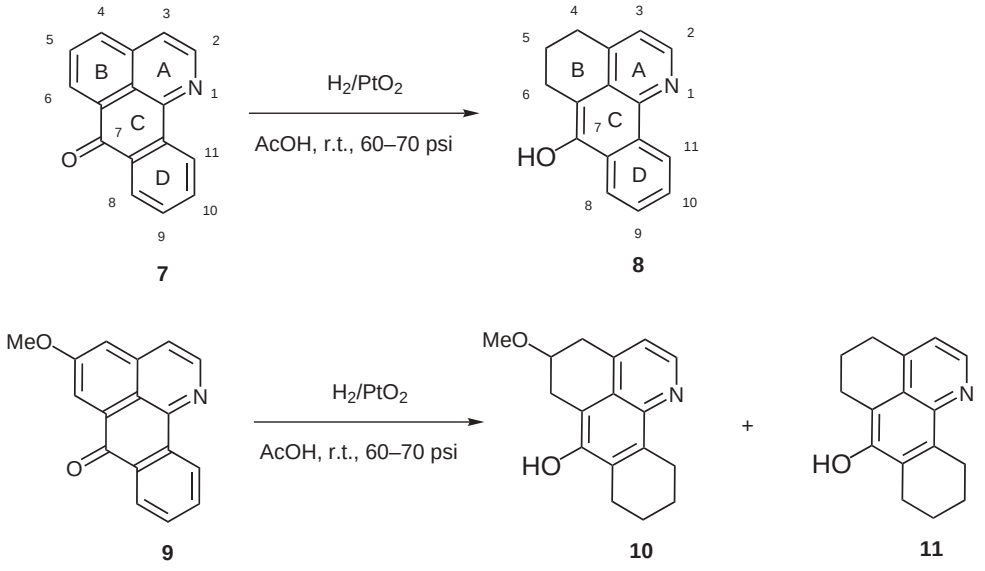
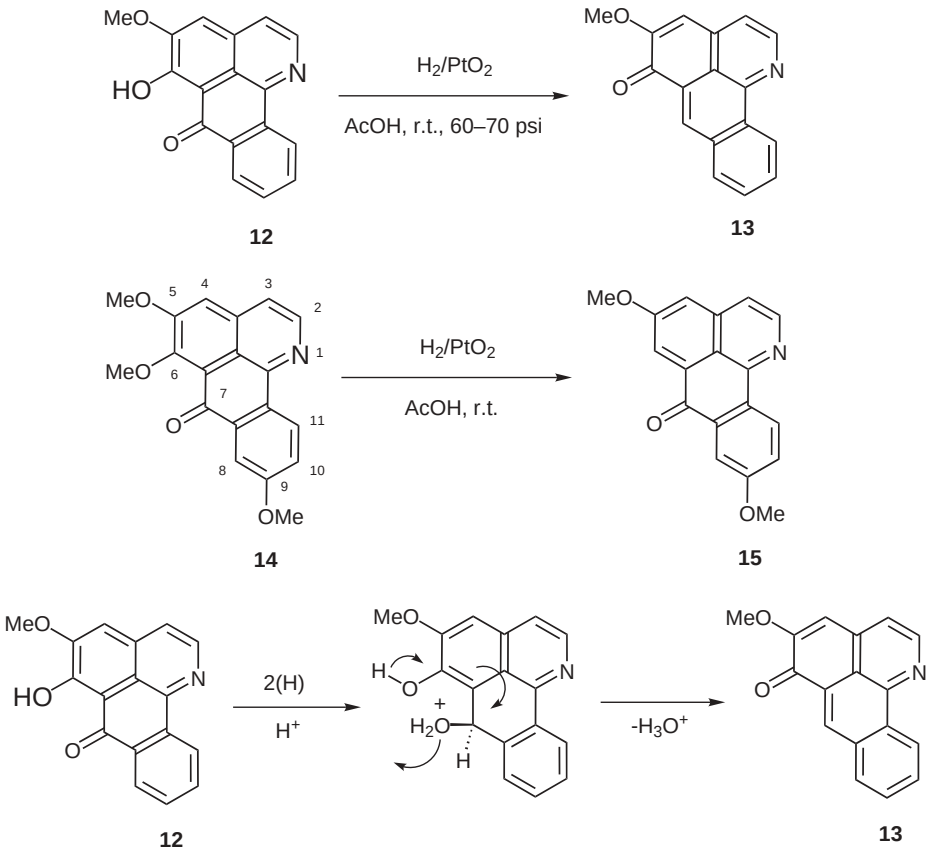


7 **8**

9 **10** **11**

Scheme 2 Synthesis of quinoline derivatives **8**, **10** and **11** by catalytic hydrogenation over Adams' catalyst



Scheme 3 Conversion of menisporphine (**14**) to bianfugecine (**15**) and possible mechanism for the conversion of **12** to **13** under acidic conditions.

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(8) **Representative Experimental Procedure:** A yellow solution of **2**, mp 164–165 ºC, prepared as described,[4] (0.5 g, 1.90 mmol) in 50 mL of AcOH was hydrogenated at 68 psi over PtO_2 (0.3 g) for 24 h at r.t. The colorless solution was diluted with 100 mL water, neutralized with NH_3 and extracted with $CHCl_3$ (200 mL). The $CHCl_3$ extract was dried over Na_2SO_4 and concentrated to dryness, and the residue subjected to flash column chromatography on silica gel, eluting with 90:10 EtOAc–hexane (v/v) to give **5** (0.390 g, 77% yield), which crystallized in MeOH as yellowish needles.
Spectroscopic data of **4**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75 (m, 4 H), 2.57 (broad s, 2 H), 2.74 (broad s, 2 H), 2.85 (t, 2 H, *J* = 7.8 Hz), 4.11 (t, 2 H, *J* = 7.8 Hz), 7.37 (d, 1 H, *J* = 7.8 Hz), 7.47 (dd, 1 H, *J* = *J′* = 7.7 Hz), 7.94 (d, 1 H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.01, 22.09, 23.58, 24.72, 24.93, 48.85, 124.7, 125.0, 129.1, 131.3, 132.1, 135.2, 139.0, 146.7, 158.5, 185.8. IR (KBr): 2929, 2876, 2855, 1639, 1593, 1296 cm^{-1}. Mp 149–150 ºC. Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.90; H, 6.47; N, 5.91.
Spectroscopic data of **5**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75 (m, 4 H), 2.56 (broad s, 2 H), 2.73 (broad s, 2 H), 2.82 (t, 2 H, *J* = 7.7 Hz), 3.89 (s, 3 H), 4.08 (t, 2 H, *J* = 7.7 Hz), 6.89 (d, 1 H, *J* = 2.2 Hz), 7.40 (d, 1 H, *J* = 2.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.65, 21.72, 23.26, 24.26, 25.00, 48.44, 55.65, 107.0, 118.69, 118.71, 130.6, 137.2, 138.5, 146.3, 157.8, 161.5, 185.4. IR (KBr): 2933, 2862, 2840, 1640, 1623, 1601 cm^{-1}. Mp 157–158 ºC. Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.03; H, 6.42; N, 5.26.
Spectroscopic data of **6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.00 (m, 1 H), 1.25 (m, 2 H), 1.40 (m, 1 H), 1.60 (m, 1 H), 1.70 (m, 2 H), 2.37 (m, 1 H), 2.61 (m, 2 H), 2.81 (s, 1 H), 2.91 (m, 1 H), 3.11 (dd, 1 H, *J* = 12.2 Hz, *J′* = 4.6 Hz), 3.44 (m, 1 H), 3.87 (s, 3 H), 4.11 (s, 1 H), 6.78 (s, 1 H), 12.93 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.07, 24.15, 26.49, 27.38, 29.36, 44.07, 45.18, 49.74, 57.65, 58.61, 116.1, 119.9, 125.3, 131.0, 148.6, 153.0, 207.6. IR (KBr): 3424, 2929, 2792, 2651, 1640, 1468, 1442, 1302, 1257, 1161, 1092, 1021 cm^{-1}. Mp 213 ºC (decomp.). Anal. Calcd. for $C_{17}H_{21}NO_3$. HCl. 1.4 H_2O: C, 58.44; H, 6.87; N, 4.01. Found: C, 58.58; H, 6.58; N, 3.97.
Spectroscopic data of **8**: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.00 (m, 2 H), 3.05 (m, 4 H), 7.33 (d, 1 H, *J* = 4.4 Hz), 7.70 (m, 2 H), 8.33 (dd, 1 H, *J* = 8.2 Hz, *J′* = 1.3 Hz), 8.66 (d, 1 H, *J* = 4.5 Hz), 9.14 (dd, 1 H, *J* = 9.1 Hz, *J′* = 1.4 Hz), 9.36

(s, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.73, 24.28, 29.84, 112.9, 121.2, 122.3, 124.4, 125.0, 126.4, 128.1, 128.2, 131.0, 141.9, 144.3, 145.8, 145.9. IR (KBr): 3426, 2930, 2875, 2820, 1604, 1575, 1434, 1415, 1272, 1253, 1199, 1186, 1098 cm^{-1}. Mp 200 ºC (decomp.). Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.55; H, 5.34; N, 5.93.

Spectroscopic data of **10**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.85 (broad s, 4 H), 2.71 (m, 2 H), 3.05 (m, 2 H), 3.25 (m, 4 H), 3.45 (s, 3 H), 3.91 (m, 1 H), 7.09 (d, 1 H, *J* = 4.3 Hz), 8.64 (d, 1 H, *J* = 4.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.31, 22.36, 23.95, 25.02, 28.77, 35.02, 56.16, 74.13, 110.7, 119.5, 124.1, 128.4, 134.2, 141.9, 142.1, 146.4, 148.7. IR (KBr): 3433, 3074, 2939, 2859, 1620, 1597, 1524, 1490, 1452, 1407, 1382, 1333, 1277, 1206, 1170, 1043, 1014 cm^{-1}. Mp 181–182 ºC. Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.78; H, 7.06; N, 5.05.

Spectroscopic data of **11**: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.77 (broad s, 4 H), 1.90 (m, 2 H), 2.73 (broad s, 2 H), 2.91 (m, 4 H), 3.14 (broad s, 2 H), 7.08 (d, 1 H, *J* = 4.3 Hz), 8.49 (d, 1 H, *J* = 4.3 Hz), 8.62 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.13, 22.70, 22.78, 24.11, 24.84, 25.21, 29.90, 114.3, 118.8, 124.4, 130.2, 133.1, 142.1, 144.3, 145.9, 149.1. IR (KBr): 3432, 2932, 2868, 1636, 1601, 1434, 1361, 1309, 1270, 1192, 1173, 1154, 1090, 1047 cm^{-1}. Mp 160–161 ºC. Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.05; H, 7.02; N, 5.81.

Spectroscopic data of **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.27 (s, 3 H), 6.81 (s, 1 H), 7.51 (d, 1 H, *J* = 4.6 Hz), 7.79 (dd, 1 H, *J* = *J*′ = 6.9 Hz), 7.91 (dd, 1 H, *J* = *J*′ = 7.0 Hz), 8.15 (d, 1 H, *J* = 7.7 Hz), 9.01 (d, 1 H, *J* = 4.6 Hz), 9.03 (s, 1 H), 9.31 (d, 1 H, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.95, 110.5, 117.9, 120.5, 124.8, 126.6, 128.9, 130.8, 131.0, 132.5, 134.3, 134.4, 135.5, 144.8, 149.7, 156.0, 179.3. IR (KBr): 2932, 2857, 1653, 1614 cm^{-1}. Mp 203 ºC (decomp.). Anal. Calcd. for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.88; H, 4.16; N, 5.33.

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