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Synthesis of 3-Indolyl-2,5-dihydroxybenzoquinones

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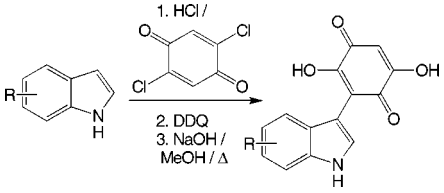
ABSTRACT



3-Indolylquinones can be efficiently prepared by the acid-catalyzed condensation of indoles with 2,5-dichlorobenzoquinone, followed by DDQ oxidation. The resulting dichloroquinones are hydrolyzed to the 3-indolyldihydroxybenzoquinones. The 3-indolylquinone substructure is of interest because of its presence in natural products that modulate biological processes through protein–protein interactions, including the asterriquinones.

The 3-indolylbenzoquinone substructure is present in a number of biologically significant natural products. The asterriquinones, a large group of compounds found in fungi, have two such units.[1] The asterriquinones exhibit a range of biological activities, including antitumor properties and inhibition of HIV reverse transcriptase. One member of the class, asterriquinone A1, has been shown to arrest the cell cycle in G_1 and promote apoptotic cell death.[2] Asterriquinone analogues inhibit the interaction between the SH2 (*Src* homology 2) domains of receptor tyrosine kinases and their "adapter" protein Grb2.[3] Known asterriquinone activities have recently expanded to non-protein, orally active insulin mimetics[4] (Figure 1). All of these properties apparently stem from the ability of asterriquinones to either promote or prevent protein−protein interactions. The asterriquinones are also notable for their modular structures, consisting of two prenylated indoles appended to a dihydroxyquinone core.

Novel synthetic methods are needed for the preparation of 3-indolylquinones. Such methods could be used in total syntheses of asterriquinones or to prepare reagents designed to probe the biological activity of the indolylquinones. The 3-indolylquinone structure may represent a "pharmacophore" for protein−protein interactions, and compounds bearing it should exhibit actions similar to or antagonistic of the bis-

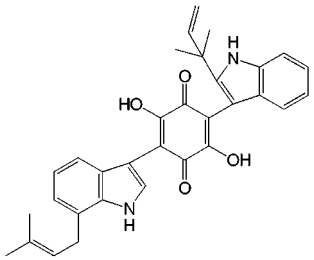


Figure 1. L-783,281, demethylasterriquinone B1.

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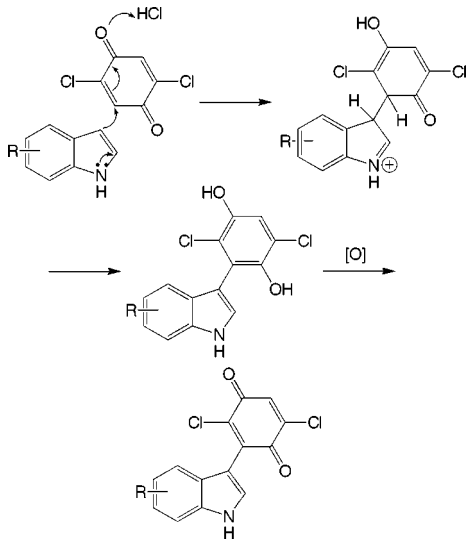
Scheme 1. Proposed Mechanism of the Acid-Catalyzed Condensation of an Indole with 2,5-Dichlorobenzoquinone



indolylquinones. A simple approach to this unit is direct reaction of an indole with a quinone. A method for the synthesis of bis-indolylquinones involving condensation of tetrabromobenzoquinone with 2 equiv of a 2-substituted indole under basic conditions was recently used in a synthesis of tetrahydroasterriquinone E.[5] Historically, the reaction of indole with benzoquinone goes back to 1911, though these workers did not isolate their red product.[6] This reaction was reinvestigated by Bu'Lock in 1951, but the indolylquinone product was only isolated in a low yield.[7] The efficiency of the condensation of excess benzoquinone with 2-methylindole was recently improved by conducting it anaerobically.[8] The second quinone molecule evidently serves to oxidize an initial hydroquinone addition product to the 3-indolylquinone (vide infra). No examples of this reaction beyond indole and 2-methylindole were presented.

As a starting point for the preparation of more highly oxidized 3-indolylquinones, we examined anaerobic condensation reactions (promoted by stoichiometric HCl in THF) of 2-methylindole with a variety of 2,5-dihalogenated or 2,5-dioxygenated benzoquinones. Among the compounds investigated, 2,5-dichlorobenzoquinone was uniquely successful in participating in this reaction. Despite the fact that, as in the precedented reaction, 2 mol of quinone was used per mole of 2-methylindole, the product was a mixture of the 3-indolylquinone and the corresponding hydroquinone. Evidently, unlike the condensation with benzoquinone, the starting quinone does not readily oxidize the hydroquinone product. Consequently, the condensation was followed by addition of dichlorodicyanoquinone (DDQ) to provide the product in a single oxidation state. Even in these early

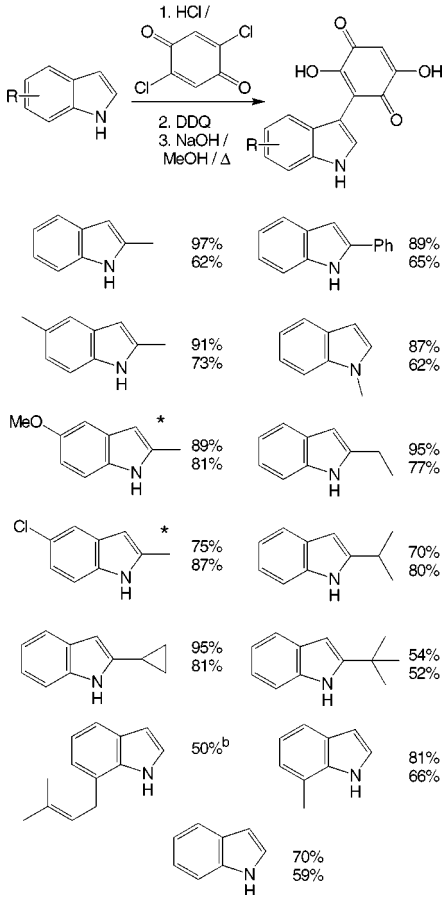


Figure 2. Indoles used in the two-step synthesis of 3-indolyl-2,5-dihydroxyquinones (yield for the condensation step is given above, and the yield for the hydrolysis step below). A superscript b indicates the yield for two steps. The intermediate dichloroquinone is unstable when concentrated and was not isolated. An asterisk indicates that this indole required the modified protocol with 0.3 equiv of HCl.

studies, the product was isolated in very high yield after chromatography. The extended conjugated system engenders strong visible absorption, and the characteristic blue color of the product makes it easy to follow.

Mechanistically, we envision this reaction proceeding as shown in Scheme 1. The nucleophilic carbon 3 of the indole adds to the quinone. A priori, one could propose nucleophilic attack at either the chlorinated or non-chlorinated carbon. The former might be favored on the basis of the "vinylogous acid chloride" character, while the latter might be favored by sterics. Molecular orbital calculations (AM1) show the Mulliken charge at the non-chlorinated carbon is −0.18 and at the chlorinated carbon is −0.1, suggesting that the former should be the favored site of nucleophilic attack. This is desirable for the indole addition step and undesirable for the following hydrolysis step. The initial addition product tautomerizes to the hydroquinone, which is oxidized either by 2,5-dichlorobenzoquinone or DDQ.

The scope of this new reaction sequence was investigated with many 3-unsubstituted indoles. A standard reaction

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(6) Mohlau, R.; Redlich, R. *Ber*. **1911**, *44*, 3605.
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(8) Corradini, M. G.; Costantini, C.; Prota, G.; Schultz, T. M. *Gazz. Chim. Ital*. **1989**, *119*, 153−6.

protocol was adopted using 0.5 mmol of indole and 1 mmol of quinone with 1 equiv of concentrated HCl in 3 mL of THF. After overnight stirring at room temperature, DDQ (1 mmol) is added and the reaction mixture is stirred for 2−4 h. Examples are collected in Figure 2.[9] With a few indoles (marked with a *), trichloro-3-indolylquinone byproducts were formed. This observation is attributed to reaction of the product 3-indolylquinone with HCl, leading to a trichlorohydroquinone that is further oxidized. This process can be eliminated by reducing the HCl to 0.3 equiv.

The reactivity of indoles in the condensation reaction is a consequence of both steric and electronic factors. Indoles bearing electron-withdrawing groups do not participate. The most electron-rich indoles with a carbon 2 substituent are the best reactants. Indoles with no substitution on the heterocycle give a slightly lower yield. The reaction is limited by steric effects, and the limit is reached at 2-*tert*-butylindole. Indoles with any higher *tert*-alkyl substitution fail completely in the reaction.

The 3-indolyldichloroquinones are closely analogous to bis-indolyldibromoquinones earlier used as intermediates in asterriquinone analogue synthesis.[5] Those materials were directly hydrolyzed in alkali, but this deceptively simple transformation proved to be problematic with the 3-indolyldichloroquinones. The unsubstituted quinone carbon can be readily attacked by hydroxide, a process similar to that observed in the formation of the trichloroquinone byproduct above, eventually leading to the hydroxylated 3-indolyldichloroquinone. Diligent experimentation provided a modified reaction protocol involving adding 10% aqueous NaOH (3 mL) to a warm solution of 3-indolyldichloroquinone (0.14 mmol) in MeOH (6 mL) and heating at reflux for 20−30 min. The concentration is crucial, as a 2-fold increase causes a decrease in yield by half. Hydrolysis reactions using this method proceed in 52−87% isolated yield (Figure 2).[10] The 3-indolyldihydroxyquinone products are generally blue-green crystalline compounds.

A challenging aspect of preparing 3-indolyldihydroxy quinones is their instability to standard silica gel chromatography. Reverse-phase HPLC has been used to purify asterriquinone analogues,[5] but a more practical alternative was sought. Oxalic acid-coated silica gel has been used for purification of the asterriquinones.[11] This adsorbent was prepared and used in the purification of all 3-indolyldihydroxyquinones in Figure 2.

In conclusion, the condensation of electron-rich indoles with 2,5-dichlorobenzoquinone followed by hydrolysis with alkali constitutes an efficient synthetic route to the 3-indolyl-2,5-dihydroxyquinone substructures of the asterriquinones, which are desirable for their abilities to modulate protein−protein interactions.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Those indoles failing include indole-2-carboxylic ester, 2-isoprenylindole, 5-nitroindole, and *N*-tosylindole.

(10) All new compounds were characterized by ^{1}H and ^{13}C NMR and MS.

(11) Yamamoto, Y.; Nishimura, K.; Kiriyama, N. *Chem. Pharm. Bull.* **1976**, *24*, 1853−1859.