Ebenaceae extractives. Part 11.[1] The synthesis of 7-methyljuglone. A re-examination

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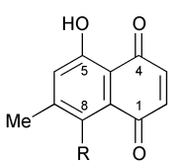
The Friedel–Crafts reaction between maleic anhydride and 4-chloro-3-methylphenol yields, besides 8-chloro-5-hydroxy-7-methylnaphthoquinone **1**, helminthosporin **5** and its 8-chloro derivative **6** and, after methylation, methyl (*E*)-β-(5-chloro-2-methoxy-4-methylbenzoyl)acrylate **4**. Treatment of the chloronaphthoquinone **1** with tin(II) chloride in hydrochloric acid and tetrahydrofuran followed by iron(III) chloride converts it efficiently into 7-methyljuglone **2**.

Introduction

The classic procedure[2,3] for the preparation of 7-methyljuglone **2** involves first the reaction of maleic anhydride with 4-chloro-3-methylphenol in an aluminium chloride–sodium chloride melt to give the chloronaphthoquinone **1**, followed by the replacement of the chlorine substituent by hydrogen in a four-step sequence. We have now investigated the by-products of the Friedel–Crafts reaction and have also found a simple one-step procedure for the reductive dechlorination of the chloronaphthoquinone **1**.

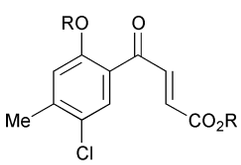


1 R = Cl
2 R = H

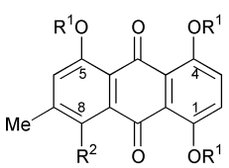
Results and discussion

Repeated solvent extraction and chromatography separated the crude product from the Friedel–Crafts reaction into three components. The chloronaphthoquinone **1** was the most abundant of these followed by the expected[4] monoacylated product, the *trans*-aroylacrylic acid **3**, which we characterised as its *O*,*O*′-dimethyl derivative **4**.

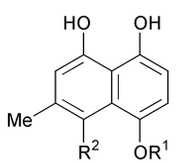
The third component was a poorly soluble red solid which showed UV–visible light absorption similar to that[5] of 1,4,5-trihydroxyanthraquinone and which appeared from its mass spectrum to be a mixture of two closely related substances. Repeated TLC enabled us to isolate from this component a small amount of helminthosporin **5** identical with an authentic specimen; larger-scale preparations gave yields of up to 0.9%. The methylation of another sample of the red solid and repeated TLC afforded the trimethyl ether (**7**) of the second component, 8-chlorohelminthosporin **6**. The formation of helminthosporin and its chloro derivative in a single operation from reactants containing only one aromatic ring between them is remarkable and requires explanation. In the presence of aluminium chloride, naphthoquinones can undergo dimerisation and subsequent loss of hydrogen to give binaphthyldiquinones[6] and consequently can act as weak *reducing* agents under these conditions. We suggest that two molecules of the initial Friedel–Crafts product, the chloronaphthoquinone **1**, react in this way and thereby bring about the reduction of a third molecule to form the corresponding naphthoquinol **10**. This then reacts with more maleic anhydride to give a tautomeric form of the chloroanthraquinone **6**, which undergoes further reduction to form the corresponding anthraquinol. Finally, replacement of the chlorine at C-8 by hydrogen to give helminthosporin **5** occurs by the type of reaction sequence described below for the reductive dechlorination of the chloronaphthoquinone **1**.



3 R = H
4 R = Me



5 $R^1 = R^2 = H$
6 $R^1 = H$; $R^2 = Cl$
7 $R^1 = Me$; $R^2 = Cl$



8 $R^1 = R^2 = H$
9 $R^1 = Me$; $R^2 = H$
10 $R^1 = H$; $R^2 = Cl$

The original four-step procedure[2,3] for the replacement of the chlorine atom in **1** by hydrogen is tedious and we therefore sought an alternative reduction method. Treatment of the quinone with tin(II) chloride in methanol and hydrochloric acid followed by iron(III) chloride gave a 72% yield of 7-methyljuglone **2**, but the reaction mixture was not homo-

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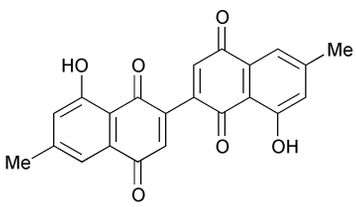
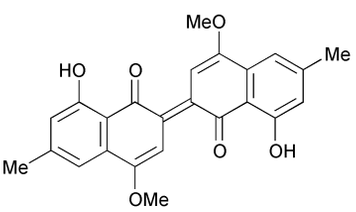
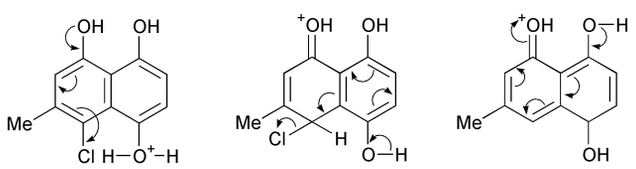
geneous and small amounts of mamegakinone **11**[7] and diosindigo A **12**[8] could be isolated from the crude product. These presumably resulted from the oxidative dimerisation of the intermediate naphthalenetriol **8** and of its monomethyl ether **9**, respectively. The use of tetrahydrofuran in place of methanol ensured a homogeneous reaction mixture for the reduction and an 81% yield of 7-methyljuglone **2** resulted. Tin(II) chloride in hydrochloric acid is known[9] to effect the reductive removal of chlorine attached to the quinonoid ring of a naphthoquinone but such a reaction involving the benzenoid ring was unexpected. It is significant that replacement of a chlorine atom in the *peri* position by hydrogen would lead to the relief of steric strain.[10] We suggest that the chloronaphthoquinone **1** is first reduced by the tin(II) chloride to the naphthoquinol **10**. In the presence of acid a proton is supplied to the *peri* carbon atom carrying the chlorine as in structure **13**. Loss of a proton and expulsion of chloride ion followed by further proton loss, as shown in the structures **14** and **15**, would give 7-methyljuglone **2**.



11



12



13 **14** **15**

Experimental

IR spectra were measured for potassium bromide discs and UV–visible spectra were obtained for ethanolic solutions using Perkin-Elmer Infracord 237 and 137UV spectrophotometers, respectively. Molar absorptivity (ε) values are given in units of $dm^3\ mol^{-1}\ cm^{-1}$. ^1H NMR spectra were measured for solutions in deuterochloroform with tetramethylsilane as internal standard using a Varian HA 100 spectrometer. Electron-impact mass spectra were measured on an AEI MS-70 instrument at 70 eV. TLC was performed on silica gel (Merck GF_{254}) plates prepared using either distilled water or aqueous 3% oxalic acid with chloroform for development. For column chromatography the silica gel was washed with 2 M hydrochloric acid before use. 'Light petroleum' refers to the fraction with bp 60–80 °C.

Reaction of maleic anhydride with 4-chloro-3-methylphenol

Repetition of the Friedel–Crafts reaction between the chlorophenol[11] (4 g) and maleic anhydride (8 g) in molten aluminium chloride–sodium chloride exactly as originally described[2] gave a crude product that was dried and extracted (Soxhlet) with light petroleum. After evaporation of the solvent the resulting solid was separated by column chromatography, using mixtures of light petroleum and benzene, into two main fractions, A and B. The faster-moving band A yielded a solid (450 mg), which was triturated with ether to remove the chloronaphthoquinone **1**. The red, insoluble residue (48 mg) after TLC on silica gel–oxalic acid using dichloromethane and crystallisation from aqueous methanol gave a mixture (10 mg) of the chloroanthraquinone **6** and helminthosporin **5** (Found: M^+, 304.0144 and 270.0535. Calc. for $C_{15}H_9{}^{35}ClO_5$: *M*, 304.0139. Calc. for $C_{15}H_{10}O_5$: *M*, 270.0528). Repeated column chromatography using tetrachloromethane–benzene (9 : 1) finally gave pure helminthosporin **5** as red needles (7 mg), mp 227–228 °C (lit.,[12] 227 °C), from ethanol, identical (IR, UV, mixed mp) with an authentic specimen. A further sample of the above insoluble residue (150 mg) was boiled under reflux with iodomethane (l ml), potassium carbonate (l g) and acetone (10 ml) for 3 h. Repeated TLC of the product gave *8-chloro-1,4,5-trimethoxy-7-methyl-9,10-anthraquinone* **7**, which crystallised from light petroleum as yellow needles, mp 246–248 °C (Found: M^+, 346.0604. $C_{18}H_{15}{}^{35}ClO_5$ requires *M*, 346.0607); ν_{max}/cm^{-1} 1666 (CO); λ_{max}/nm 225, 261, 350 and 428 (log ε 4.49, 4.42, 3.40 and 3.79); δ_H 2.45 (3H, s, ArMe), 3.92 (6H, s, OMe, C-4 and C-5), 3.94 (3H, s, OMe, C-1), 7.04 (1H, s, 6-H) and 7.13 (2H, s, 2-H and 3-H); *m/z* 346 (81%, M^+), 331 (100, M − Me), 329 (24, M − OH), 316 (12, M − CH_2O) and 302 (12, 331 − CHO).

The slower-moving component B from the original column chromatography afforded a yellow solid (2.6 g), a portion (150 mg) of which was heated under reflux with iodomethane (1 g), potassium carbonate (1 g), and acetone (10 ml) for 3 h. The product, after evaporation and subsequent TLC on silica gel using dichloromethane, *methyl (E)-β-(5-chloro-2-methoxy-4-methylbenzoyl)acrylate* **4**, was obtained as yellow needles (107 mg), mp 94–95 °C from light petroleum (bp 80–100 °C) (Found: M^+, 268.0502. $C_{13}H_{13}{}^{35}ClO_4$ requires *M*, 268.0503); ν_{max}/cm^{-1} 1720 (conj. ester CO) and 1664 (conj. CO); λ_{max}/nm 229, 244infl, 276sh and 345 (log ε 4.33, 4.08, 3.75 and 3.56); δ_H 2.42 (3H, s, ArMe), 3.82 (3H, s, ArOMe), 3.90 (3H, s, CO_2Me), 6.76 and 7.80 (2H, ABq, J_{AB} 16, *trans*-CH=CH-), 6.86 and 7.68 (each 1H, s, 3- and 6-H); *m/z* 268 (M^+, 30%), 237 (14, M − MeO), 209 (52, 237 − CO), 183 (100, 209 − C_2H_2).

8-Chloro-5-hydroxy-7-methyl-1,4-naphthoquinone 1 and its conversion into 7-methyljuglone 2†

The ether-soluble material from the above fraction A after column chromatography on silica gel using benzene–light petroleum (1 : 9) gave the chlorohydroxynaphthoquinone **1** (350 mg), which crystallised as red needles, mp 160–161 °C (lit.,[2] 159–161 °C) from chloroform or aqueous methanol; ν_{max}/cm^{-1} 1663 and 1646 (quinone CO); λ_{max}/nm 256.5, 350infl, 422infl, 435 and 450infl (log ε 4.09, 3.08, 3.55, 3.61 and 3.55); δ_H 2.47 (3H, s, ArMe), 6.88 (2H, s, 2-H and 3-H), 7.18 (1H, s, ArH) and 12.75 (1H, s, ArOH). The corresponding *acetate* crystallised from light petroleum as yellow needles, mp 220 °C (Found: C, 58.8; H, 3.5; Cl, 13.4. $C_{13}H_9ClO_4$ requires C, 58.9; H, 3.4; Cl, 13.4%); ν_{max}/cm^{-1} 1776 (aryl acetate CO) and 1664 (quinone CO); λ_{max}/nm 239 and 360 (log ε 4.19 and 3.49); δ_H 2.38 (3H, s, ArOCOMe), 2.46 (3H, s, ArMe), 6.73 and 6.85 (2H, ABq, J_{AB} 10, 2-H and 3-H) and 7.23 (1H, s, ArH).

A solution of the chloroquinone **1** (1 g) in THF (100 ml) was added dropwise to a solution of tin(II) chloride (5 g) in 4 M hydrochloric acid (350 ml) and THF (100 ml) at 60 °C. The mixture was kept at 60 °C for 3 h, cooled and filtered into a solution of iron(III) chloride (25 g) in water (200 ml). The resulting yellow solid was collected and crystallised from aqueous methanol or chloroform–light petroleum to give 7-methyljuglone as orange needles (685 mg, 81%), mp 126.5–

† Carried out with the assistance of T. J. Lillie and B.C. Maiti.

127 °C (lit.,[2] 125.5–126.5 °C), identical (IR, mixed mp) with an authentic specimen.

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