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Convenient Synthesis of 3-Acyl- and 3-Alkyl-1,2-naphthoquinones

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Synopsis. 3-Acyl-1,2-naphthalenediols prepared by the photoinduced addition reaction of 1,2-naphthoquinone with alkanals were oxidized with Fremy's salt to give 3-acyl-1,2-naphthoquinones in good yields. The diols were reduced with amalgamated zinc, followed by oxidation to afford 3-alkyl-1,2-naphthoquinones in moderate yields.

The quinone moiety plays an extremely important role in biological systems. For instance, it is well-known that 2-methyl-1,4-naphthoquinone (menadione) is a key structure for the physiological activities of the vitamin K series.[1] 3-Alkyl-1,2-naphthoquinones, analogues of menadione, are therefore of interest for their biological activities. Acylquinones are also distributed in nature.[2] However, no effective synthesis of 3-aklyl- and 3-acyl-1,2-naphthoquinones has been reported so far.[3] A direct introduction of an alkyl or acyl group into the quinonoid nucleus of 1,2-naphthoquinone by the Friedel-Crafts reaction has been very difficult, because 1,2-naphthoquinone easily decomposes under acidic reaction conditions owing to the inherent unstableness of the quinones.[4] However, the photochemical reaction of 1,2-naphthoquinone (**1**) with alkanals proceeded under neutral conditions via a radical process to give 3-acyl-1,2-naphthalenediols (**2**).[5] The products, **2**, directly produced by introducing an acyl group into position 3 of **1**, can be useful starting materials for the preparation of the title compounds. In this paper we describe the effect of an additive metal ion on the yields of **2** and the preparation and physical properties for the title quinones.

Results and Discussion

After irradiation of an acetonitrile-benzene (3 : 7 v/v) solution of **1** and acetaldehyde with a 300-W high-pressure mercury arc lamp through Pyrex, 3-acetyl-1,2-naphthalenediol (**2a**) was easily isolated by column chromatography in 7 % yield. In order to increase the yield of **2a**, the reaction was undertaken in the presence of a metal perchlorate, the results of which are shown in Table 1. The effect of the additive metal perchlorates on the yield of **2a** increased in the order Mg(II)>Co(II)>Ce(III)>Ni(II)>Ca(II)>Li(I). Thus, the effect of magnesium perchlorate on the yields of **2a** was superior to that of other metal perchlorates examined in this work. Though the molar ratio of $Mg(ClO_4)_2$ to **1** was varied up to 3 equivalents, the yield of **2a** remained almost unchanged, as shown in Table 1. Thus, the yield of **2a** increased up to 30% when the reaction was carried out in the presence of one equivalent mole of $Mg(ClO_4)_2$.

When tetrabutylammonium perchlorate (n-Bu_4NClO_4) was used in the place of metal perchlorates, no additive effect on the yield of **2a** could be observed. This result clearly indicates that the increase in the yield of **2a** is not caused by perchlorate anion, but by metal cation.[6] The irradiation of **1** with propanal, butanal, and pentanal in the presence of $Mg(ClO_4)_2$ also yielded **2b**, **2c**, and **2d** in yields of 29, 27, and 25%, respectively (Table 1 and Eq. 1).

Table 1. Effect of Metal Perchlorates on the Yields of 3-Acyl-1,2-naphthalenediol (**2**) in the Photoaddition Reaction of 1,2-Naphthoquinone (**1**) with Alkanal[a)]

Alkanal	Metal perchlorate	Molar ratio **1** : Metal	Yield of **2** /%[b)]
CH_3CHO	c)		7
	$LiClO_4$	1 : 1	9
	$Mg(ClO_4)_2$	1 : 1	30
		1 : 2	28
		1 : 3	26
	$Ca(ClO_4)_2 4H_2O$	1 : 1	16
	$Co(ClO_4)_2 6H_2O$	1 : 1	28
	$Ni(ClO_4)_2 6H_2O$	1 : 1	18
	$Ce(ClO_4)_3 8H_2O$	1 : 1	21
	n-Bu_4NClO_4	1 : 1	5
CH_3CH_2CHO	$Mg(ClO_4)_2$	1 : 1	29
$CH_3(CH_2)_2CHO$	$Mg(ClO_4)_2$	1 : 1	27
$CH_3(CH_2)_3CHO$	$Mg(ClO_4)_2$	1 : 1	25

a) Reaction was carried out in acetonitrile-benzene (3 : 7 v/v). b) Yield is isolated yield based on the quinone used. c) Reaction was carried out in the absence of metal perchlorate.

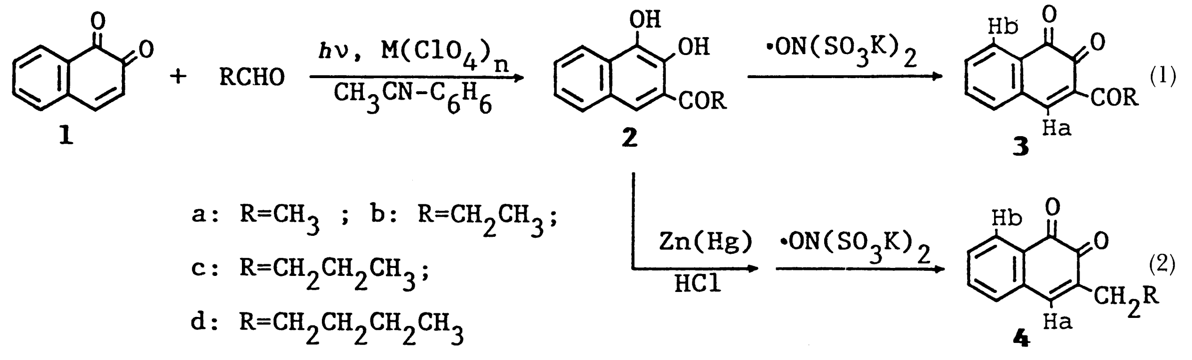
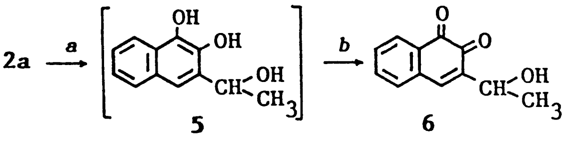


Table 2. ^{1}H NMR, IR, and Mass Spectral Data of 3-Acyl-1,2-naphthoquinone (**3**)

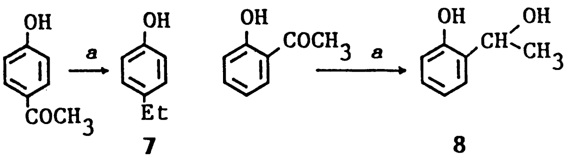
Quinone	^{1}H NMR(CDCl$_3$, δ)	IR(KBr)/cm^{-1}	MS m/z(M$^+$)	Mp/°C$^{a)}$	Yield/%$^{b)}$
3a	2.65 (s, CH$_3$), 7.58—7.78 (m, 3H), 8.16 (d, Hb), 8.22 (s, Ha)	1715, 1690, 1665	200	134—136	98
3b	1.16 (t, CH$_3$), 3.04 (q, CH$_2$), 7.57—7.77 (m, 3H), 8.16 (d, Hb), 8.20 (s, Ha)	1705, 1680, 1665	214	135—137	97
3c	0.98 (t, CH$_3$), 1.69 (six, CH$_2$), 2.99 (t, CH$_2$), 7.56—7.76 (m, 3H), 8.16 (d, Hb), 8.18 (s, Ha)	1680, 1660	228	88—89	95
3d	0.94 (t, CH$_3$), 1.37 (six, CH$_2$), 1.64 (qui, CH$_2$), 3.01 (t, CH$_2$), 7.57—7.77 (m, 3H), 8.15 (d, Hb), 8.17 (s, Ha)	1680, 1660	242	138—139	96

a) Uncorrected melting point. b) Yield is isolated yield based on used **2**.

Potassium nitrosodisulfonate (Fremy's salt; •ON(SO$_3$K)$_2$) is an useful reagent for the oxidation of phenols to benzoquinones (i.e., *o*-benzoquinones and *p*-benzoquinones) under very mild conditions. However, one of the disadvantages of this oxidation is that electron-withdrawing substituents in phenol can usually inhibit the reaction.[7)] However, when 3-acyl-1,2-naphthalenediols (**2**) were treated with Fremy's salt in Teuber's conditions[8)] (see Experiment), the oxidation smoothly proceeded to give 3-acyl-1,2-naphthoquinones (**3**) in almost quantitative yields (Table 2 and Eq. 1). This successful oxidation with Fremy's salt in spite of the presence of electron-attracting acyl group is probably due to the 1,2-diol structure of **2**.



(3)



(4)

a LiAlH$_4$-AlCl$_3$ in Et$_2$O then H$^+$
b Air or Silica gel

It has been reported that alkyl aryl ketones are readily reduced by mixed hydride (LiAlH$_4$-AlCl$_3$) to hydrocarbons.[9)] However, when this reducing agent was applied for the reduction of **2a**, the alcohol (**5**) was obtained, which was very unstable and easily oxidized into the corresponding quinone (**6**) during purification (Eq. 3). This finding suggests that an intramolecular hydrogen-bonded carbonyl group in **2a** is hardly reduced to methylene group even with the powerful reducing agent. This was supported by the fact that the reduction of 4′-hydroxyacetophenone with the reducing reagent yielded 4-ethylphenol, but that of 2′-hydroxyacetophenone afforded 2-(1-hydroxyethyl)phenol (Eq. 4).

We next examined the Clemmensen reduction of **3a**. The ketone **3a** was conveniently reduced by the Clemmensen reduction to 3-ethyl-1,2-naphthalenediol, which was unstable and partially oxidized into 3-ethyl-1,2-naphthoquinone (**4a**) and other unidentified products under chromatographic separation conditions. Therefore, the reducing product was not isolated and, subsequently, oxidized with Fremy's salt to afford **4a** in 58% yield (Eq. 2). Similarly, other 3-acyl-1,2-naphthalenediols (**2b**—**d**) were reduced with amalgamated zinc, followed by oxidation to yield 3-alkyl-1,2-naphthoquinones (**4b**—**d**) in considerable yields, as listed in Table 3.

Table 3. ^{1}H NMR, IR, and Mass Spectral Data of 3-Alkyl-1,2-naphthoquinones (**4**)

Quinone	^{1}H NMR(CDCl$_3$, δ)	IR(KBr)/cm^{-1}	MS m/z(M$^+$)	Mp/°C$^{a)}$	Yield/%$^{b)}$
4a	1.18 (t, CH$_3$), 2.48 (q, CH$_2$), 7.17 (s, Ha), 7.27—7.64 (m, 3H), 8.04 (d, Hb)	1698, 1662	186	97—98	58
4b	0.98 (t, CH$_3$), 1.58 (six, CH$_2$), 2.41 (t, CH$_2$), 7.17 (s, Ha), 7.27—7.63 (m, 3H), 8.04 (d, 1H)	1700, 1665	200	72—73	60
4c	0.94 (t, CH$_3$), 1.39 (m, CH$_2$), 1.52 (m, CH$_2$), 2.44 (t, CH$_2$), 7.17 (s, Ha), 7.29—7.64 (m, 3H), 8.04 (dd, Hb)	1695, 1660	214	78—80	55
4d	0.91 (t, CH$_3$), 1.32—1.61 (m, CH$_2$×3), 2.43 (dt, CH$_2$), 7.17 (s, Ha), 7.30—7.64 (m, 3H), 8.04 (dd, Hb)	1695, 1658	228	90—92	52

a) Uncorrected melting point. b) Yield is isolated yield based on used **2**.

Though the yields of **2** are still not satisfactory, there is no method superior to the present one for a direct introduction of an acyl group into position 3 of **1**. Therefore, the present methods provide a short-step synthesis of the title compounds, which have not been reported so far.

Experimental

The NMR spectra were measured on a JEOL GX-270 FT-NMR spectrometer using TMS (δ=0.00) as an internal standard. IR spectra were recorded on a Hitachi 260-50 spectrometer. The mass spectra (MS) were recorded with ESCO EMD-05A spectrometer. Elemental anslysis data (C and H) agreed within ±0.3% for the calculated values. The yields of 3-acyl-1,2-naphthalenediols are based on the quinone used.

Photochemical Preparation of 3-Acyl-1,2-naphthalenediols (2). The typical procedure was as follows: To a solution of 1,2-naphthoquinone (79 mg, 0.5 mmol)[10] and magnesium perchlorate (111.6 mg, 0.5 mmol) in 20 ml of $CH_3CN-C_6H_6$ (3 : 7 v/v) an excess amount of acetaldehyde (1 ml) was added; and the solution was irradiated with a 300-W high-pressure Hg arc lamp through Pyrex for 15 h at room temperature. The irradiating solution was concentrated and 10% of an aqueous solution of NH_4Cl was added to the residue, and then extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and concentrated in vacuo. The residual oil was chromatographed on a silica-gel column using benzene as an eluting solvent. The first yellow component was collected and evaporated to give **2a** as orange prisms (60 mg, 30%).

In all other cases, **2b—d** were also easily isolated by silica-gel chromatography with benzene in 29, 27, and 25% yields, respectively. The physical properties of these products were described in our previous paper.[5]

Synthesis of 3-Acyl-1,2-naphthoquinones (3). The diol (**2**, 0.5 mmol) was dissolved in MeOH (10 ml) and added to a solution of Fremy's salt (0.6 g) dissolved in water (20 ml) and 1/6 M KH_2PO_4 solution (5 ml; 1 M=1 mol dm^{-3}). After stirring for 1 h at room temperature, the solution was extracted with $CHCl_3$; the organic layer was then washed with water, dried over Na_2SO_4, and finally evaporated to give the quinone (**3**) as red needles in almost quantitative yields. The acylquinones were purified by recrystallization from benzene-hexane. The physical properties of the quinones are shown in Table 2.

Reduction of 2a with $LiAlH_4$-$AlCl_3$. To an ether solution (10 ml) of $LiAlH_4$ (24.7 mg, 0.65 mmol) a solution of granular $AlCl_3$ (86 mg, 0.65 mmol) in 10 ml of ether was added rapidly. Five minutes later, a solution containing 101 mg (0.5 mmol) of **2a** and 66.7 mg (0.5 mmol) of $AlCl_3$ in 20 ml of ether was introduced at a rate such as to produce gentle reflux. After stirring for 30 min, the reaction mixture was carefully hydrolyzed and ether layer was separated; the aqueous layer was then extracted with ether. The combined ether extracts were dried and evaporated to give **5**, which was easily oxidized during purification by silica-gel column to 3-(1-hydroxyethyl)-1,2-naphthoquinone (**6**): orange plates (43 mg, 47%), mp 103—105 °C; ^{1}H NMR ($CDCl_3$) δ=1.48 (d, 3H, CH_3, J=7.0 Hz), 2.65 (br, 1H, OH), 4.94 (q, 1H, CH, J=7.0 Hz), and 7.35—8.12 (m, 5H, aromatic protons); IR (KBr) 3410 (m, OH), 1693 (w, C=O), and 1655 (s, C=O) cm^{-1}.

When 4′-hydroxyacetophenone was treated as described above, 4-ethylphenol was obtained in 63% yield. However, a similar treatment of 2′-hydroxyacetophenone with $LiAlH_4$-$AlCl_3$ gave 2-(1-hydroxyethyl)phenol in 54% yield: oil; ^{1}H NMR ($CDCl_3$) δ=1.53 (d, 3H, CH_3, J=6.6 Hz), 3.43 (s, 1H, OH), 5.01 (q, 1H, CH, J=6.6 Hz), 6.79—7.17 (m, 4H, aromatic protons), and 8.15 (s, 1H, OH); IR ($CHCl_3$) 3600 (OH) and 3375 (OH) cm^{-1}.

Synthesis of 3-Alkyl-1,2-naphthoquinones (4). A mixture of amalgamated zinc prepared from 600 mg of zinc sand and 45 mg of mercury(II) chloride, 0.3 ml of water, 0.6 ml of conc. hydrochloric acid, and 0.5 mmol of **2a** was refluxed for 1.5 h. The reaction mixture was cooled to room temperature and extracted with ether. The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated to afford 3-ethyl-1,2-naphthalenediol as a pale red oil. Since the diol was unstable, it was subsequently oxidized with Fremy's salt without isolation to give 3-ethyl-1,2-naphthoquinone (**4a**). The quinone was purified by preparative TLC and then carefully recrystallized from benzene-hexane. The other quinones, **4b—d**, were prepared by the same methods from **2b—d** and were obtained as red prisms or needles; their physical properties and yields are summarized in Table 3.

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2) R. H. Thomson, "Naturally Occurring Quinones," Academic Press, London (1971), Chaps. 1, 3, and 4.

3) 3-Methyl-1,2-naphthoquinone has been synthesized via very complicate processes (6 steps) starting from benzyl methyl ketone. This is only report for the synthesis of the quinone. F. Weygand and K. Schoder, *Ber.*, **74**, 1844 (1941).

4) Since 1,2-naphthoquinone is highly sensitive to acid or heat, the treatment of the quinone with acetyl chloride under the Friedel-Crafts conditions resulted to decompose the quinone into a blackish viscous oily substance. Cf. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, New York (1967), Vol. 1, p. 712.

5) A. Takuwa, *Bull. Chem. Soc. Jpn.*, **49**, 2790 (1976). K.Maruyama, A. Takuwa, S. Matsukiyo, and O. Soga, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1414. Another product was naphthalene-1,2-diol monoacyl esters.

6) The reason for the effect of a metal ion on the yield of **2** is still not clear.

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