

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

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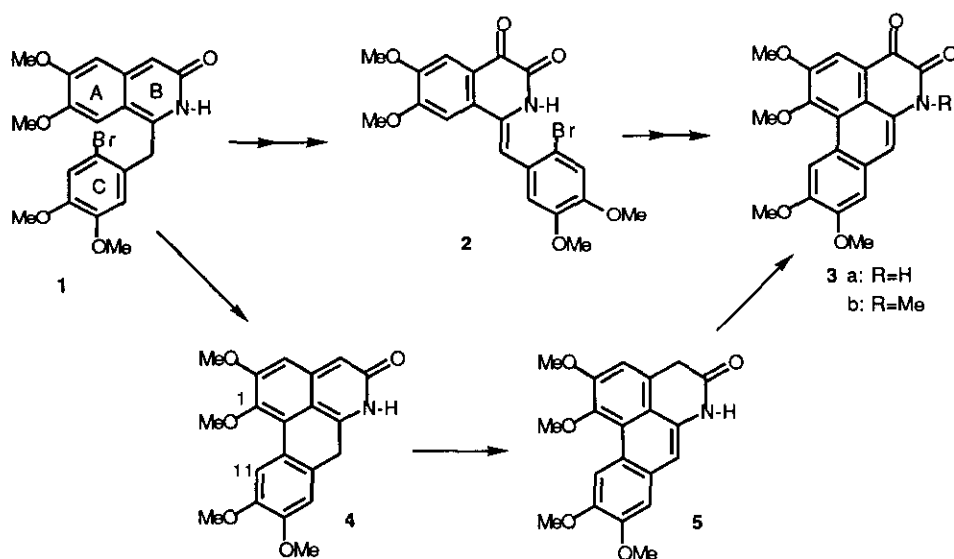
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Abstract- Tributyltin hydride induced intramolecular radical cyclization of
1-bromobenzylisoquinolin-3-one (**1**) allowed us to obtain the new 5-oxoaporphines
(**4** and **5**), which were converted into the 4,5-dioxoaporphine pontevedrine (**3b**).

As a continuation of our work concerning the synthesis of aporphinoids by routes in which the key step is the formation of the bi-aryl 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 interest⁵ 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 C₁₁ 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 pondevedrine (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 ($\nu_{\max}$, cm^{-1} , KBr): 1760 (C=O); uv ($\lambda_{\max}$, 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 ($\nu_{\max}$, cm^{-1} , KBr): 1680 (C=O); uv ($\lambda_{\max}$, 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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