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Radical Cyclization to Aporphines. A New, Efficient Total Synthesis of the Aporphine Glaucine and the 4,5-Dioxoaporphine Pontevedrine, and the First Total Synthesis of 5-Oxoaporphines.

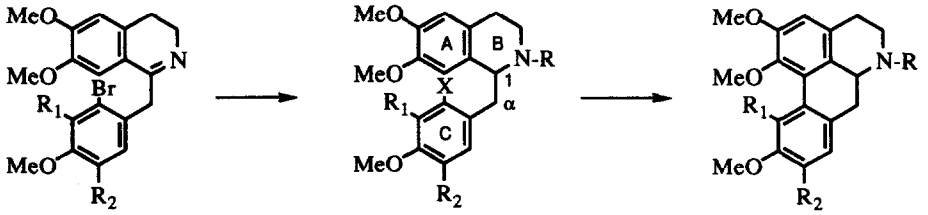
Juan C. Estévez, M. Carmen Villaverde, Ramón J. Estévez and Luis Castedo*.

Departamento de Química Orgánica, Facultade de Química, Universidade de Santiago de Compostela, 15706 Santiago de Compostela, (Spain).

Abstract. We describe the radical cyclization of bromobenzylisoquinolines and benzylisoquinolin-3-ones, which afford aporphines or the novel 5-oxoaporphines and 5-oxodehydroaporphines respectively. Oxidation of the latter compounds provides a new route to 4,5-dioxoaporphines.

The synthesis of naturally occurring compounds with biaryl bonds continues to be a very active field of investigation because of the lack of satisfactory methods for constructing the biaryl axes of biologically active natural products[1] such as aporphinoids,[2] a large group of isoquinoline alkaloid derivatives characterized by their having a tetracyclic structure which includes a phenanthrene ring system. Due to the pharmacological interest of aporphines, many attempts to improve their synthesis have been made, most of them based on the biomimetic route involving cyclization of 1-benzylisoquinolines.[2,3] Thus until 1966 aporphines were synthesized (usually in quite low yield) by a Pschorr-type cyclization of the corresponding 1-(2'-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines. Later, other ways to link the aromatic rings A and C of 1-benzylisoquinolines were developed, the most general being two different photochemical procedures. In the first, aporphines resulted in poor to moderate yields from photolysis of 1-(2'-bromobenzyl)-1,2,3,4-tetrahydroisoquinolines or 1-(2'-iodobenzyl)-1,2,3,4-tetrahydroisoquinolines. A subsequent more efficient photochemical route to aporphines is based on oxidative stilbene-phenanthrene photocyclization to a dehydroaporphine which can readily be reduced to an aporphine. More recently, aporphines have been obtained by a different strategy involving the construction of the phenanthrene ring system by means of an intermolecular benzyne cycloaddition reaction between 1-methyleneisoquinolines and arynes,[4] but yields are again at best moderate. We have now studied the conversion of 1-benzylisoquinolines into aporphines by intramolecular cyclization of aryl radicals generated from aryl halides and n-tributyltinhydride, one of the more successful recent methods for the formation of biaryl bonds.[5]

As benzylisoquinolines with a halogen at position $C_{2'}$ are required, we decided to study the case of the 1-(2'-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline **2a**, which was prepared by reduction of the 1-(2'-bromobenzyl)-3,4-dihydroisoquinoline **1a** (obtained by means of a Bichler-Napieralski sequence from 2-bromo-4,5-dimethoxyphenylacetic acid and 3,4-dimethoxyphenylethylamine).[6] Refluxing **2a** with n-Bu_3SnH and AIBN in benzene for 18 hours under argon[5d] gave unsatisfactory results: the ^1H NMR spectrum of the resulting complex reaction mixture failed to exhibit the low field C_{11} proton signal that is typical of aporphines. The main product of the reaction was the 6,7-dimethoxy-3,4-dihydroisoquinoline arising from rupture of the C_1-C_α bond, perhaps because of the availability of the unshared electron pair at the nitrogen atom (as in the photolysis of similar benzylisoquinolines).[7] This snag disappeared when the nitrogen atom was protected in a urethane or amide.



1 a: R_1=H, R_2=OMe
b: R_1=OMe, R_2=H

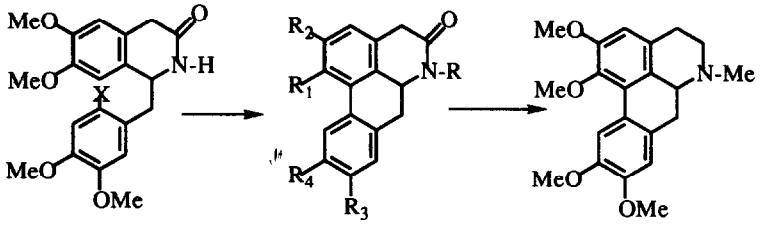
2 a: R_1=H, R_2=OMe, R=H, X=Br
b: R_1=H, R_2=OMe, R=CO_2Et, X=Br
c: R_1=OMe, R_2=H, R=CO_2Et, X=Br
d: R_1=OMe, R_2=H, R=CO_2Et, X=H

3 a: R_1=H, R_2=OMe, R=CO_2Et
b: R_1=H, R_2=OMe, R=Me
c: R_1=OMe, R_2=H, R=Me

When the *N*-protected 1-bromobenzylisoquinoline **2b** resulting from treatment of bromobenzylisoquinoline **2a** with ethyl chloroformiate[8] was reacted with n-Bu_3SnH and AIBN as above, the expected *N*-ethoxycarbonylaporphine **3a** was obtained in 81% yield, as deduced from its spectroscopic and analytical data. Its ^1H NMR spectrum showed singlets at 6.64, 6.78 and 8.17 ppm corresponding to its three aromatic protons (the last the deshielded proton at C_{11}). Reduction of this *N*-ethoxycarbonylaporphine with LAH[8] readily transformed it into a compound identical (ccf, IR, UV) to an authentic sample of the aporphine glaucine (**3b**).[9]

This new, highly efficient method of cyclizing 1-benzylisoquinolines to aporphines turned out to have an unexpected limitation in that aporphines substituted at C_{11} could not be obtained. This was discovered when the *N*-ethoxycarbonyl-1-(2'-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline **2c** (prepared in a similar way to **2b** from 2-bromo-3,4-dimethoxyphenylacetic acid through compound **1b**)[8,10] was treated with n-Bu_3SnH, as above: the only product of the reaction was the 1-benzylisoquinoline **2d** resulting from hydrogenolysis of the C-Br bond, a common side process in this type of radical reactions[11]. In the reaction in question, this process was probably favoured by the conformation required for the desired cyclization being of high energy due to steric interaction between the substituents on rings A and C.

To evaluate *N*-protection as amide, we studied the case of the 1-(2'-bromobenzyl)isoquinolin-3-one **4b**. This compound was efficiently obtained by direct bromination of the known benzylisoquinolin-3-one **4a**[12] and then treated with n-Bu3SnH/AIBN, as above, to produce the desired 5-oxoaporphine **5a**[13] in 60% yield. The structure of **5a** was established from its spectroscopic and analytical data, and further confirmed by transformation into glaucine (**3b**) through *N*-methylation with MeI/NaH followed by reduction of the resulting *N*-methyl derivative **5b** with B_2H_6/THF. This is the first synthesis of a 5-oxoaporphine, a family of oxoaporphines whose only known natural member, fuseine (**5c**),[14] may be a biogenetic precursor of aristolochic acids of known antitumour activity.[14]



4 a: X=H
b: X=Br

5 a: R=H, R_1=R_2=R_3=R_4=OMe
b: R=Me, R_1=R_2=R_3=R_4=OMe
c: R=R_3=R_4=H, R_1+R_2=OCH_2O

3b

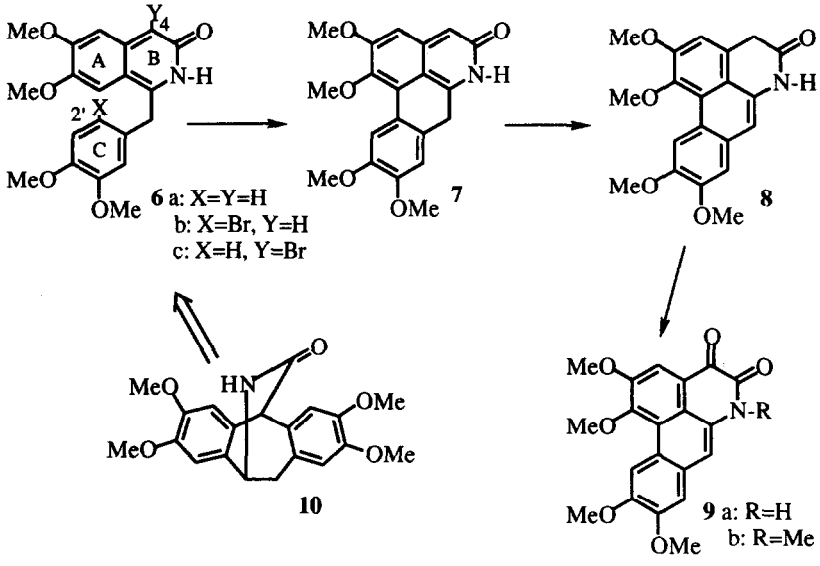
In view of this satisfactory result, we also studied the cyclization of the 1-(2'-bromobenzyl)isoquinoline-3-one **6b**, which is closely related to **4b** and has previously been used by us as starting material in the first total synthesis of a 4,5-dioxoaporphine, pontevedrine (**9b**).[12] When bromobenzylisoquinolinone **6b** was treated with n-Bu3SnH and AIBN as previously, two isomeric compounds were obtained, as deduced from their microanalysis and mass spectrum data. Their aporphine character was easily established from the corresponding ^{1}H NMR data, the major component (60% yield) showing the expected deshielded C_{11} proton signal at 9.10 ppm and the minor component (36% yield) at 9.09 ppm. The rest of the ^{1}H NMR signals of the two compounds were also very similar.

We hypothesized that the minor product of the reaction was the expected 5-oxoaporphine **7** arising from the direct cyclization of the starting bromobenzylisoquinolinone **6b**, and that the major product was the 5-oxoaporphine **8** (probably the result of tautomerization of **7** in the reaction medium or during the work-up of the reaction mixture). The chemical behaviour of both new 5-oxoaporphines is in keeping with these structural assignments: oxoaporphine **7** was irreversibly converted into **8** when allowed to stand in chloroform for 24 hours or more; while, as expected, the more stable oxoaporphine **8** was quantitatively oxidized to norpontevedrine (**9a**) when a basic solution of **8** in acetonitrile saturated with oxygen was stirred at room temperature for four days. Furthermore, when the cyclization mixture obtained from 1-bromobenzylisoquinolinone **6b** was similarly oxidized, norpontevedrine (**9a**) was obtained directly in 90%

yield, probably by transformation of **7** into **8** and subsequent benzylic oxidation of the latter. Norpontevedrine (**9a**) was converted into pontevedrine (**9b**) by *N*-methylation.[12]

We later attempted to obtain the isopavine derivative **10** from 1-benzylisoquinoline-3-one **6c**[15] by inducing biaryl bond formation between C_4 and $C_{2'}$. However treatment of **6c** with tributyltin hydride under the usual conditions was unsuccessful, the only product being compound **6a**, obtained by hydrogenolysis of the C-Br bond.

In conclusion, the above results prove that radical cyclization of 1-benzylisoquinolines constitutes and excellent way of preparing aporphines, 5-oxoaporphines and 4,5-dioxoaporphines. However this interesting route to biaryl bonds seems to be very sensitive to steric factors, the favoured process for compounds such as **2c** and **6c** by the radical arising from the homolytic rupture of th C-Br bond being not the desired C-C coupling but instead the capture of hydrogen .



EXPERIMENTAL SECTION

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1420 spectrophotometer. The nuclear magnetic resonance spectra were recorded on a Bruker WM-250 apparatus in deuteriochloroform solution containing tetramethylsilane as internal standard. Mass spectra were obtained on a Kratos MS 50 TC mass spectrometer. Thin layer chromatography (tlc) was performed using Merck GF-254 type 60 silica gel and methylene chloride-methanol mixtures as eluant; the tlc spots were visualized with ultraviolet light or iodine vapour. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per ref. 16. Dryings were performed with anhydrous sodium sulphate. Reduction of compound **3a** to glaucine (**3b**) was carried out as per ref. 8.

6,7-Dimethoxy-3,4-dihydroisoquinoline.

AIBN (125 mg) and tributyltin hydride (0.62 ml, 1.65 mmol) were added to a solution of bromobenzylisoquinoline **2a**[8] (500 mg, 1.2 mmol) in dry benzene (250 ml), and the resulting mixture was stirred and refluxed for 18 hours in an argon atmosphere. Then the solvent was removed in vacuo and the remaining solid was dissolved in acetonitrile (250 ml) and washed with hexane (3 x 50 ml). The extract was dried and concentrated in vacuo to give a solid residue which on tlc showed a complex mixture of products. This was subjected to column chromatography (eluant: 95:5 dichoromethane/methanol) to afford 160 mg of 6,7-dimethoxy-3,4-dihydroisoquinoline, which was compared with an authentic sample (tlc, ir, ^{1}H nmr).

***N*-Ethoxycarbonyl-1,2,9,10-tetramethoxyaporphine (3a).**

Starting from bromobenzylisoquinoline **2b**[8,10] (500 mg, 1.0 mmol), the same procedure as above gave 0.339 g (81% yield) of aporphine **3a**. Mp 124-125 °C (methanol). Ir (ν, cm^{-1}, KBr): 1690 (C=O). ^{1}H nmr (δ, ppm): 1.30 (t, J=7.1 Hz, 3H, -CH_3), 2.60-3.06 (m, 5H, 2 x -CH_2- and -CH-), 3.66 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 3.93 (s, 3H, -OCH_3), 4.23 (q, J=7.1 Hz, 2H, -CH_2-), 4.39-4.80 (m, 2H, -CH_2-), 6.64 (s, 1H, Ar-H), 6.78 (s, 1H, Ar-H), 8.17 (s, 1H, Ar-H). Ms (m/e, %): 414 ((M+1)$^+$, 19), 413 (M$^+$, 65), 384 (10), 311 (100), 198 (60). Anal. calcd. for $C_{23}H_{27}NO_6$, C 66.83, H 6.54, N 3.39; found, C 66.61, H 6.38, N 3.39.

1-(3',4'-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-one (2d).

Treatment of compound **2c**[6,10] (100 mg, 0.20 mmol) with tributyltin hydride and AIBN as above yielded 80 mg (95%) of benzylisoquinoline **2d**. Mp 134-135 °C (methanol). ^{1}H nmr (δ, ppm): 1.05-1.20 (m, 3H, -CH_3), 2.45-3.40 (m, 6H, 3 x -CH_2), 3.60-3.90 (m, 12H, 4 x -OCH_3), 3.90-4.14 (m, 2H, -CH_2-), 5.05-5.18 (m, 1H, -CH-), 6.10 and 6.19 (2s, 1H, Ar-H), 6.34-6.49 (m, 3H, 3 x Ar-H) and 6.72-6.83 (m, 1H, Ar-H) . Ms (m/e, %): 415 (M$^+$, 4), 264 (100), 236 (18).

1,2,9,10-Tetramethoxy-5-oxonoraporphine (5a).

Compound **4b**[12] (500 mg, 1.1 mmol) was treated with tributyltin hydride and AIBN as above to give 245 mg (60%) of 5-oxonoraporphine **5a**. Mp 253-254 °C (methanol). Ir (ν, cm^{-1}, KBr): 3190 (N-H), 1680 (C=O). ^1H nmr (δ, ppm): 2.90 (m, 2H, $-CH_2-$), 3.60 (m, 2H, $-CH_2-$), 3.70 (s, 3H, $-OCH_3$), 3.91 (s, 3H, $-OCH_3$), 3.92 (s, 3H, $-OCH_3$), 3.93 (s, 3H, $-OCH_3$), 4.58 (m, 1H, -CH-), 6.62 (s, 1H, Ar-H), 6.79 (s, 2H, Ar-H and N-H), 8.13 (s, 1H, Ar-H). Ms (FAB, m/e, %): 357 (M^{+2}, 23), 356 (M^{+1}, 100), 355 (M^+,75), 231 (19), 154 (37), 137 (81), 109 (96). Anal. calcd. for $C_{20}H_{21}NO_5$, C 67.60, H 5.92, N 3.94; found, C 67.47, H 6.17, N 3.73.

1,2,9,10-Tetramethoxy-5-oxoaporphine (5b).

To a stirred suspension of compound **5a** (0.1 g, 0.28 mmol) and 100 mg of sodium hydride in 20 mL of dry THF, 10 mL of MeI were added dropwise over 10 minutes under argon at room temperature, and the mixture was after stirred for 1 hour. Then the mixture was poured into 200 mL of water and the resulting suspension was extracted with methylene chloride (3 x 25 mL). The organic layers were washed with water, dried with anhydrous sodium sulphate and concentrated in vacuo, and the resulting residue was subjected to preparative tlc (eluant: 99:1 methylene chloride/methanol) to give 58 mg (56%) of 5-oxoaporphine **5b**. Mp 260-262 °C (methanol). Ir (ν, cm^{-1}, KBr): 1680 (C=O). ^1H nmr (δ, ppm): 3.21 (s, 3H, $-N-CH_3$), 3.65 (m, 4H, 2 x $-CH_2-$), 3.92 (s, 3H, $-OCH_3$), 3.95 (s, 9H, 3 x $-OCH_3$), 4.27-4.33 (m, 1H, -CH-), 6.80 (s, 2H, 2 x Ar-H), 8.11 (s, 1H, Ar-H). Ms (m/e, %): 369 (M^+, 6), 340 (5), 197 (21), 135 (23), 97 (100). Anal. calcd. for $C_{21}H_{23}NO_5$, C 68.29, H 6.23, N 3.79; found, C 68.16, H 6.48, N 3.57.

Reduction of 1,2,9,10-tetramethoxi-5-oxoaporphine (5b) to 1,2,9,10-tetramethoxy-aporphine (glaucine, 3b).

A mixture of 5-oxoaporphine **5b** (50 mg, 0.14 mmol) and 20 mL of a 1 M solution of diborane in THF was stirred at room temperature for 18 hours under argon. Then, 3 mL of 10% aqueous sodium hydroxide solution were added, and the new mixture was refluxed for 5 minutes and once cold was poured into 100 mL of water. The resulting suspension was extracted with methylene chloride (3 x 15 mL) and the organic extracts were washed with water, dried with anhydrous sodium sulphate and concentrated in vacuo. The solid residue was subjected to preparative tlc (eluant: 95:5 methylene chloride/methanol) and 30 mg (63%) of glaucine (**3b**) were isolated and compared with an authentic sample.[9]

Reaction of 1-(2'-bromo-4',5'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline-3-one (6b) with tributyltin hydride.

Following the same procedure as above, reaction of bromobenzylisoquinoline-3-one **6b** (500 mg, 1.1 mmol) with tributyltin hydride and AIBN in benzene gave a residue which was subjected to preparative tlc (eluant: 95:5 methylene chloride/methanol). From the less mobile spot, 225 mg (60%) of 5-oxodehydroaporphine **8** were isolated. Mp 220-221 °C (methanol). Ir (ν, cm^{-1}, KBr): 1680 (C=O). ^1H nmr (δ, ppm): 3.93 (s, 3H, $-OCH_3$), 3.99 (s, 3H, $-OCH_3$), 4.01 (s, 3H, $-OCH_3$), 4.05 (s, 3H, $-OCH_3$), 4.17 (m, 2H, $-CH_2-$), 6.86 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 9.10 (s, 1H, Ar-H), 9.58 (bs, 1H, N-H). Ms (m/e, %): 353

(M^+, 100), 339 (17), 280 (27), 242 (15), 105 (31). Anal. calcd. for $C_{20}H_{19}NO_5$, C 67.99, H 5.38, N 3.97; found, C 68.24, H 5.53, N 4.13.

The faster spot afforded 145 mg (36%) of 5-oxoaporphine **7**. Mp 195-196 °C (methanol). Ir (ν, cm^{-1}, KBr): 1760 (C=O). ^1H nmr (δ, ppm): 3.92 (s, 3H, $-OCH_3$), 4.03 (s, 3H, $-OCH_3$), 4.04 (s, 3H, $-OCH_3$), 4.06 (s, 3H, $-OCH_3$), 4.24 (m, 2H, $-CH_2-$), 7.02 (s, 1H, Ar-H), 7.12 (s, 2H, 2 x Ar-H), 9.09 (s, 1H, Ar-H). Ms (m/e, %): 353 (M^+, 100), 339 (48), 312 (27), 252 (21).

Conversion of 5-oxonoraporphine 7 into 1,2,9,10-tetramethoxy-6a,7-dehydro-5-oxonoraporphine (8).

A solution of 5-oxoaporphine **7** (50 mg, 0.14 mmol) in chloroform (5 mL) was allowed to stand at room temperature for 24 hours. After removal of the solvent in a rotary evaporator, the solid residue was subjected to preparative tlc (eluant: 95:5 methylene chloride/methanol) to give 40 mg (80% yield) of 5-oxoaporphine **8**.

1,2,9,10-Tetramethoxy-6a,7-dehydro-4,5-dioxonorporphine (norpontevedrine, 9a).

Procedure A: Ten pellets of sodium hydroxide were added to a solution of 250 mg of the crude reaction mixture obtained from compound **6b** in 200 mL of acetonitrile saturated with oxygen. The resulting mixture was stirred at room temperature for 24 hours. After removal of the solvent, the solid residue was subjected to preparative tlc (eluant: methylene chloride-methanol, 85:15) to give 190 mg (90% yield) of norpontevedrine (**9a**) identical to an authentic sample (tlc, ir, uv).[12]

Procedure B: When compound **8** was subjected to the same oxidative conditions as in procedure A, norpontevedrine (**9a**) was obtained quantitatively.

1-(3',4'-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline-3-one (6a).

Reaction of **6c**[15] (100 mg, 0.23 mmol) with tributyltin hydride and AIBN as above gave aquantitative yield of lactam **6a**[12] identical to an authentic sample (tlc, ir, uv).

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