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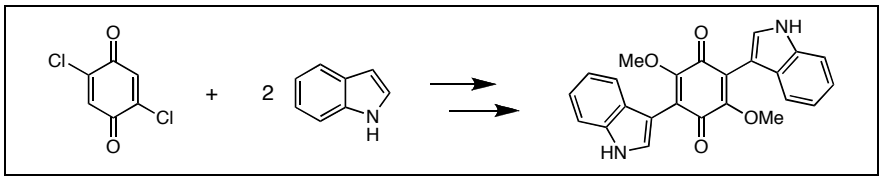

Asterriquinone D was easily synthesized in three steps from 2,5-dichloro-1,4-benzoquinone. The reaction of benzoquinone with indole in the presence of $Pd(OAc)_2$, followed by oxidation with cerium (IV) ammonium nitrate (CAN) produced 3,6-dichloro-2,5-bis (3-indolyl)-1,4-benzoquinone. The methoxylation of the dichloride with NaOH in CH_3OH afforded asterriquinone D.

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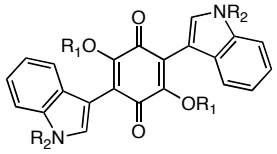
INTRODUCTION

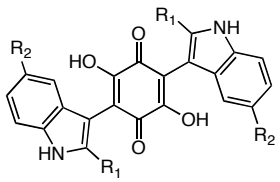
Asterriquinone (**1**), which has a bis(indolyl)benzoquinone skeleton, has been isolated by Yamamoto *et al.* [1] from *Asperigillus terreus* IFO 6123 as one of the intracellular metabolic products. They have also reported its antitumor activity [2] and other asterriquinones [3] such as asterriquinone A-D. There are many reports on other medicinal activities [4]. Didemethylasterriquinone, another isomer of hinnuliquinone (**3**) [5] and cochliodinol (**4**) [6], has similar properties.

The total synthesis of the natural product asterriquinone B_1 and demethylasterriquinone B_1 has been accomplished by Liu *et al.* [7], Tatsuta *et al.* [8], and Pirrung *et al.* [9]. Tetrahydroasterriquinone E has also been reported by Harris *et al.* [10].

Asterriquinone D (**2**) has also been isolated by Yamamoto *et al.* [3] and it has been reported that didemethylasterriquinone D is an attractive lead compound for inhibitors of HIV-1 protease [11]. The compound **2** has no dimethylallyl group; therefore, it is the fundamental compound on the asterriquinone group. We now report a convenient synthesis of asterriquinone D.



1. Asterriquinone: R_1=Me, R_2= -$C(CH_3)_2CH=CH_2$
2. Asterriquinone D: R_1=Me, R_2=H



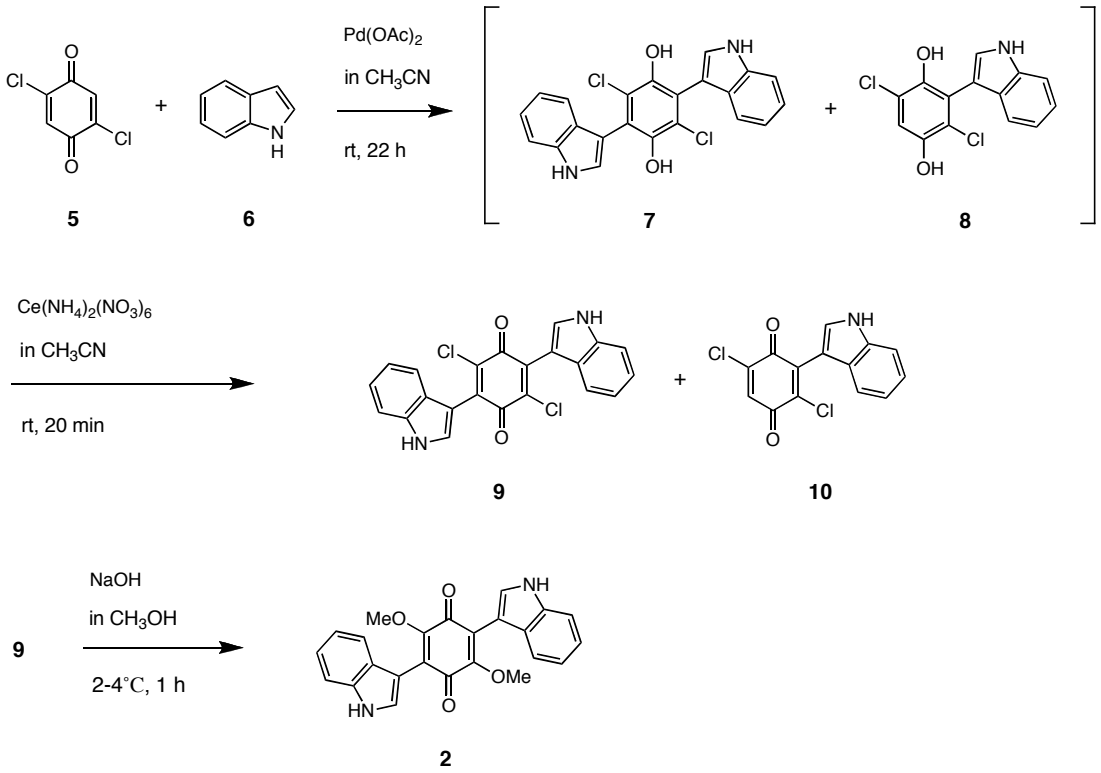
3. Hinnuliquinone: R_1= -$C(CH_3)_2CH=CH_2$, R_2=H
4. Cochliodinol: R_1=H, R_2= -$CH_2CH=C(CH_3)_2$

Figure 1

RESULTS AND DISCUSSION

The reaction of 2,5-dichloro-1,4-benzoquinone (**5**) [12] with 3 equiv. of indole (**6**) in the presence of a palladium (II) acetate catalyst in acetonitrile at room temperature for 22 h produced the hydroquinones (**7** and **8**). Attempts to separate **7** and **8** by column chromatography were unsuccessful. The total ion chromatogram of the EI-MS of the mixture products showed two peaks, and the molecular ion peaks appeared at m/z 408 and 209, respectively. On the other hand, the bands due to the NH and OH stretching modes in the IR spectrum of the products were observed at 3415 cm^{-1} and 3280 cm^{-1},

Scheme 1



respectively. The structures of the hydroquinone (**7** and **8**) were determined by these data.

The oxidation of the mixture (**7** and **8**) with 3 equiv. of cerium (IV) ammonium nitrate (CAN) [13, 14] gave two products, 3,6-dichloro-2,5-bis(3-indolyl)-1,4-benzoquinone (**9**) (23%) and 3,6-dichloro-2(3-indolyl)-1,4-benzoquinone (**10**) (11%) [15]. The product mixture could be separated by the difference in the solubility for chloroform and the ratio of these products was about 2:1. The ^{13}C NMR spectrum of **9** shows only one (C=O) signal, indicative of *para* regiochemistry. On the other hand, the ^{13}C NMR spectrum of **10** contains two (C=O) signals, indicative of the asymmetric regiochemistry.

Asterriquinone D (**2**) was synthesized in 35% yield from **9** by treatment with NaOH in CH_3OH for 1 hour. The compound was insoluble in most organic solvents [3]. Thus, **2** was prepared in three simple steps from the commercially available 2,5-dichloro-1,4-benzoquinone.

EXPERIMENTAL

The ^1H NMR and ^{13}C NMR spectra were obtained using a JEOL JNM-A500 (500 MHz) spectrometer in dimethyl sulfoxide-d_6 at room temperature. Chemical shifts are given in ppm relative to tetramethylsilane as the internal reference standard. Mass spectra were performed using a JEOL JMS-SX 102A mass spectrometer. The infrared spectra were recorded using a Shimadzu IR 470 spectrometer in potassium bromide pellets. The melting points were obtained using a Yanaco MS-S3 micro melting point apparatus (hot-plate type). For preparative column chromatography, Wakogel C-200 silica gel was employed. Thin-layer chromatography (TLC) was accomplished on precoated plates of silica gel 60 $F_{254+365}$(Merck). Indole and 2,5-dichloro-1,4-benzoquinone were purchased from Tokyo Kasei Kogyo Co, Ltd. (Tokyo, Japan).

The Reaction of 2,5-Dichloro-1,4-benzoquinone (5) with Indole (6). To a solution of **5** (100 mg, 0.565 mmol) and **6** (199 mg, 3× 0.565 mmol) in acetonitrile (10 mL) was added palladium (II) acetate (12.7 mg, 0.0565 mmol). The mixture was stirred at room temperature for 22 h. After concentration under reduced pressure, the residue was chromatographed on silica-gel to give the mixture (123 mg) of 3,6-dichloro-2,5-bis(3-indolyl)hydroquinone (**7**) and 3,6-dichloro-2(3-indolyl)hydroquinone (**8**). ir: NH, OH 3500-3100, 1433, 1179, 867, 805, 746 cm^{-1}; EI-ms: m/z (relative intensity) 408 (M^+,100%), 410 (M+2, 66.0), 412(M+4, 12.7), 293 (M^+, 100%), 295 (M+2, 61.4), 297 (M+4, 9.7).

Oxidation of Indolylhydroquinones (7 and 8) with CAN. A solution of **7** and **8** (123 mg) in acetonitrile (8 mL) was cooled to 2-4°C. To the solution was added dropwise over 5 min a solution of cerium (IV) ammonium nitrate (493 mg, 0.9 mmol) in water (3 mL). After stirring for 20 min, the reaction mixture was diluted with water and extracted with chloroform. The chloroform solution was washed with brine, dried over anhydrous sodium sulfate, and evaporated. To the residue was added 1 mL of chloroform and the insoluble product was filtered, and washed with 0.3 mL of chloroform to give 3,6-dichloro-2,5-bis(3-indolyl)-1,4-benzoquinone (**9**) (48.2 mg). The filtrate was concentrated and chromatographed by preparative

TLC (silica gel; $CHCl_3$:EtOH = 5:1) to give **9** (5 mg) and 3,6-dichloro-2-(3-indolyl)-1,4-benzoquinone (**10**) (18.6 mg).

9; mp 282 – 284°C; ir: NH 3370, C=O 1654, 1557, 1421, 1251, 1209, 1114, 743 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.11 (m, 2H, 5'-H), 7.19 (m, 2H, 6'-H), 7.42 (d, 2H, 7'-H, J = 8.3 Hz), 7.50 (d, 2H, 4'-H, J = 8.3 Hz), 7.73 (d, 2H, 2'-H, J = 2.5 Hz), 11.80 (d, 2H, NH, J = 2.5 Hz); ^{13}C nmr (DMSO-d_6) : δ 105.96, 112.04, 119.72, 121.32, 121.65, 125.47, 130.63, 135.80, 135.84, 138.30, 177.48 (C=O); FAB-ms : m/z (relative intensity) 408 ($[M+2H]^+$, 28%), 307 (81), 289 (41). HRMS (FAB): calcd for $C_{22}H_{12}C_{l2}N_2O_2$ $[M+2H]^+$ 408.0432, found 408.0458.

10; mp 166 – 168°C (lit. [15] 124 – 125°C) ; ir: NH 3390, C=O 1673, C=O 1650, 1560, 1421, 1270, 1248, 1010, 881, 748, 596 cm^{-1}; ^{1} H nmr (DMSO-d_6): δ 7.07 (m, 1H, 5'-H), 7.16 (m, 1H, 6'-H), 7.33 (d, 1H, 7'-H, J = 7.5 Hz), 7.47 (d, 1H, 4'-H, J = 8.0 Hz), 7.53 (s, 1H, 5-H), 7.65 (d, 1H, 2'-H, J = 3.0 Hz), 11.88 (s, 1H, NH); ^{13} C nmr (DMSO-d_6): δ 105.39, 111.64, 119.34, 120.86, 121.29, 124.88, 130.27, 132.66, 135.04, 135.40, 138.28, 142.51, 176.75 (C=O), 177.43 (C=O); FAB-ms: m/z (relative intensity) 293 ($[M+2H]^+$, 71%), 232 (8), 192 (22), 79 (100). HRMS (FAB): calcd for $C_{14}H_7C_{l2}NO_2$ $[M+2H]^+$ 293.0010, found 292.9997.

Synthesis of Asterriquinone D (2). A solution of the indolylbenzoquinone (**9**) (22.1 mg, 0.054 mmol) in methanol (30 mL) was cooled to 2-4°C. To the solution was added finely crushed sodium hydroxide (4.3 mg). After stirring for 1 h, the reaction mixture was evaporated under reduced pressure and the residue was chromatographed by preparative TLC (silica gel; $CHCl_3$:EtOH = 10:1) to give **2** (7.5 mg, 35%). Mp > 300°C (lit. [3] > 300°C); ir: NH 3330, C=O 1638, 1581, 1506, 1421, 1278, 1253, 1236, 1124, 1043, 737 cm^{-1}; ^1H nmr (DMSO-d_6) : δ 3.75 (s, 6H, OCH_3), 7.05 (m, 2H, 5'-H), 7.14 (m, 2H, 6'-H), 7.43 (d, 2H, 7'-H, J = 8.0Hz), 7.46 (d, 2H, 4'-H, J = 8.0 Hz), 7.59 (d, 2H, 2'-H, J = 2.5 Hz), 11.62 (s, 2H, NH); ^{13}C nmr (DMSO-d_6): δ 60.06 (OCH_3), 104.08 (3'-C), 111.63(7'-C), 119.29, 120.83. 121.21, 122.81, 126.50 (8'-C), 128.68 (2'-C), 135.75 (9'-C), 153.22 (3-C), 183.13 (1-C); EI-ms: m/z (relative intensity) 398 (M^+, 100%), 355 (57.9), 327 (27.3), 256 (27.7), 128 (33.2), 44 (33.0). HRMS (EI): calcd for $C_{24}H_{18}N_2O_4$ M^+ 398.1267, found 398.1295.

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