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Electrosynthesis of tryptanthrin

Belen Batanero and Fructuoso Barba*

Department of Organic Chemistry, University of Alcalá, 28871 Alcalá de Henares, Madrid, Spain

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Abstract—Tryptanthrin is obtained in a high yield by cathodic reduction of isatin via a low-energy consumption process where an electron transfer to the oxygen in air is involved.

Tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione) (**2**) is a weak basic alkaloid formed in a number of plant species.[1] This compound possesses antibacterial activity against a variety of pathogenic bacteria, particularly the causative agent of tuberculosis[2] and has displayed remarkable in vitro antileishmanial activity against *Leishmania donovani*,[3] and against *Trypanosoma brucei*, an extracellular protozoan parasite, that is, transmitted by *tsetse* flies.[4]

Tryptanthrin is the active principal of a traditional Japanese herbal remedy for fungal infections.[5] Indolo[2,1-*b*]quinazoline-6,12-dione can be produced by *Candida lipolytica* when grown in media containing an excess of tryptophan,[6] hence the name tryptanthrin. Synthetic methods have been achieved.[1–3,7,8]

The present letter describes a novel, high yielding and interesting synthesis of this useful heterocycle from 1*H*-indole-2,3-dione (**1**).

Cyclic voltammetry of isatin (**1**) in dichloromethane/Et_4NCl as solvent-supporting electrolyte system (SSE) at a Pt or Hg cathode showed two peaks at E_{pc} values of -0.84 V and -1.42 V (vs Ag/Ag^+). Preparative electrolysis of **1** under potentiostatic conditions afforded, at mercury-pool cathode and working at the first wave potential, 92% yield of indolo[2,1-*b*]quinazoline-6,12-dione (**2**), with a charge consumption corresponding to a 0.5 electron/substrate–molecule process. The electrolyzes at platinum and Pb plate cathodes afforded 63% and 60% yields of **2**, respectively. In all cases the only new product was **2**.

The electrosynthesis of **2** can be rationalized through a first electrochemical step where isatin is reduced in a $1e^-$/substrate–molecule process, with hydrogen evolution, to the corresponding anion. This fresh anion reacts with the keto-carbonyl group of another substrate molecule to provide a new anion (**a**) (Scheme 1). This sequence is repeated until isatin is not in solution anymore, and the cathodic current falls almost to a value of zero. The total consumed charge by this mechanism is 0.5 electron per substrate molecule.

Preparative electrolyzes have been performed under an argon atmosphere. However, once the reduction is finished, the cell is opened to air and an electron transfer from **a** to molecular oxygen takes place producing a radical (**b**) and superoxide anion, as is indicated in Scheme 1.

Superoxide anion is coupled with **b** to form a molozonide species, well documented in the literature,[9] which evolves to the ozonide and finally, by hydrolysis, to the corresponding carbonyl and carboxyl groups. The generated carbamic acid is immediately decarboxylated to the amine, which is further condensed with a carbonyl group, allowing tryptanthrin (**2**) to be obtained.

The remaining N-anion of **1** is transformed into isatin during the work-up by proton abstraction from a water molecule.

The yield of **2** depends on the cathode material. This yield is in an inverse relationship with the amount of

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Keywords: Indolo[2,1-*b*]quinazoline-6,12-dione; Electrolysis; Electron-transfer; Isatin.

* Corresponding author. Tel.: +34 91 8854617; fax: +34 91 8854686; e-mail: fructuoso.barba@uah.es

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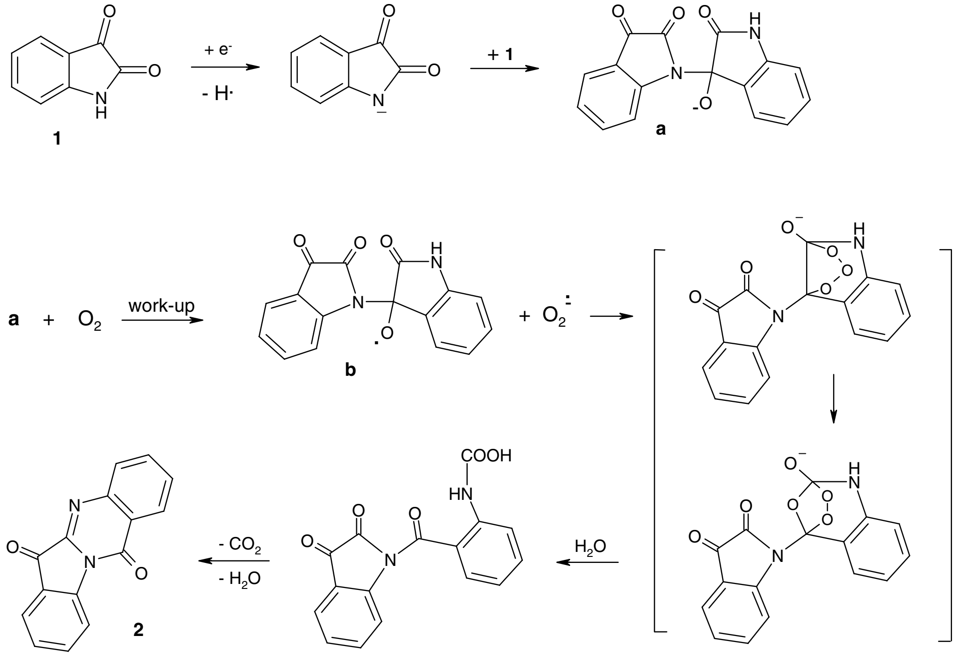

Scheme 1.

isatin recovered in the process. When platinum plate is used as a cathode, the charge consumption of the process is slightly higher (0.5–1 e^-/substrate–molecule) than when mercury is used as a cathode. Nevertheless, as isatin is the side product, it can be recovered and electrolyzed again.

However, preparative electrolysis using a platinum cathode with a circulation of 50% of the theoretical charge for a 0.5 e^-/substrate–molecule process has been performed. Once the potentiostat was switched off, the crude mixture was divided into two identical portions. The first one was immediately treated as indicated in the experimental section,[10] and the second one was allowed to stay for 3 h under an argon atmosphere and with continual stirring. Afterwards it was treated in exactly the same way. It was observed that the yield of **2** in the second portion was two times higher than that of the first one. From this result it can be postulated that with a platinum electrode the formation of the anion **a** is slow, compared to a Hg cathode. A plausible explanation is that when mercury is used, the fresh electrogenerated anion immediately attacks the carbonyl group of adsorbed **1.** However with platinum this attack takes place in solution and consequently the formation of **2** is slow and needs time to be completed.

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References and notes

1. Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 1–19; Mitscher, L. A.; Wong, W. C.; De Meulenere, T.; Sulko, J.; Drake, S. *Heterocycles* **1981**, *15*, 1017.
2. Baker, W. R.; Mitscher, L. A. US Patent 5, 441,955, 1995.
3. Bhattacharjee, A. K.; Skanchy, D. J.; Jennings, B.; Hudson, T. H.; Brendle, J. J.; Werbovetz, K. A. *Bioorg. Med. Chem.* **2002**, *10*, 1979.
4. Scovill, J.; Blank, E.; Konnick, M.; Nenortas, E.; Shapiro, Th. *Antimicrob. Agents Chemother.* **2002**, *46*, 882.
5. Honda, G.; Tabata, M. *Planta Med.* **1979**, *36*, 85.
6. Fiedler, E.; Fiedler, H. P.; Gerhard, A.; Keller-Schierlein, W. *Arch. Microbiol.* **1976**, *107*, 249.
7. Staskun, B.; Wolfe, J. F. S. *Afr. J. Chem.* **1992**, *45*, 5.
8. Eguchi, S. *Top Heterocycl. Chem.* **2006**, *6*, 113–156; Eguchi, S.; Takeuchi, H.; Matsushita, Y. *Heterocycles* **1992**, *33*, 153.
9. Swern, D. In *Organic Peroxides*; Wiley Interscience. Wiley and Sons, 1971; Vol. II, Chapter VII, pp 708–712.
10. The electrochemical reductions were performed under constant-potential conditions in a concentric cell with two compartments separated by a porous (D4) fritted-glass diaphragm and equipped with a magnetic stirrer. A mercury pool (20 cm^2), a platinum plate (12 cm^2) or a lead plate (12 cm^2) were used as the cathode, another platinum plate as the anode, and a saturated calomel electrode (SCE) as the reference. The solvent-supporting electrolyte system (SSE) was nominally anhydrous dichloromethane containing 0.05 M Et_4NCl.
A solution of the electroactive isatin (3.0 mmol in 50 ml of SSE) was electrolyzed, under an argon atmosphere, at a constant potential of −0.9 V (vs SCE). The initial current, 200 mA, decreased as the substrate was consumed. Once the reduction was finished, the solvent in the cathodic solution was removed under reduced pressure. The residue was extracted with diethyl ether (3×100 cm^3)/H_2O and the organic phase dried over Na_2SO_4 and concentrated by evaporation. The resulting solid was chromatographed on a

silica gel (22×3.5 cm) column, using CH_2Cl_2/EtOH (60/1) as eluent. A spectroscopic description of **2** is given below.

Indolo[2,1-*b*]quinazoline-6,12-dione (**2**): mp 267 °C (from EtOH) [Lit,[3] 267–268 °C]. IR(KBr) v_{max}/cm^{-1} 1734, 1694, 1595, 1459, 1353, 1315, 1116, 925, 756. δ_H (300 MHz; $CDCl_3$): 7.43 (1H, t, $J = 7.7$ Hz), 7.67 (1H, t, $J = 8.0$ Hz), 7.75–7.9 (2H, m), 7.91 (1H, d, $J = 7.7$ Hz), 8.0 (1H, d, $J = 8.0$ Hz), 8.44 (1H, dd, $J_1 = 7.7$ Hz, $J_2 = 1.4$ Hz), 8.63 (1H, d, $J = 8.0$ Hz). δ_C (75.4 MHz, $CDCl_3$): 117.9, 121.9, 123.7, 125.4, 127.2, 127.5, 130.2, 130.7, 135.1, 138.3, 144.1, 146.3, 146.6, 158.0, 182.2. MS *m*/*z* (relative intensity) EI: 249 (M^++1, 17), 248 (M^+, 100), 220 (M^+ −28, 33), 192(24), 164(9), 144(6), 124(8), 102(21), 90(14), 76(27), 63(15), 50(18).