RADICAL CYCLIZATION OF 1-BENZYLISOQUINOLIN-3-ONES: A NEW SYNTHESIS OF THE 4,5-DIOXOAPORPHINE PONTEVEDRINE

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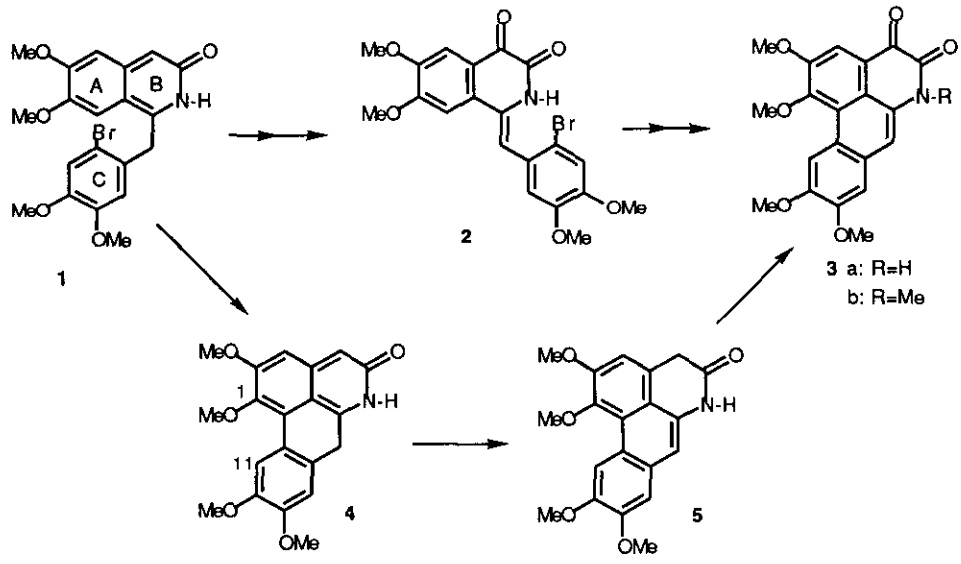
Abstract- Tributyltin hydride induced intramolecular radical cyclization of 1-bromobenzylisoquinolin-3-one (**1**) allowed us to obtain the new 5-oxoaporphines (**4** and **5**), which were converted into the 4,5-dioxoaporphine pontevedrine (**3b**).

As a continuation of our work concerning the synthesis of aporphinoids by routes in which the key step is the formation of the bi-arylic bond by means of a tributyltin-hydride-mediated radical cyclization,[1-3] we describe here the application of this method to the synthesis of 4,5-dioxoaporphines,[4] a small group of oxoaporphine alkaloids of significant biological interest[5] that are only present in very low proportions in natural sources. Pontevedrine (**3b**), the first natural 4,5-dioxoaporphine,[5a,6] has in the past been synthesized in poor overall yield by an intermolecular cycloaddition reaction between 1-methylene-6,7-dimethoxyisoquinoline-3,4-dione and an appropriate aryne,[7] and by photochemical electrocyclization of 1-benzylideneisoquinoline-3,4-dione (**2**)[8] obtained by controlled oxidation of bromobenzylisoquinolin-3-one (**1**).[9] The least efficient step in the latter approach was the formation of the biaryl bond. We therefore decided to investigate its formation by radical cyclization.

When a solution of isoquinolin-3-one (**1**)[9] was refluxed for 18 hours in a dry atmosphere with tributyltin hydride and AIBN in dry benzene,[1] a mixture of two compounds shown by their microanalyses and mass spectra to be isomers was obtained.[10] Their aporphine character was easily established; the expected signal

of the deshielded C_{11} proton appeared at 9.09 ppm in the spectrum of the major isomer (60% yield) and at 9.10 ppm in that of the other (36%). The other ^1H nmr signals of the two compounds were also very similar.[10]



We believe that the minor reaction product is the expected 5-oxoaporphine (**4**) arising from direct cyclization of the starting bromobenzylisoquinolinone (**1**), and that the major product is the 5-oxoaporphine (**5**), which is probably the result of tautomerization of **4** in the reaction medium or during work-up. The chemical behaviour of **4** and **5** agrees with these structural assignments. Oxoaporphine (**4**) proved to be an unstable product which was irreversibly converted into **5** when left standing in chloroform solution for 24 hours, while the more stable oxoaporphine (**5**) was quantitatively oxidized to norpontevedrine (**3a**)[9] when oxygen was bubbled for 15 minutes through a solution of **5** in acetonitrile containing a pellet of sodium hydroxide and the resulting mixture was stirred at room temperature for 24 hours. Furthermore, similar

treatment of the crude reaction mixture resulting from cyclization of 1-bromobenzylisoquinolone (1) yielded norpontevedrine (**3a**) in 90% yield, probably because of the initial transformation of **4** into **5** being followed by oxidation of **5** under the basic conditions of the reaction. As previously,[2,9] norpontevedrine (**3a**) was converted into pontevedrine (**3b**) by *N*-methylation.

This application of our method for constructing the bi-aryl bond in aporphinoids seems to be of general interest for simple, efficient synthesis of 5-oxoaporphines and 4,5-dioxoaporphines. Further work is now under way to confirm this generality.

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10. All new compounds gave satisfactory spectroscopic and analytical data. 5-Oxoaporphine **4**, mp 195-196°C (methanol); ir (ν_{max}, cm^{-1}, KBr): 1760 (C=O); uv (λ_{max}, nm, EtOH): 256, 290, 306, 320, 380 ; ^1H nmr (δ, ppm, $CDCl_3$): 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 (s, 2H, CH_2), 7.02 (s, 1H, Ar-H), 7.12 (s, 2H, 2xAr-H), and 9.09 (s, 1H, Ar-H); ms (m/z, %): 353 (M^+, 100). 5-Oxoaporphine **5**, mp 220-221°C (methanol); ir (ν_{max}, cm^{-1}, KBr): 1680 (C=O); uv (λ_{max}, nm, EtOH): 260, 286 (sh), 316, 352 (sh), 376 (sh); ^1H nmr (δ, ppm, $CDCl_3$): 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 (s, 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) and 9.58 (bs, 1H, N-H); ms (m/z, %): 353 (M^+, 100).

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