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Facile synthesis of 5-Isopropyl-2,3-dimethylbenzene-1,4-diol by Friedel-Crafts and Determination of Partition Coefficient in *n*- Octanol/Water

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Abstract

The wide therapeutic effect of quinone-based drugs has received considerable interest for a long time. In this research, Friedel-Crafts performed a facile synthesis of quinone derivatives using the mixture of Brønsted acid. Reflux of 2,3-dimethylhydroquinone (1), isopropanol, glacial acetic acid, and H_2SO_4 for 15 minutes gave yellow oil product of 5-isopropyl-2,3-dimethylbenzene-1,4-diol (2) as a major product. Characterization using Nuclear Magnetic Resonance (NMR) revealed the methine proton splitting for isopropyl at δ 3.13 ppm, which has a cross-coupling with aromatic carbon at δ 119.6 ppm suggested the substitution of a proton on quinone ring with isopropyl group. Analysis Fourier Transform Infra-Red (FT-IR) showed the broad spectrum of –OH, the vibration of CH sp^3, and isopropyl groups. The minor products identified as 5-isopropyl-2,3-dimethylcyclohexa-2,5-diene-1,4-dione (3), 5-isopropyl-2,3-dimethyl-1,4 phenylene diacetate (4), and 2,3-dimethylbenzene-5,6-isopropyl-1,4-diol (5) confirmed from 2D HETCOR and MS analysis. The partition coefficient (log *P*) of compound 2 showed a higher solubility by 1.9-fold compared to hydroquinone 1. It is suggested that an additional methyl group increased the partition into the organic phase.

1. Introduction

Over the years, the therapeutic effect of black seed Nigella sative to exert antitumor, antioxidant, anticancer, and anti-inflammatory have been reported [1, 2, 3, 4]. Thymoquinone (TQ, 2-isopropyl-5-methyl-1,4-benzoquinone) and thymohydroquinone (THQ, 5-isopropyl-2-methylbenzene-1,4-diol) are two main bioactive compounds found in the essential oil of the black seed. TQ and THQ have a quinone framework, reported as the principal skeleton for its pharmaceutical activity [5]. TQ research is leading because it exhibits selective cytotoxic against many cancer cell types without affecting the normal cells [6, 7]. Some studies on THQ for antitumor agents recently revealed that it works similarly to TQ [8]. Thus, the development of THQ for prospective drug candidates has become an exciting research area.

Account to synthesis TQ has been reported. Synthesis of cationic plastoquinone possesses potent antioxidant activity by using phenyl phosphonium ion channels, increasing the penetrating ability into membranes, mitochondria, cells, and organisms (Fig. 1) [9]. The insertion of bromoalkyl substituent in benzoquinone derivatives , such as in 3-(10-bromodecyl)-5-isopropyl-2-methyl-1,4-benzoquinone [10], 5-(7-bromoheptyl)-2,3- dimethyl- 1,4- benzoquinone and 5- (10- bromodecyl)- 2,3- dimethyl- 1,4- benzoquinone [11], 2- (5- bromoamyl)-3,5-dimethyl-1,4-benzoquinone and 2-(5-bromoamyl)-5-methyl-1,4-benzoquinone have been reported to increase the solubility of the compounds in n-octanol/water system. The presence of alkyl substituents also demonstrated the increasing cytotoxicity against human cancer cell lines and mouse macrophage cell lines [12].

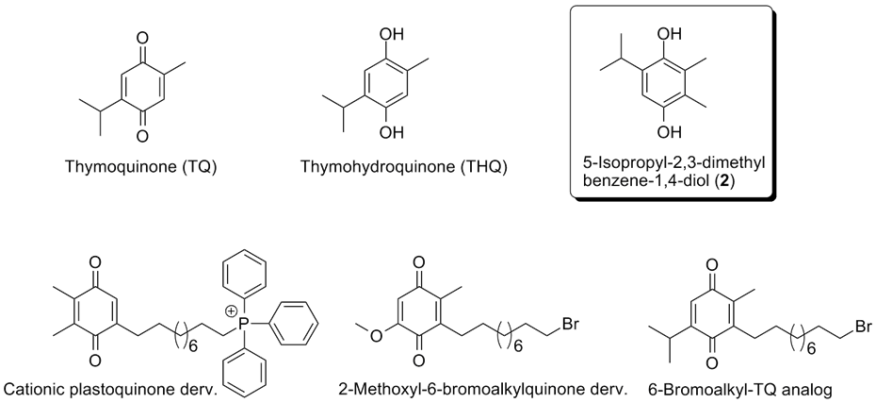


Figure 1. Examples of the reported quinone-based compounds

Due to the overall therapeutic effect of quinone derivatives, this research proposes the synthesis of 5-isopropyl-2,3-dimethylbenzene-1,4-diol (2) (Scheme 1). The synthesis of compound 2 was carried out by Friedel-Crafts using a mixture of Brønsted acid, H_2SO_4, and acetic acid. Isopropanol is used as an electrophile to generate isopropyl carbocation [13]. Compound 2 is fascinating; it has two hydroxyl groups engaged in the hydrogen bonds and the isopropyl or dimethyl groups increasing the hydrophobic contacts with nonpolar residues inside the binding site [14]. Because hydrophobicity is a general property that controls the distribution of compounds between membrane lipid and aqueous phase. The partition coefficients and the steric fits to its natural binding sites can significantly affect [15]. In this regard, each compound's biological function and activity might be different.

Herein, we reported the synthesis of 5-isopropyl-2,3-dimethylbenzene-1,4-diol (2) by modified Friedel-Crafts. The synthesized compound differs from TQ in the number of methyl substituents and hydroxyl groups, making it possible to tailor the hydrophobic-hydrophilic balance to penetrate the cell membrane.

2. Methodology

2.1. Materials and Instrumentation

2,3-Dimethylhydroquinone ($C_8H_{10}O_2$) and sulfuric acid (H_2SO_4 98%) were obtained from Sigma Aldrich, Singapore, and used as received. Isopropanol (C_3H_7OH) and glacial acetic acid (CH_3COOH) were received from Merck, Singapore. N-hexane, ethyl acetate, chloroform, and methanol for column chromatography were obtained in technical grade from the Malang vendor and distilled before use. The solvent for the solubility test, *n*-octanol (organic phase), and phosphate buffer (water phase) were prepared freshly before the experiment.

The FTIR spectrum was measured using Shimadzu 8400S with NaCl salt plate. The UV-Visible was measured using spectrophotometer UV-Visible Shimadzu 1600. ^{1}H-NMR and ^{13}C-NMR were recorded using JEOL ECS400 with TMS as internal standard (δ 0.00 ppm) and $CDCl_3$ as a solvent (^{1}H-NMR, δ 7.26 ppm, singlet; ^{13}C-NMR, δ 77.04 ppm, triplet). High-Performance Liquid Chromatography (HPLC) Shimadzu LC-20AD Prominence connected with COSMOSIL packed column 5C18-MS-II 10ID x 250 mm and FID detector used for purification of the product.

2.2. Experiment

2.2.1. Friedel-Crafts reaction of 2,3- dimethylhydroquinone

The Friedel-Crafts reaction performed based on reported method [16]. The reaction temperature modified to optimize the product yield. 2,3-Dimethylhydroquinone (1) (7.3 mmol; 1 g), isopropanol (21.2 mmol; 1,6 mL), and glacial acetic acid (52.4 mmol; 3 mL) put in the three-neck round bottom flask and stirred until all the solid reagent dissolved. Put the flask on the ice bath then slowly added 4 mL cold H_2SO_4 98% and stirred slowly. Continued stirred until the solution reach to room temperature. After that, refluxed the solution at 55–60°C for 15 minutes, remove from water bath and pour into ice cube, added with water, and slowly stirred to get dark brown precipitate. Filtered the precipitate using Buchner funnel, dried in the oven at 120°C for a night. The crude product as black solid collected in 760 mg, and then subjected into SiO_2 column chromatography using *n*-hexane (100%) as an eluent. The major compound collected from fraction 3 as yellow oil (371 mg; 52.3%).

TLC analysis using *n*-hexane/ethyl acetate (9:1) gave Rf = 0.28; UV-Vis analysis showed the l_{max} 256 nm. The FTIR analysis revealed the bending of CH_3 at 1468 and 1378 cm^{-1}, has a splitting with the same intensity characteristic for isopropyl absorption. The NMR analysis of products is as follows: **5-Isopropyl-2,3-dimethylbenzene-1,4-diol** (**2**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H, H-6), 4.63 (s, 2H, OH), 3.13 (sext., 1H, *J* = 6.8 Hz, H-9), 2.03 (s, 3H, H-7), 2.01 (s, 3H, H-8), 1.20 (d, 6H, *J* = 6.8 Hz, H-10; H-11); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.7 (C-1), 144.6 (C-4), 130.8 (C-5), 122.0 (C-3), 120.1 (C-2), 119.6 (C-6), 27.8 (C-9), 23.8 (C-10; C-11), 12.6 (C-7), 12.5 (C-8). **5-Isopropyl-2,3-dimethylcyclohexa-2,5-diene-1,4-dione** (**3**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H, H-6), 3.04 (sext., 1H, *J* = 6.8 Hz, H-9), 2.05 (s, 6H, H-7; H-8), 1.10 (d, 6H, *J* = 6.8 Hz, H-10, H-11); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 188.2 (C-1), 187.3 (C-4), 154.6 (C-5), 141.3 (C-2), 140.1 (C-3), 130.1 (C-6), 27.2 (C-9), 21.6 (C-10, C-11), 13.6 (C-7; C-8). **5-Isopropyl-2,3-dimethyl-1,4-phenylene diacetate** (**4**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H, H-6), 2.90 (sext., 1H, *J* = 6.8 Hz, H-9), 2.34 (s, 6H, H-2"), 2.04 (s, 6H, H-7; H-8), 1.09 (d, 6H, *J* = 6.8 Hz, H-10; H-11); ^{13}C-NMR (100 MHz, $CDCl_3$) d 169.8 (C-1'; C=O), 148.8 (C-1), 144.3 (C-4), 140.1 (C-5), 132.3 (C-3), 128.2 (C-

2), 120.1 (C-6), 28.2 (C-9), 21.9 (C-2"), 21.6 (C-10, C-11), 12.9 (C-7; C-8).

2.2.2. Determination of partition coefficients (log *P*) in n-octanol/water system

Determination of partition coefficient (log *P*) carried out by shake-flask methods using aqueous phases buffered phosphate (pH 7.4) and saturated *n*-octanol according to the published procedure [17, 18]. Ten mM of compound 2 dissolved in saturated *n*-octanol. Partition of *n*-octanol/water prepared in the ratio of 3:7 (v/v). The partition system is shaken using an orbital shaker for one hour at room temperature. After equilibrium, both the *n*-octanol and aqueous phase were injected into HPLC eluted with acetonitrile/water (70:30) in 3% acetate acid. Log *P* calculated according to equation 1:

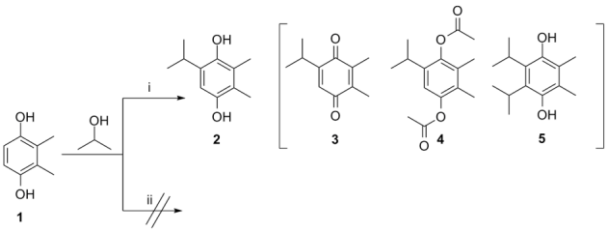
$$\text{Log } P = log \frac{C_{octanol}}{C_{water}} = log \frac{A_o/V_o}{A_w/V_w} \quad (1)$$

C stands for the compound's concentration, A the area of the compound under the spectrum curve, V the volume of the phase, and subscripts, w and o refer to the water phase and organic phase (*n*-octanol phase).

3. Results and Discussion

3.1. Friedel-Crafts reaction of 2,3- dimethylhydroquinone

The synthetic pathways to obtain THQ derivatives compound 2–5 is described in Scheme 1. The mixed acid, H_2SO_4, and CH_3COOH act as a protic acid catalyst and isopropanol act as a nucleophile which is protonated by acid and eliminate H_2O to give isopropyl carbocation. Since the intermediate cation is stable and does not undergo rearrangement, it becomes an excellent electrophile to initiate Friedel-Crafts reaction [13].



Scheme 1. Reagents and reaction conditions: (i) CH_3COOH, H_2SO_4 98%, 55–60°C, 15 min; (ii) H_2SO_4 98%, 55–60°C, 15 min

TLC analysis of crude product gave three spots; Rf1 0.05, Rf2 0.15, and Rf3 0.28 eluted using 100% n-hexane. The spot in origin is confirmed as unreacted starting material 2,3-dimethylhydroquinone (1). Separation using SiO2 column chromatography collected fraction 3 as the primary isolated product (370.96 mg; 52.3%). Even fraction 3 has one spot in the TLC plate. Further analysis using HPLC detected four individual peaks (Fig. 2). It is predicted that four compounds consist in fraction 3. Further separation using HPLC was carried out using isocratic eluent MeOH/ACN (90:10 v/v) to give four compounds 2–5.

The NMR data show in Table 1. Proton and carbon NMR of compounds 2–4 are quite similar. By combining the Mass Spectra (MS) and NMR data analysis, the structure determination of 2–4 is proposed. Due to the similarity of the quinone skeleton, only compound 2 was discussed in detail. The analogous structure of compounds 3 and 4 is derived based on compound 2.

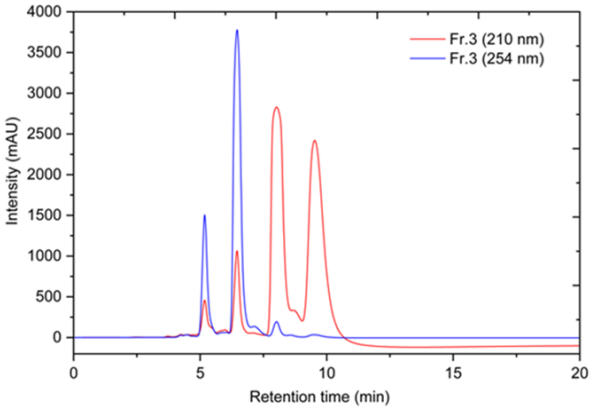


Figure 2. The HPLC spectrum of fraction 3 consists of four peaks analyzed at 210 nm and 254 nm, suggesting four compounds

Table 1. NMR data for compounds 2, 3, and 4

Comp.	Position	d_C, type	d_H (*J* in Hz)
2	1	148.7	-
	2	120.1	-
	3	122.0	-
	4	144.6	-
	5	130.8	-
	6	119.6	6.95 (s, 1H)
	7	12.6	2.03 (s, 3H)
	8	12.5	2.01 (s, 3H)
	9	27.8	3.13 (sext., 1H, *J* = 6.8)
	10-11	23.8	1.20 (d, 6H, *J* = 6.8)
	1' (-OH)	-	4.63 (s, 2H)
	4' (-OH)	-	-
3	1	188.2	-
	2	141.3	-
	3	140.1	-
	4	187.3	-
	5	154.6	
	6	130.1	6.47 (s, 1H)
	7	13.6	2.05 (s, 3H)
	8	13.6	2.05 (s, 3H)
	9	27.2	3.04 (sext., 1H, *J* = 6.8)
	10-11	21.6	1.10 (d, 1H, *J* = 6.8)
4	1	148.8	-
	2	128.2	-
	3	132.3	-
	4	144.3	-
	5	140.1	-
	6	120.1	7.03 (s, 1H)
	7	12.9	2.04 (s, 3H)
	8	12.9	2.04 (s, 3H)
	9	28.2	2.90 (sext., 1H, *J* = 6.8)
	10-11	21.6	1.09 (d, 1H, *J* = 6.8)
	1' (C=O)	169.8	-
	2"	21.9	2.34 (s, 6H)

The chemical shift analysis of compound 2 is defined at 6.95 ppm (s, 1H) for aromatic proton and 3.13 ppm (sext., 1H, *J* = 6.8 Hz) for methine proton in isopropyl framework CH_3-CH-CH_3 [19]. The other proton was observed at 1.27 ppm (d, 6H, *J* = 6.8 Hz) for an equivalent methyl proton directly attached to isopropyl CH_3-CH-CH_3. HMBC correlation from H-9 (δ 3.13) to C-4 (δ 144.6), C-5 (δ 130.8), and C-6 (δ 119.6) suggested that isopropyl attached at C-5. Furthermore, HMBC cross-coupling showed the correlation of H-8 (δ 2.01) with C-1 (δ 148.7) and C-3 (δ 122.0); H-7 (δ 2.03) with C-2 (δ 120.1) and C-4 (δ 144.6), then situated the dimethyl substituent at C-2 and C-3, respectively. The presence of OH is considered from the singlet peak at δ 4.36 ppm, which shifted into δ 4.76 ppm by D_2O exchange NMR. Furthermore, FTIR analysis confirmed the broad spectrum at 3613-3275 cm^{-1}. Thus, the structure determination of compound 2 is depicted in Fig. 3.

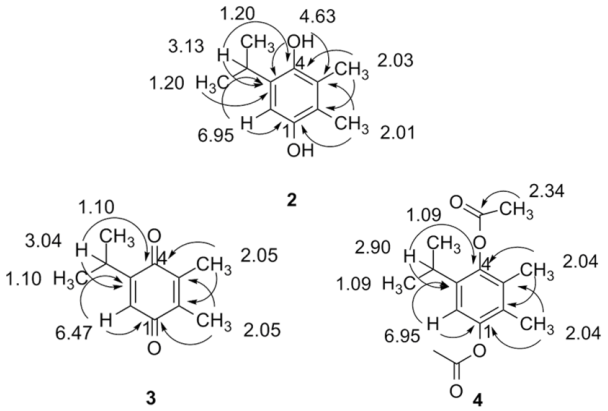


Figure 3. Structure of compounds 2, 3, and 4

Analysis of compound 3 predicted the presence of aromatic carbonyl (C=O) from the quinone skeleton at 187.3 and 188.3 ppm. Proton at C-3 is shifted to a lower chemical shift 6.47 ppm (s, 1H) due to the shielding effect of carbonyl groups. HMBC analysis showed the cross-coupling of H-9 (δ 3.04) to C-4 (δ 187.3), C-5 (δ 154.6), and C-6 (δ 130.1). The sharp peak of aromatic carbonyl from FTIR analysis was detected at 1649 cm^{-1}. Compound 4 based on FTIR spectrum showed the ester group C=O at 1769 cm^{-1}. Carbon NMR analysis suggested the characteristic of C=O ester at 169.8 ppm. Cross-coupling of methyl proton at 2.34 ppm with C=O ester supports the prediction for compound 4. The structure of compound 3 and 4 are shown in Fig. 3. Thus, the ESI analysis of compound 2–5 are determined by MS analysis data in Table 2.

Table 2. MS analysis for compound 2–6

Comp.	Experiment	Calculation	
	m/z	m/z	Formula
2	180.1153	180.1150	$C_{11}H_{16}O_2$
3	178.1004	178.0994	$C_{11}H_{14}O_2$
4	264.1367	264.1362	$C_{15}H_{20}O_4$
5	222.1625	222.1620	$C_{14}H_{22}O_2$
6	194.2773	194.2701	$C_{12}H_{18}O_2$

The Friedel-Crafts reaction was also performed using H_2SO_4 without CH_3COOH (Scheme 1, route ii). A similar reaction was carried out. The crude reaction mixture was purified by SiO_2 column chromatography and gave fraction four as a significant isolated product. Proton NMR analysis of the isolated products did not provide any characteristics of compounds 2–5. Further analysis using MS spectrometry detected molecular ion peak m/z 194.2773 ($C_{12}H_{18}O_2$ required 194.2701), indicating compound 6 has four degrees of unsaturation arising from the benzene ring. From this experiment, the presence of acetic acid is essential for protecting the hydroxyl group, leading to the insertion of isopropyl into the benzene ring [13].

3.2. Partition coefficient (log *P*) in n-octanol/water system

Partition coefficient (log *P*) of compounds tabulated in Table 3. Log *P* experiment using shake flask methods of compound 2 is 1.9-fold higher than compound 1, which expresses that the substitution of isopropyl increased the ability of the compound to penetrate the cell wall [20]. A log *P* value of 2 is identical to TQ, suggesting that the compound's pharmacology effect is possibly similar to TQ [8]. The calculated log *P* data showed the same order as the experiment. It means that the partition ratio of the *n*-octanol/water system (3:7 v/v) used in this experiment is appropriate [18].

Further, the Topological Surface Area (TPSA) analysis showed that compound 2 has a higher surface polarity than starting material 1 or TQ. It is predicted that hydroxyl groups are more potent in activating hydrogen bonding than carbonyl groups [21]. The hydroquinone headgroup reported has similar polarity with the quinone, but it can form stronger hydrogen bonding with water or *n*-octanol solution.

Table 3. Partition coefficient (log *P*) of the synthesized products

Comp.	Log *P*		TPSA[c]
	Experiment[a]	Calculated[b]	
TQ	2.04	2.00	34.14
1	1.02	1.22	40.46
2	1.93	2.45	40.46

a) Shake-flask method then chromatographed using HPLC
b) ALOGPS2.1 program
c) Predicted using molinspiration program

4. Conclusion

Friedel-Crafts reaction of 2,3-dimethylhydroquinone (1) using mixed acid, H_2SO_4, and glacial acetic acid gave 5-isopropyl-2,3-dimethylbenzene-1,4-diol (2) as a significant product. The formation of side products quinone derivatives compounds 3–5 was observed as minor products. Partition coefficient analysis in *n*-octanol/water systems showed the increasing solubility of compound 2, meaning the presence of isopropyl substitutions may influence the activity of the compound to penetrate the cell membrane.

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