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A New Synthesis of 3-Hydroxy-2,5-dialkyl-1,4-benzoquinones Using Iodine-Copper(II) Acetate

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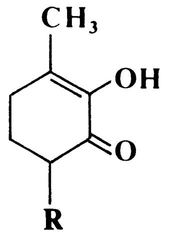
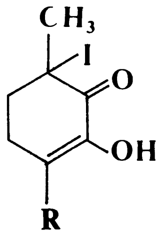
Reactions of diosphenol and 3,6-dimethyl-1,2-cyclohexanedione with iodine-copper(II) acetate in acetic acid-water (5:1) at 80 °C gave the respective 3-hydroxy-2,5-dialkyl-1,4-benzoquinone in 25-80% yields. 2-*t*-Butyl-5-methylcyclohexanone similarly gave the corresponding 3-hydroxy-1,4-benzoquinone in 66% yield.

3-Hydroxy-2,5-dialkyl-1,4-benzoquinones are important as intermediates,[1-3] and hydroxy-1,4-benzoquinone derivatives are known as natural products.[4-8] They are usually prepared by one of the following methods: the reaction of 2,4-dinitrothymol with hydrazine hydrate and Raney nickel;[1] the oxidation of 3-*t*-butyl-6-methylcatechol using Fremy's salt;[2] or the reaction of dimethyltriacetoxybenzene with iron(III) chloride.[9] Also Eastman and Selover reported that the reaction of thujone with selenium dioxide gave the 3-hydroxythymo-1,4-quinone, although, in poor yield.[10] In fact, all of these methods give only a low yield and involve several steps in preparing the starting materials. Now in this paper, we would like to report that reactions of 3,6-dialkyl-1,2-cyclohexanediones with iodine-copper(II) acetate[11-15] gave the corresponding 3-hydroxy-2,5-dialkyl-1,4-benzoquinones in good yields.

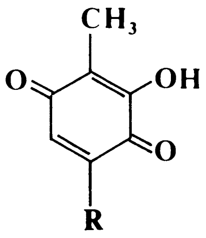
The reaction of menthone (1) with iodine (1.0 mol equiv.)-copper(II) acetate (1.0 mol equiv.) in acetic acid under refluxing for 20 h gave only a 40% yield of 3-hydroxythymo-1,4-quinone (8), mp 167-168 °C,[16] and 21% 2-hydroxy-2-isopropyl-5-methylcyclohexanone (11). Moreover, in the case of 2,5-dimethylcyclohexanone (2), 2-hydroxyketone (12) (45%) was obtained, and no 3-hydroxy-1,4-benzoquinone. The reaction of 2-*t*-butyl-5-methylcyclohexanone (3) did give 3-hydroxy-1,4-benzoquinone (10) (66%).[18] In the case of compound 2, since iodination occurs in the direction of the methyl group, the hydroxymethylketone was obtained. Hence, we attempted the reaction of each of two α-diketone derivatives (4 and 5) with iodine-copper(II) acetate. The reaction of diosphenol (4) with iodine (1.0 mol equiv.)-copper(II) acetate (1.0 mol equiv.) in acetic acid-water (5:1) at 80 °C gave 8 (80%); while the reaction of 3,6-dimethyl-1,2-cyclohexanedione (5) yielded 3-hydroxy-2,5-dimethyl-1,4-benzoquinone (9) (25%),17) 4-iodo-3,6-dimethyl-1,2-benzenediol (13) (23%),19) and 3,3',4,4'-tetrahydroxy-2,2',5,5'-tetramethylbiphenyl (14) (6%).20) In order to clarify this reaction pathway, 3-iodo-3,6-dialkyl-1,2-cyclohexanediones (6 21) and 7 22)) were synthesized by the iodination of 3,6-dialkyl-1,2-cyclohexanediones (4 and 5) with iodine (1.0 mol equiv.)-copper(II) acetate (1.0 mol equiv.) in acetic acid-water (5:1) at room temperature. Further treatment of 3-iodo-3-methyl-6-isopropyl-1,2-cyclohexanedione (6) with iodine-copper(II) acetate yielded 8 (80%). In the case of the 3-iodo-3,6-dimethyl derivative (7), 9 (50%) and 4-iodo-3,6-dimethyl-1,2-benzenediol (13) (34%) were obtained. Moreover, the reaction of thymocatechol (14) with iodine-copper(II) acetate under the same conditions as described above yielded 8 (85%). Similarly, the reaction of 4-iodo-3,6-dimethyl-1,2-benzenediol (13) gave 9 and 14.



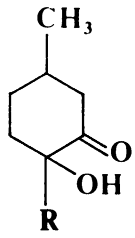
4: R=$(CH_3)_2CH$
5: R=CH_3



6: R=$(CH_3)_2CH$
7: R=CH_3



8: R=$(CH_3)_2CH$
9: R=CH_3
10: R=$(CH_3)_3C$

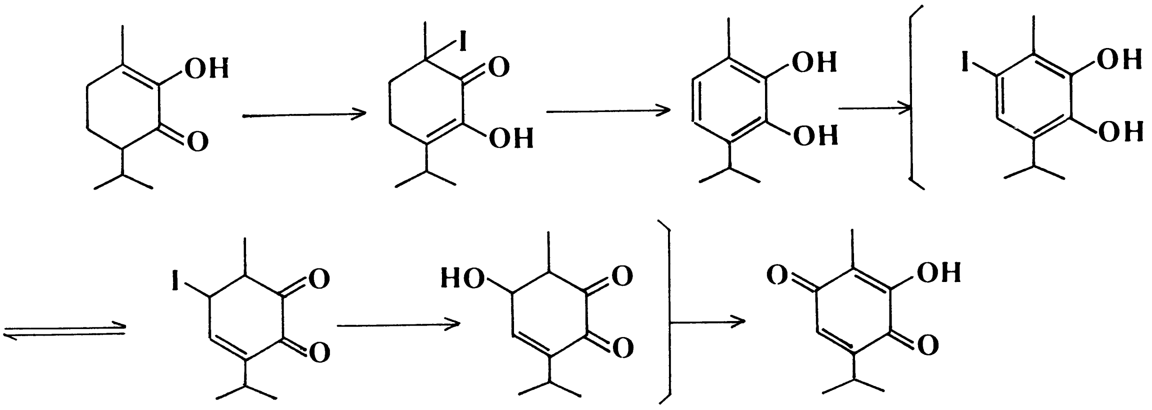


11: R=$(CH_3)_2CH$
12: R=CH_3

A typical procedure is as follows. A mixture of diosphenol (4) (500 mg, 3.0 mmol), iodine (3.0 mmol), and copper(II) acetate (3.0 mmol) in acetic acid-water (5:1) was stirred at 80 °C for 8 h. The precipitated copper(I) iodide was removed by filtration, and then the solvent was removed under reduced pressure. The residue was poured into water and extracted with ether. The ethereal solution was washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated. Crystallization of the residue from ethanol gave needles of 8 (426 mg, 79%), mp 167-168 °C.16)

Thus, on the basis of all of the foregoing results, it is possible to state the following findings: (i) the reaction of 2-*t*-butyl-5-methylcyclohexanone with iodine-copper(II) acetate gave the corresponding 3-hydroxy-1,4-benzoquinone due to the iodination at C_6-position; (ii) the reaction of diosphenol with this reagent gave the 3-hydroxythymo-1,4-quinone in good yield; and (iii) these reactions proceed by the following reaction pathway.

Reaction Pathway



This is the first time that the synthesis of 3-hydroxy-2,5-dialkyl-1,4-benzoquinones has been successfully accomplished by a one-pot method from 3,6-dialkyl-1,2-cyclohexanediones. It is particularly noteworthy that this reaction affords a new synthetic method for 3-hydroxy-2,5-dialkyl-1,4-benzoquinones, more convenient than the methods used heretofore.

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16) 8: mp 167-168 °C(lit,[1]168-169 °C); IR(KBr): 3300, 1670, 1640, and 1620 cm^{-1}; ^{1}H-NMR(CDCl$_3$):δ 1.15(d, 6H), 1.94(s, 3H), 3.82(m, 1H), 6.46(d, 1H, J=1.0 Hz), and 6.88(s, 1H); ^{13}C-NMR(CDCl$_3$):δ 188.2, 183.2, 151.4, 150.4, 132.4, 116.8, 26.7, 21.3, and 7.8. Found: m/e 180.079. Calcd for $C_{10}H_{12}O_3$: M, 180.079.

17) 9: mp 138-140 °C(lit,[9]141-142 °C); IR(KBr): 3250, 1660, 1642, and 1618 cm^{-1}; ^{1}H-NMR(CDCl$_3$):δ 1.91(s, 3H), 2.05(d, 3H, J=1.6 Hz), 6.52(q, 1H, J=1.6 Hz), and 6.88(br.s, 1H); ^{13}C-NMR(CDCl$_3$):δ 187.7, 183.8, 151.3, 141.1, 135.3, 14.8, and 7.9. Found: m/e 152.047. Calcd for $C_8H_8O_3$: M, 152.047.

18) 10: mp 199-200 °C(lit,[2]202 °C); IR(KBr): 3250, 1660, 1640, and 1630 cm^{-1}; ^{1}H-NMR(CDCl$_3$):δ 1.29(s, 9H), 1.93(s, 3H), 6.53(s, 1H), and 7.65(br.s, 1H); ^{13}C-NMR(CDCl$_3$):δ 183.1, 152.0, 151.6, 133.5, 115.9, 34.8, 29.0, and 7.7. Found: m/e 194.093. Calcd for $C_{11}H_{14}O_3$: M, 194.094.

19) 13: mp 88-90 °C; IR(KBr): 3380, 1590, and 800 cm^{-1}; ^{1}H-NMR(CDCl$_3$):δ 2.23(s, 6H), 5.13(br.s, 2H), and 6.61(s, 1H). Found: m/e 263.967. Calcd for $C_8H_9O_2I$: M, 263.966.

20) 14: mp 224-226 °C; IR(KBr): 3425, 1620, 1580, and 855 cm^{-1}; ^{1}H-NMR(CDCl$_3$):δ 1.26(s, 12H), 1.59(s, 4H), and 7.25(s, 2H). Found: m/e 274.116. Calcd for $C_{16}H_{18}O_4$: M, 274.121.

21) 6: Yield 80%; mp 85-87 °C; IR(KBr): 3400, 1645, and 1620 cm^{-1}; ^{1}H-NMR(CDCl$_3$):δ 1.08(dd, 6H), 2.12(s, 3H), 3.14(m, 1H), and 6.15(s, 1H); ^{13}C-NMR(CDCl$_3$):δ 190.4, 138.6, 129.4, 46.0, 41.6, 30.9, 28.0, 24.3, 20.0, and 19.2. Found: m/e 294.012. Calcd for $C_{10}H_{15}O_2I$: M, 294.012.

22) 7: Yield 83%; mp 109-110 °C; IR(KBr): 3450, 1665, and 1625 cm^{-1}; ^{1}H-NMR(CDCl$_3$): δ 1.92(s, 3H), 2.12(s, 3H), and 6.07(s, 1H); ^{13}C-NMR(CDCl$_3$):δ 189.8, 140.2, 130.0, 45.9, 41.5, 31.0, 30.9, and 17.1. Found: m/e 265.980. Calcd for $C_8H_{11}O_2I$: M, 265.980.

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