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Halogenated *p*-Quinols of Marine Sponges. Synthesis via Anodic Oxidation of Phenols and NHI-Like Rearrangement

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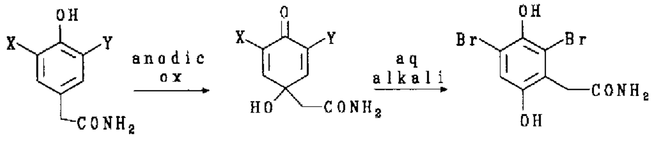
Abstract: Oxidation of either 2,6-dibromo- (1), 2-bromo- (3), or 2-bromo-6-chloro-*p*-acetamidophenol (5) at a Pt anode in aq. $HClO_4$ affords the corresponding common, 2, or rare, 4 and 6, marine halo-*p*-quinols in practicable yields, whereas literature recipes as to either chemical or electrochemical oxidations proved to be ineffective; these halo-*p*-quinols proved to be extremely alkali-labile, in part due to a NHI-like rearrangement.

p-Quinols bearing *o,o'*-Br, such as 2,[1,2] *o*-Br, such as 4,[2] or *o*-Br-*o'*-Cl, such as 6,[2] besides a *p*-acetamido group, which are collectively called verongiaquinols,[2] have been isolated in large, (2), or trace, (4 and 6), amounts from marine sponges of the order Verongida, which are magicians in the manipulation of halotyrosines.[2] Either arene-oxide[3] or phenol-oxidative-coupling routes[2,4] to these central metabolites or to their presumed, although obscure,[3] natural precursors[5] have been proposed.



(1) X=Y=Br (2) X=Y=Br (7)
(3) X=H, Y=Br (4) X=H, Y=Br
(5) X=Cl, Y=Br (6) X=Cl, Y=Br

For any further progress in this area a better understanding is needed of the chemistry of the verongiaquinols, which are also interesting *per se* owing to their antibacterial and antitumoral activities However, only 2 is easily available from sponges of the genus *Aplysina*[1,2] or can be synthesized from 2,5-dibromoquinone, though with expensive organometallics.[6] Proposed oxidative syntheses proved unreliable: the reported high yield (82%) in the oxidation of 1 to 2 with Tl(III)[7] in our hands was only 8%.[2,8] Equally disappointing proved the recipes for the oxidation of non-halogenated phenols at a lead anode[9]: dibromoquinol

2 was thus obtained from **1** in very poor yield.

It is reported here, however, that **2** and the rare verongiaquinols **4** and **6** can be easily obtained by oxidation at a Pt anode in practicable yields, using a rudimentary cell. Thus, either **1**, **3**, or **5** (ca. 2 mmol) were oxidized at a 18 cm^2 Pt anode in stirred 500 ml 0.1 M aq. $HClO_4$ in a divided cell (15 cm length x 4 cm diameter 0.8 M Na_2SO_4 salt bridge), c.d. 0.01 A/cm^2. The non optimized yields (on reacted phenols) of **2**, **4**, and **6** were found (reversed-phase HPLC) to decrease with the progress of the electrolysis, being 44 (33), 36 (26), and 58 (48%) at 60 (90%) conversion of the respective phenols. The anodic mixture at the higher conversion was adjusted to pH 4-5 with solid $NaHCO_3$ and repeatedly extracted with n-BuOH The organic phase was evaporated to dryness *in vacuo*, the solid residue was taken in acetone and filtered and the filtrate was added to Et_2O whereby the crude verongiaquinol was precipitated and was finally purified by silica gel TLC with EtOAc. Recovered yields proved to be 31, 25, and 46% for **2**, **4**, and **6**, respectively.

These verongiaquinols proved to be labile in aqueous alkali at r.t., decomposing slowly at pH 8 but rapidly at higher pH values; degradation of **2**, which was studied in some detail, at pH 12 gave rapidly a complex mixture containing ca. 40% of dibromohomogentisamide (**7**) (reversed-phase HPLC against an authentic sample[11]) formed in a NHI-type rearrangement.[12] The extreme lability of **2** in alkali poses intriguing problems of origin of dibromohomogentisamide in the extracts from the marine sponge *Aplysina fistularis* [5,11]

The verongiaquinols are under study, together with their halophenol precursors, by cyclic voltammetry, while also the electrosynthesis of cyclized analogues, such as the cavernicolins,[2] is under exploration. We hope to report on these studies in a full paper.

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