Chemistry of naphthazarin derivatives
11.* Trisubstituted hydroquinone derivatives in the preparative synthesis of naphthazarins

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The Friedel—Crafts acylation of trimethylhydroquinone, 3,5-diethyl-2-hydroxyhydroquinone, and 3,5-diethyl-1,2,4-trimethoxybenzene with dichloromaleic or citraconic anhydride in an $AlCl_3$—NaCl melt is accompanied by *o*-*C*-dealkylation to afford functionally substituted naphthazarins.

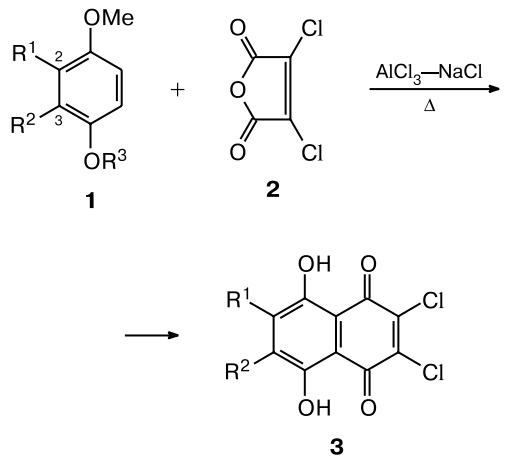
Key words: hydroquinone derivatives; dichloromaleic anhydride, citraconic anhydride; 5,8-dihydroxy-1,4-naphthoquinone, naphthazarin; the Friedel—Crafts reaction; dealkylation.

Cycloacylation of 2,3-disubstituted hydroquinone ethers of the type **1** with dichloromaleic anhydride (**2**) is a simple and efficient method for the formation of structures related to naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) **3** (Scheme 1).[2,3] The reaction is accompanied by *O*-dealkylation to liberate hydroxy groups in the product formed. This is caused, first, by drastic conditions of the process and, second, the possibility to form a thermodynamically favorable naphthazarin structure.** The reductive dehalogenation of dichloronaphthazarins of the type **3** [5] can produce a series of natural naphthazarins[6] and helpful by-products in the synthesis of antibiotics.[7—10] This reaction is also the basis of an approach to the synthesis of pharmacologically active polyhydroxynaphthazarins, *viz.*, sea urchin metabolites and their analogs.[11,12]

It is noteworthy that most of 2,3-disubstituted hydroquinones used are not commercially available compounds. For example, *O*,2,3-trimethylhydroquinone was synthesized from dimethylanisole by the Vilsmeier formylation[13] followed by the oxidative cleavage of 4-methoxy-2,3-dimethylbenzaldehyde formed by hydrogen peroxide in an acidic medium.[14]

In the present work, we showed that the target naphthazarin structures can also be prepared from more accessible 2,5-di- and 2,3,5-trialkylhydroquinones.*** This is associated with the fact that *C*-dealkylation can occur under the conditions of the Friedel—Craft acylation.[15] Evidently, the efficiency of this cycloacylation depends on the easiness of migration (elimination) of the alkyl substituent from position 5 of the substrate used. We performed comparative studies of the reactivities of hydroquinone derivatives **4** and **5a,b** in the reactions with dichloromaleic (**2**) and citraconic (**6**) anhydrides.

Scheme 1



1: R^1, R^2 = H, Alk, OMe; R^3 = H, Me
3: R^1, R^2 = H, Alk, OH

The condensation of compound **2** with thymohydroquinone (**4**) affords dichloro(methyl)naphthazarin (**3a**) in high yield. The absence of even trace amounts of alternative dichloro(isopropyl)naphthazarin **3b** under the reaction conditions is related to the higher proneness of the isopropyl group to undergo elimination compared to the methyl group. Under the same conditions, the condensation of 2,3,5-trimethylhydroquinone (**5a**) with com-

* For Part 10, see Ref. 1.

** Hereafter, as well as in Ref. 4, methyl ether of substituted hydroquinones are shown to give higher yields of the desired products in this reaction than nonmethylated substrates.

*** For example, 2,3,5-trimethylhydroquinone (**5a**), unlike *O*,2,3-trimethylhydroquinone, is a commercially available product (Fluka).

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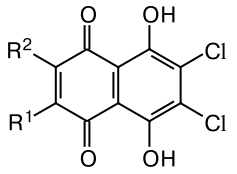
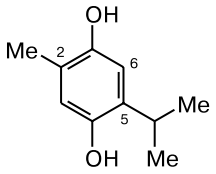
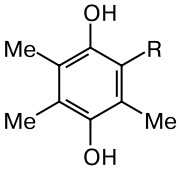


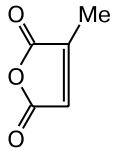
3a—c



4



5a,b

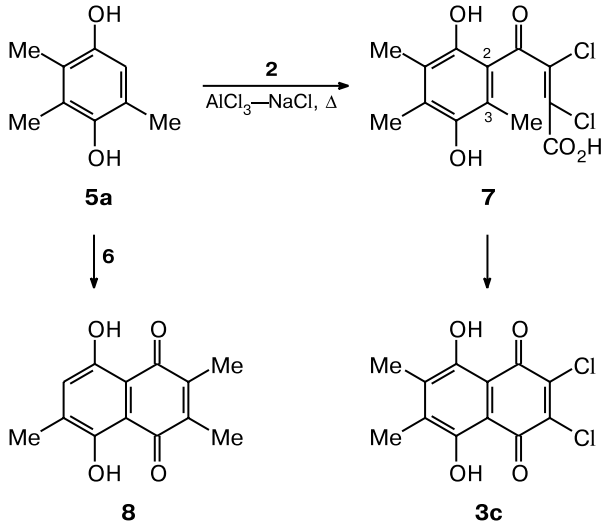


6

3: R^1 = H, R^2 = Me (**a**); R^1 = Pr^i, R^2 = H (**b**); R^1 = R^2 = Me (**c**)
5: R = H (**a**), Me (**b**)

pound **2** gave dichloro(dimethyl)naphthazarin **3c** (75%) (Scheme 2).

Scheme 2

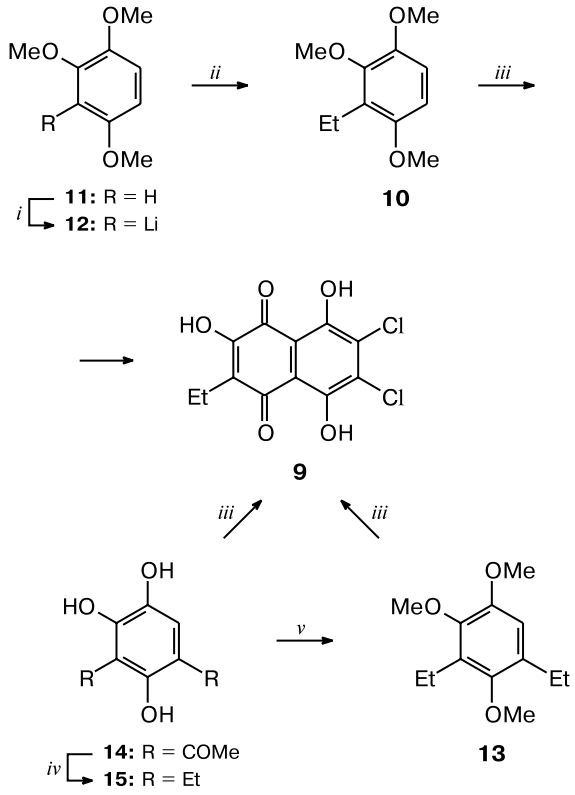


Durohydroquinone (**5b**) was not involved in cycloacylation, indicating that, first, the reaction always begins from the electrophilic attack of the acylating substrate on the unsubstituted carbon atom of the benzene ring and, second, the acylating agent formed from compound **2** cannot directly substitute the alkyl group. The latter is eliminated only in the second step of cycloacylation (**7** → **3c**) (see Scheme 2).

Citraconic anhydride (**6**) also turned out to be an efficient cycloacylating agent with respect to 2,3,5-trimethylhydroquinone (**5a**), which made it possible to synthesize trimethylnaphthazarin (**8**) in 82% yield (see Scheme 2). This reaction is a good alternative to the approach based on the use of the Diels—Alder reaction in the synthesis of compound **8**.[16]

The practical application of the developed approach is the preparative synthesis of 6,7-dichloro-3-ethyl-2,5,8-trihydroxy-1,4-naphthoquinone (**9**),[17] which is the key by-product in the synthesis of one of the sea urchin pigments, being the active principle of a drug Hystochrome™.[18] Two schemes of the synthesis of compound **9** have been described previously.[11,12] One of them is based[12] on the cycloacylation of 3-ethyl-1,2,4-trimethoxybenzene (**10**), which can be synthesized, in turn, by the lithiation of 1,2,4-trimethoxybenzene (**11**) followed by ethylation of lithium derivative **12** with diethyl sulfate (Scheme 3).

Scheme 3



Reactants and conditions: *i*. BuLi, THF, −30 °C, 2 h;
ii. Et_2SO_4, 0 °C, then ~20 °C, 2 h;
iii. **2**, $AlCl_3$—NaCl, 190 °C, 5 min;
iv. Zn/Hg, HCl, refluxing, 2 h; *v*. Me_2SO_4, NaOH.

We have shown that 3,5-diethyl-1,2,4-trimethoxybenzene (**13**) can be used as an equivalent of synthon **10**. Compound **13** is readily synthesized by reduction of diacetyltrihydroxybenzene **14** followed by methylation of diethyltrihydroxybenzene **15** formed with dimethyl sulfate (see Scheme 3). The condensation of derivative **13** with compound **2** afforded the desirable product **9** in 59% yield. The cycloacylation of trihydroxy-substituted de-

rivative **15**, unlike trimethyl ether **13**, occurred less efficiently: product **9** was obtained in 35% yield only.

Thus, the reactions of 2,5-di- and 2,3,5-trisubstituted hydroquinone derivatives with cyclic anhydrides in an $AlCl_3$—NaCl melt afford cycloacylation products, *viz.*, functionally substituted naphthazarins. The use of accessible trisubstituted hydroquinone derivatives substantially simplifies the general scheme of synthesis of the important representatives of this class of compounds.

Experimental

Melting points were determined on a Boetius heating stage and are uncorrected. IR spectra were recorded on a Bruker Vector 22 spectrophotometer in $CHCl_3$. ^{1}H NMR spectra were obtained on a Bruker AC-250 spectrometer (250.13 MHz) in $CDCl_3$ using Me_4Si as the internal standard. Mass spectra (EI) were obtained on an LKB-9000S instrument with a direct inlet at energies of ionizing electrons of 18 and 70 eV. The course of reactions and purity of synthesized compounds were monitored by TLC on Silufol-254 plates in a hexane—acetone (2 : 1) mixture. The yields of synthesized compounds were not optimized. Compounds **2**, **5a**, and **6** are commercially available (Aldrich, Fluka). Thymohydroquinone (**4**)[19] and durohydroquinone (**5b**)[20] were synthesized according to known procedures.

Cycloacylation of hydroquinone derivatives 4 and 5a with anhydrides 2 and 6 (general procedure). A mixture of a substituted hydroquinone (5 mmol) and anhydride (10 mmol) was introduced with stirring at 160—170 °C into a melt of anhydrous $AlCl_3$ (26.7 g, 0.2 mol) and NaCl (5.85 g, 0.1 mol). The temperature was increased to 207—210 °C, and the melt was additionally stirred for 3—4 min. The reaction mixture was cooled, 5% HCl (400 mL) was added, and left for 12 h. The precipitated product was separated, washed with hot water, and dried to a constant weight.

6,7-Dichloro-5,8-dihydroxy-2-methyl-1,4-naphthoquinone (3a) was synthesized from hydroquinone **4** and anhydride **2**. The yield was 77%, m.p. 147—149 °C (from light petroleum) (*cf.* Ref. 2: m.p. 148—150 °C). IR ($CHCl_3$), ν/cm^{-1}: 3500—2200 (α-OH); 1618 (C=O); 1578 (C=C); 1562, 1443, 1406, 1342, 1300, 1276, 1078, 1024. ^{1}H NMR, δ: 2.34 (d, 3 H, Me, J = 1.2 Hz); 7.11 (dq, 1 H, H(7), J = 1.2 Hz, J = 0.5 Hz); 12.56 (s, 1 H, OH); 12.88 (d, 1 H, OH, J = 0.5 Hz).

6,7-Dichloro-5,8-dihydroxy-2,3-dimethyl-1,4-naphthoquinone (3c) was synthesized from hydroquinone **5a** and anhydride **2**. The yield was 75%, red needles, m.p. 238—240 °C (from toluene) (*cf.* Ref. 4: m.p. 235—236 °C). IR ($CHCl_3$), ν/cm^{-1}: 3600—2300 (α-OH); 1608 (C=O); 1562 (C=C); 1448, 1393, 1291, 1275, 1203, 1109. ^{1}H NMR, δ: 2.28 (s, 6 H, 2 Me); 13.20 (s, 2 H, 2 OH). MS (18 eV), m/z (I_{rel} (%)): 286/288/290 $[M]^+$ (100), 285/287/289 $[M - 1]^+$ (41).

5,8-Dihydroxy-2,3,6-trimethyl-1,4-naphthoquinone (8) was synthesized from hydroquinone **5a** and anhydride **6**. The yield was 83%, red needles, m.p. 167—170 °C (sublim.) (*cf.* Ref. 16: m.p. 165 °C (sublim.)). IR ($CHCl_3$), ν/cm^{-1}: 3600—2300 (α-OH); 1601 (C=O); 1576 (C=C); 1456, 1439, 1403, 1380, 1364, 1305, 1283, 1192, 1129, 1108, 1067, 1011. ^{1}H NMR, δ: 2.20 (s, 6 H, 2 Me); 2.29 (d, 3 H, Me, J = 1.0 Hz); 7.01 (q, 1 H, H(7), J = 1.0 Hz); 12.79, 13.12 (both s, 1 H each, OH). MS (18 eV), m/z (I_{rel} (%)): 233 $[M + 1]^+$ (14); 232 $[M]^+$ (100).

3,5-Diethyl-1,2,4-trihydroxybenzene (15). Solid zinc amalgam[21] (600 g), 3,5-diacetyl-1,2,4-trihydroxybenzene (**14**)[22] (31.5 g, 0.15 mol), and concentrated HCl (375 mL) were placed in a 3-L flask. The reaction mixture was heated to boiling with vigorous stirring. After 30 min, compound **14** (31.5 g, 0.15 mol) and concentrated HCl (375 mL) were added portionwise. The mixture was refluxed with stirring for 3 h, and the hot solution was decanted and left for 12 h. A solid layer formed on the solution surface and a precipitate formed were separated, washed with ice-cold water (30 mL), and dried to a constant weight. Crude 3,5-diethyl-1,2,4-trihydroxybenzene (**15**) was obtained (58 g), the content of the main substance was 80% (^{1}H NMR). ^{1}H NMR, δ: 1.18, 1.20 (both t, 3 H each, Me, J = 7.8 Hz); 2.52, 2.68 (both q, 2 H each, CH_2, J = 7.8 Hz); 4.35, 4.54, 5.15 (all br.s, 1 H each, OH); 6.56 (s, 1 H, H arom.). The product was used for the synthesis of 3,5-diethyl-1,2,4-trimethoxybenzene (**13**) without purification.

3,5-Diethyl-1,2,4-trimethoxybenzene (13). Crude diethyltrihydroxybenzene **15** (56.9 g) was treated with 10% NaOH (400 mL) with vigorous stirring under nitrogen with Me_2SO_4 (94.5 g, 0.75 mL), maintaining the temperature of the mixture not above 40 °C. After Me_2SO_4 was added, the reaction mixture was heated for 30 min in a boiling water bath. After the mixture was cooled, the organic layer was separated, and the aqueous layer was extracted with benzene. The combined organic layers were washed with 5% NaOH and water and dried with anhydrous $CaCl_2$. The solvent was removed under reduced pressure. The residue was fractionated *in vacuo*. The fraction with b.p. 133—139 °C (7 Torr) was 3,5-diethyl-1,2,4-trimethoxybenzene (**13**), the yield being 45.9 g (82%). ^{1}H NMR, δ: 1.19, 1.24 (both t, 3 H each, Me, J = 7.8 Hz); 2.64, 2.66 (both q, 2 H each, CH_2, J = 7.8 Hz); 3.71, 3.82, 3.83 (both s, 3 H each, OMe); 6.60 (s, 1 H, H arom.).

6,7-Dichloro-3-ethyl-2,5,8-trihydroxy-1,4-naphthoquinone (9). A mixture of 3,5-diethyl-1,2,4-trimethoxybenzene (**13**) (44.8 g, 0.2 mol) and anhydride **2** (76.8 g, 0.46 mol) was added at 140 °C with vigorous stirring to a melt of anhydrous $AlCl_3$ (410 g, 3.07 mol) and NaCl (80.8 g, 1.38 mol). The temperature of the mixture was increased to 195 °C, and the melt was stirred for 5 min. The reaction mixture was cooled and hydrolyzed with a solution of concentrated HCl (300 mL) in H_2O (4.0 L). After 12 h, a precipitate was separated, washed with hot water (2.0 L), and dried. Product **9** was isolated by the extraction with hot chloroform and recrystallized from an EtOH—H_2O mixture. Compound **9** was obtained in 59% yield (36.0 g), m.p. 156—158 °C (*cf.* Ref. 12: m.p. 156—158 °C). ^{1}H NMR, δ: 1.18 (t, 3 H, Me, J = 7.7 Hz); 2.66 (q, 2 H, CH_2, J = 7.7 Hz); 7.42 (br.s, 1 H, β-OH); 12.07 (br.s, 1 H, α-OH); 13.60 (s, 1 H, α-OH). MS, m/z (I_{rel} (%)): 302/304/306 $[M]^+$ (100).

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