SHORT PAPER

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Sodium metaperiodate oxidation of isocarvacrol†

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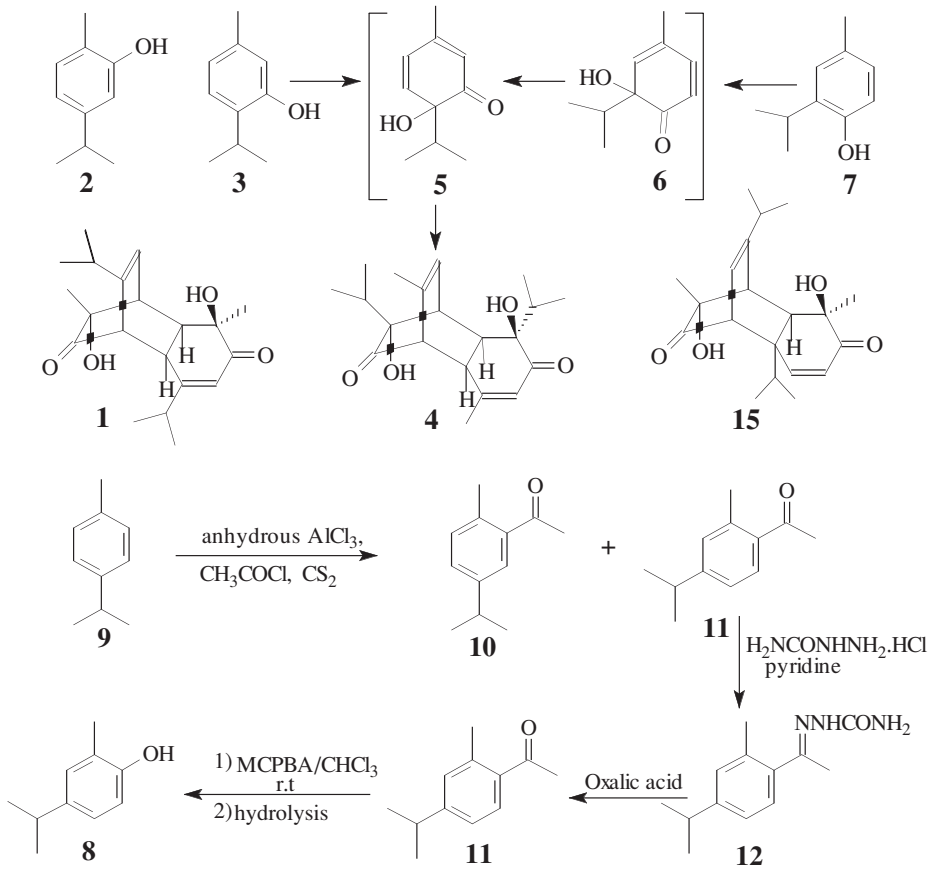
Sodium metaperiodate oxidation of isocarvacrol **8**, a monoterpene phenol has been found to give hydrothymoquinone **13**, a natural product and a ring cleavage product 7-oxo-5-isopropyloct-3-en-2,5-olide **14**.

Keywords: isocarvacrol (4-isopropyl-2-methylphenol), $NaIO_4$ oxidation, hydrothymoquinone, 7-oxo-5-isopropyloct-3-en-2,5-olide

Sodium metaperiodate ($NaIO_4$) oxidation of phenols having a substituent at 2-position has been studied extensively[1] and it was observed that the intermediate *o*-quinol is usually not isolable and gives directly a dimer by the hetero-Diels–Alder self-condensation reaction.[1] This observation was used for the biomimetic synthesis of **1** a natural product[2] by $NaIO_4$ oxidation of carvacrol **2**. Similarly it was found that $NaIO_4$ oxidation of thymol **3** directly gives the dimer **4** through the intermediate *o*-quinol **5** whereas, the o-quinol **6** formed by $NaIO_4$ oxidation of isothymol **7** rearranges to *o*-quinol **5**, and then gives the same dimer **4**.[3]

It was of interest therefore, to study the $NaIO_4$ oxidation of isocarvacrol (4-isopropyl-2-methylphenol) **8**, which had not been studied previously. Isocarvacrol has not been identified unequivocally to be a natural product[4] but has been synthesised before.[5a,b]

Isocarvacrol **8** required for this study was prepared by a new sequence as follows: Friedel-Crafts acylation of *p*-cymene **9** gave a mixture of two isomeric acetophenone derivatives **10** and **11**.[6] The desired isomer, 4-isopropyl-2-methylacetophenone **11** was then separated by preferential preparation of its semicarbazone **12**[7] followed by regeneration of **11** using oxalic acid and aqueous formaldehyde[8]. Baeyer-Villiger oxidation of **11** using *m*-chloroperbenzoic acid gave the desired phenol **8**[9].



Scheme 1

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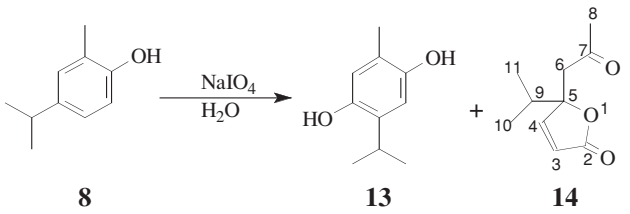
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

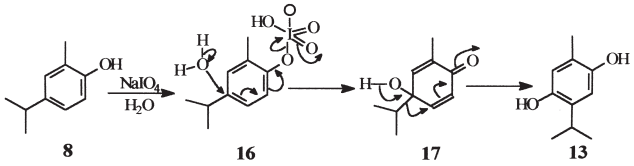


Reaction of an ethanolic solution of **8** with an aqueous solution of $NaIO_4$ followed by usual work-up and chromatography gave two products. The less polar product (33%), a white crystalline solid (m.p. 142°C) was identified as hydrothymoquinone **13**, on the basis of its spectral data (IR, ^1H, ^{13}C NMR and Mass). Natural occurrence of **13** is reported.[10-12] The m.p.[10] and spectral data (^1H and ^{13}C NMR) of **13** were identical with those reported in literature.[11-13]

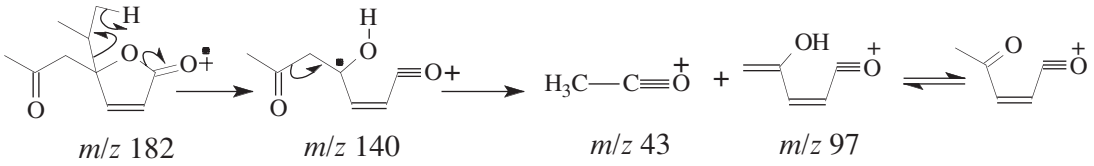
The more polar component (21%), a viscous liquid was identified as a ring cleavage product, 7-oxo-5-isopropyl-3-en-2,5-olide **14** on the basis of its spectral data (Table 1) and mechanistic considerations (Scheme 3). The IR spectrum of **14** supported the presence of an ester carbonyl (1766 cm^{-1}) and a ketone carbonyl (1712 cm^{-1}). The mass spectral fragmentation pattern is consistent with the proposed structure **14** and the genesis of the major fragment ions is presented below.

Table 1 NMR spectral data of **14** in $CDCl_3$

Carbon no.	^1H NMR (δ_H)	^{13}C NMR (δ_C)
2	—	172.2
3	6.17 (1H, d, *J*=5.7 Hz)	121.2
4	7.74 (1H, d, *J*=5.7 Hz)	158.7
5	—	91.3
6	2.92 and 3.21 (2H, d, *J*=16.0 Hz)	48.4
7	—	204.8
8	2.29 (3H, s)	31.5
9	2.3–2.35 (1H, sept, *J*=6.9 Hz)	33.5
10, 11	1.07 (3H, d, *J*=6.9 Hz)	17.0
	0.99 (3H, d, *J*=6.9 Hz)	17.2



Scheme 2



It may be noted that the expected dimer **15** was not formed in this reaction. A probable mechanism, which can explain the formation of **13** and **14**, is shown in Schemes 2 and 3 respectively.

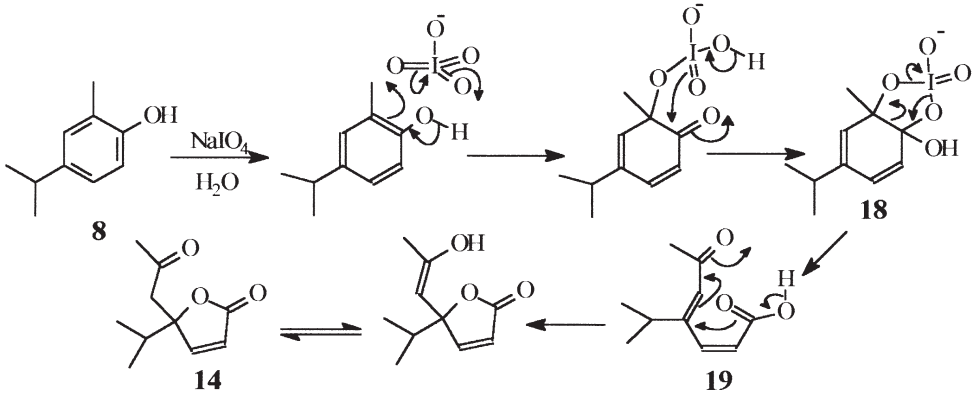
Sodium metaperiodate oxidation of isocarvacrol **8**, is assumed to give the ester **16** by co-ordination of the phenolic -OH group to the iodine of periodate anion[14,15]. Ester **16** can further give *p*-quinol **17** by a concerted two-electron transfer to iodine accompanied by nucleophilic attack of water at the *p*-position. The *p*-quinol **17** thus formed undergoes a dienone-phenol rearrangement to give **13**. On the other hand, a two-electron transfer to iodine[16] followed by intramolecular nucleophilic attack could give the cyclic iodate ester **18** which may undergo ring cleavage to form the acid **19**. Subsequent cyclisation, of **19** via intramolecular Michael type addition probably results in the formation of **14**.

Experimental

IR spectra were recorded on a Shimadzu 8101A FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker WT 300 MHz FT NMR spectrophotometer in $CDCl_3$ with TMS as an internal standard. All yields refer to pure isolated products.

5-Isopropyl-2-methylacetophenone **(10)** *and 4-isopropyl-2-methylacetophenone* **(11):** A mixture of **10** and **11** was obtained by acetylation of *p*-cymene **9** using the reported procedure[6].

Semicarbazone **(12)** *of 4-isopropyl-2-methylacetophenone* **(11)**[7]**:** To a mixture of **10** and **11** (4.4 g, 25 mmol) in ethanol (25 ml) was added an aqueous solution of semicarbazide hydrochloride (2.78 g in 2.5 ml of water) and pyridine (2.8 ml). The reaction mixture was then allowed to stand at room temperature for 30 minutes. The semicarbazone that separated out as a white solid was filtered off, washed with dilute HCl until free from pyridine and then with water. The product was dried in air and recrystallised several times from aqueous methanol to give silvery white flakes of **12** (3.02 g, 52%) having m.p. 172°C as reported[17].



Scheme 3

Regeneration of 4-isopropyl-2-methylacetophenone **(11)**[8] *from its semicarbazone* **(12):** A mixture of the semicarbazone **12** (1.87 g, 8 mmol), ethanol (30 ml), oxalic acid (3.74 g) in water (100 ml), aqueous formaldehyde (40%, 16 ml) and petroleum ether (40-60°C, 200 ml) was refluxed with stirring for 6 h. The organic layer was separated, washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave **11** (1.36 g, 96%) as pale yellow oil, which was further purified by distillation under reduced pressure. IRν_{max} (film): 2960, 1680(CO), 1610, 1360, 1250, 960, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.25 [6H, d, ($C\underline{H}_3)_2$–CH–], 2.54 (3H, s, $C\underline{H}_3$–CO), 2.56 (3H, s, Ar–$C\underline{H}_3$), 2.8–2.9 [1H, sept, $(CH_3)_2$–C$\underline{H}$-], 7.1 (2H, dd, *J* = 8.0, 2.0 Hz, C_3–H and C_5–H), 7.86 (1H, d, *J* = 8.0 Hz, C_6–H).

4-Isopropyl-2-methylphenol **(8):** To a well-stirred solution of 4-isopropyl-2-methylacetophenone **11** (6.3 g, 35 mmol) was added dropwise a solution of *m*-chloroperoxybenzoic acid (15 g, 87 mmol) and a small amount of *p*-toluenesulphonic acid in chloroform (122 ml). The reaction mixture was allowed to stand and was periodically monitored by TLC (hexane) until the reaction was complete (25 days). After completion of the reaction, the organic extracts were washed with saturated $NaHCO_3$, followed by water until free from acid, dried over anhydrous Na_2SO_4 and concentrated to give a dark brown coloured oil (3.51 g, 66%). Chromatography of the oil over silica gel with hexane-ether (9:1) afforded **8** (2.67 g, 50%) as pale yellow viscous oil. IR ν_{max} (film): 3400(OH), 2970, 1505, 1260, 1120, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.2 (6H, d, C_8, C_9-Hs), 2.23 (3H, s, C_{10}-Hs), 2.81 (1H, sept, C_7-H), 4.0 (1H, bs, OH), 6.69 (1H, d, *J* = 8.1 Hz, H-6), 6.92 (1H, dd, *J* = 8.1, 2.0 Hz, H-5), 6.97 (1H, d, *J* = 2.0 Hz, H-3).

Hydrothymoquinone **(13)** *and 7-oxo-5-isopropyloct-3-en-2,5-olide* **(14):** To a solution of $NaIO_4$ (1.124 g, 5.25 mmol) dissolved in water (73 ml) was added with stirring, a solution of **8** (0.396 g, 2.6 mmol) in ethanol (25 ml). The reaction mixture was then stirred for 24 h at room temperature, extracted with chloroform, washed with 5% $Na_2S_2O_3$, water and dried over anhydrous Na_2SO_4. The solvent was evaporated to give an orange gum (0.293 g). Column chromatographic separation over silica gel using petroleum ether-ethylacetate (4:1) gave hydrothymoquinone **13** (0.145 g, 33%), a white crystalline solid, m.p.142°C (Lit.[10,11] 142–143°C). IR ν_{max} (KBr): 3330(OH), 2980, 1430, 1245, 1180, 870, 820, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22 (6H, d, *J* = 6.9 Hz, C_9-Hs, C_{10}-Hs), 2.15 (3H, s, C_7-Hs), 3.07-3.2 (1H, sept, C_8-H), 6.55 (1H, s, C_3-H), 6.62 (1H, s, C_6-H); ^{13}C NMR ($CDCl_3$): δ 15.3 (C-7), 22.7 (C-9, C-10), 26.9 (C-8), 113.1 (C-3), 117.7 (C-6), 121.6 (C-5), 133.1 (C-2), 146.3 (C-4), 147.7 (C-1); EIMS *m*/*z* (rel. int): 166(M^+, 32), 151(100), 133(6), 121(7), 77(4%). Further elution with petroleum ether-ethylacetate (7:3) gave **14** (0.102 g, 21%) as viscous oil. IR ν_{max} (film): 2880, 1766(CO), 1712(CO), 1643, 1421, 1363, 1166, 1128, 1095, 927, 827 cm^{-1}; ^1H and ^{13}C NMR (Table 1); EIMS *m*/*z* (rel. int): 183.1(M^++1, 4), 182.1(M^+, 16), 140(24), 125(10), 124.1(6), 97(100), 82(8), 43(24%); HREI-MS found 182.0940, $C_{10}H_{14}O_3$ requires 182.0943, deviation –1.6 ppm.

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