

Synthesis of Naturally Occurring Quinones

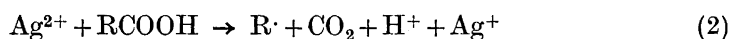
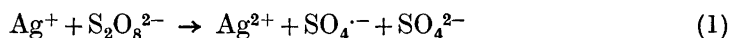
Alkylation with the Silver Ion-Peroxydisulphate-Carboxylic Acid System

N. JACOBSEN and K. TORSSELL

Department of Organic Chemistry, University of Aarhus, 8000 Aarhus C, Denmark

The syntheses of some naturally occurring quinones (primin, lapachol, 2-undecyl-1,4-benzoquinone (intermediate), *etc.*) are reported. The syntheses are performed by alkylation of quinones with radicals obtained from the decarboxylation of carboxylic acids with the silver ion-peroxodisulfate system.

We have previously reported¹ that radicals generated by decarboxylation of carboxylic acids with silver ions and peroxodisulfate (Eqns. 1 and 2) can be used for the alkylation of quinones.



In this paper we demonstrate the utility of this method in the synthesis of some naturally occurring quinones.

RESULTS

Primin. Pentylation of 2-methoxy-1,4-benzoquinone with pentyl radicals from the decarboxylation of hexanoic acid gave the natural product, primin (2-methoxy-6-pentyl-1,4-benzoquinone), together with the two isomeric monopentylated and the three possible dialkylated isomers (Table 1).

It is interesting to note that the methoxy group possesses a stronger directing effect in this type of reaction than does the methyl group.

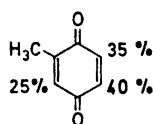
Table 1. Pentylation of 2-methoxy-1,4-benzoquinone.

Products (2-Methoxy-1,4- benzoquinones)	No.	Yield %	M.p. °C	M.p. (Ref.).
3-Pentyl	1	2	Oil	
5-Pentyl	2	34	115–116	(114–115) ^a
6-Pentyl	3	13	62–63	(62–63) ^a
3,5-Dipentyl	4	1 ^a	Oil	
3,6-Dipentyl	5			
5,5-Dipentyl	6	2	Oil	

^a 4:5 ~ 2:1, approximately determined by NMR.

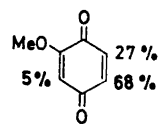
*Isopropylation of
toluquinone*¹

Isomer ratio



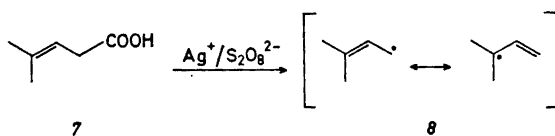
*Pentylation of 2-methoxy-1,4-
benzoquinone*

Isomer ratio



In view of the nucleophilic character of the alkyl radical this distribution pattern is expected.

γ,γ-Dimethylallylquinones. The decarboxylation of 4-methyl-3-pentenoic acid **7** was expected to give a delocalized 3,3-dimethylallyl radical **8**.



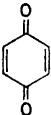
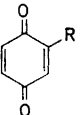
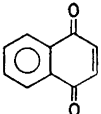
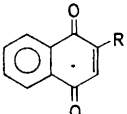
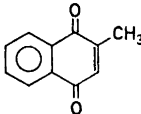
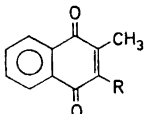
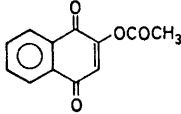
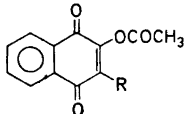
In principle, **8** should be able to attack a quinone molecule with either of the two carbon atoms bearing high spin density, giving rise to either a α,α -dimethylallyl- or a γ,γ -dimethylallylquinone.

Various quinones were alkylated and in all cases only the γ,γ -dimethylallylquinone was isolated.

The same results were obtained when the isomeric 2,2-dimethyl-3-butenoic acid **9** was used instead of **7**, indicating that the same radical is formed in both cases (Table 2).

The 4-methyl-3-pentenoic acid used in these syntheses was contaminated with 15 % of *trans*-4-methyl-2-pentenoic acid **14**, which under the conditions used did not disturb the reaction.

Table 2. Products from the alkylation of quinones with radicals from 7 and 9.

Quinone	Carboxylic acid	Molar ratio quinone: carboxylic acid: peroxodi-sulfate	Product R = -CH ₂ -CH=C(CH ₃) ₂	Yield % (based on the quinone)	m.p. °C	m.p. (Ref.)
	7	1:1.5:1.7		10	34	25-28 (30.5) ⁴
	7	1:1.3:1.3	 Deoxylapachol	11	58	60-61 (62) ⁵
	9	1:1.3:2	 Menaquinone - 7	12	70	
	7 9	1:1:1.8 1:1.2:2	 Lapachol acetate	13	73 79	79-80 (65-66) ⁶ 79-80 (65-66) ⁶

Various α,β -unsaturated carboxylic acids were found to require higher temperatures (10–20°) for their decarboxylation than those of their saturated or β,γ -unsaturated analogs; however, when they were decarboxylated in the presence of a quinone, this was recovered unchanged.

Alkaline hydrolysis of lapachol acetate **13** gave lapachol **15**, overall yield calculated on 2-acetoxy-1,4-naphthoquinone or **7**, 61 %.

2-Undecyl-1,4-benzoquinone 16. This compound was used as an intermediate in the synthesis of embelin (2-undecyl-3,6-dihydroxy-1,4-benzoquinone) by Asano and Hase.⁷

Decarboxylation of lauric acid in the presence of a fourfold excess of benzoquinone gave **16** in 37 % yield calculated on the lauric acid.

EXPERIMENTAL

The melting points are uncorrected. NMR spectra were recorded on a Varian A-60, IR spectra on a Perkin-Elmer Infracord, and UV spectra on a Perkin-Elmer 402 spectrometer.

Alkylation of quinones. Details of the reaction have been described earlier.¹

General procedure. To a vigorously stirred water-acetonitrile solution or two-phase system of the quinone, the carboxylic acid, and silver nitrate at 60–65°C was added an aqueous solution of ammonium peroxodisulfate during 1 h. After further 10 min stirring at 60–65°C, the mixture was cooled to room temperature and worked up.

Pentylation of 2-methoxy-1,4-benzoquinone. The general procedure was followed. To 2-methoxy-1,4-benzoquinone (2.07 g, 0.015 mol), hexanoic acid (2.61 g, 0.0225 mol), silver nitrate (1.5 g) in acetonitrile (60 ml), and water (60 ml) was added ammonium peroxodisulfate (5.13 g, 0.0225 mol) in water (25 ml). The mixture was extracted with methylene chloride, the extract was washed with 10 % sodium bicarbonate until neutral, dried, and concentrated to 10 ml *in vacuo* at room temperature.* Careful chromatography of the solution on silica gel (eluent CH₂Cl₂) gave five fractions:

I. 50 mg of a yellow oil 4 and 5. NMR (CCl₄): δ 0.9 (6 H, distorted t, $J \sim 6$), 1.4 (12 H, m), 2.3 (4 H, distorted t, $\sim J6$), 3.96 and 4.00 (3 H, two singlets assigned to 5 and 4, resp.), 6.27 and 6.34 (1 H, two triplets, $J = 1.5$ assigned to 4 and 5, resp.).

II. 75 mg of a yellow oil 1. Analytical data (after molecular distillation at 120°C/10⁻⁴ mmHg. (Found: C 68.9; H 7.66. Calc.: C 69.2; H 7.74.) UV (EtOH): λ_{\max} nm (log ϵ) 254 (4.0), 275 (2.9). IR (film): cm⁻¹ 1670(s), 1650(s), 1590(m), 840(m). NMR (CCl₄): δ 0.9 (3 H, distorted t, $J \sim 6$), 1.3 (6 H, m), 2.4 (2 H, t, $J = 7$), 4.0 (3 H, s), 6.5 (2 H, AB-system, $\Delta\nu_{AB} = 3.2$, $J_{AB} = 9.5$).

III. 100 mg of a yellow oil 6. Analytical data (after molecular distillation at 140°C/10⁻⁴ mmHg. (Found: C 72.9; H 9.48. Calc.: C 73.4; H 9.42.) UV (EtOH): λ_{\max} nm (log ϵ) 278 (4.2), 380 (2.8). IR (film): cm⁻¹ 1675(s), 1650(s), 1605(s), 850(m). NMR (CCl₄): δ 0.9 (6 H, distorted t, $J \sim 6$), 1.4 (12 H, m), 2.4 (4 H, distorted t, $J \sim 7$), 3.8 (3 H, s), 5.7 (1 H, s).

IV. 1.06 g of yellow crystals 2. M.p. 115–116°C (from CCl₄) (lit. 114–115).² UV (EtOH): λ_{\max} nm (log ϵ) 266 (4.2), 360 (2.9). IR (CHCl₃): cm⁻¹ 1680(s), 1650(s), 1610(s), 990(m), 900(m), 860(m). NMR (CDCl₃): δ 0.9 (3 H, distorted t, $J \sim 6$), 1.4 (6 H, m), 2.4 (2 H, distorted t, $J \sim 7$), 3.8 (3 H, s), 5.9 (1 H, s), 6.5 (1 H, t, $J = 1$).

V. 420 mg of yellow crystals 3. M.p. 62–63°C (from light petroleum) (lit. 62–63).³ UV (EtOH): λ_{\max} nm (log ϵ) 269 (4.1), 366 (2.8). IR (CCl₄) cm⁻¹ (1680(s), 1655(s), 1605(s), 900(m). NMR (CCl₄): δ 0.9 (3 H, distorted t, $J \sim 6$), 2.4 (6 H, m), 2.4 (2 H, distorted t, $J \sim 7$), 3.8 (3 H, s), 5.8 (1 H, d, $J = 2$), 6.3 (1 H, d, t, $J_1 = 2$, $J_2 = 1$).

4-Methyl-3-pentenoic acid 7. 1-Cyano-3-methyl-2-butene, prepared by the method of Ultee,⁸ was hydrolyzed according to Reichstein⁹ to give 7, b.p. 101–102°C/10 mmHg. It contained 15 % of *trans*-4-methyl-2-pentenoic acid (NMR and GC).

2,2-Dimethyl-3-butenoic acid 9 was prepared according to Engel and Schexsnayder.¹⁰

2-Acetoxy-1,4-naphthoquinone was prepared from 2-hydroxy-1,4-naphthoquinone by the method of Thiele and Winther.¹¹ M.p. 129–131°C (lit. 130°).¹¹

2-(γ,γ -Dimethylallyl)-1,4-benzoquinone 10. The general procedure was followed. To benzoquinone (1.08 g, 0.01 mol), 7 (2.01 g, 85 %, 0.015 mol) and silver nitrate (0.5 g) in water (100 ml) was added ammonium peroxodisulfate (3.88 g, 0.017 mol) in water (20 ml). The reaction mixture was extracted with methylene chloride and the extract washed with 10 % sodium bicarbonate until neutral, dried, and evaporated. The crude oily product, 0.85 g, was crystallized from methanol to give 0.59 g 10, 34 % based on benzoquinone, m.p. 25–28°C (lit. 30.5°).⁴ UV (EtOH): λ_{\max} nm (log ϵ) 248 (4.2), 320 (2.8). IR (film): cm⁻¹ 1660(s), 1605(m), 900(m), 850(m), 815(w), 785(w). NMR (CCl₄): δ 1.66 (3 H, broad s), 1.76 (3 H, d, $J \sim 1$), 3.1 (2 H, broad d, $J = 7.5$), 5.1 (1 H, t, m, $J = 7.5$), 6.5 (1 H, m), 6.7 (2 H, m).

2-(γ,γ -Dimethylallyl)-1,4-naphthoquinone (*deoxylapachol*) 11. The general procedure was followed. To 1,4-naphthoquinone (1.58 g, 0.01 mol), 7 (1.73 g, 85 %, 0.013 mol), silver nitrate (0.5 g) in acetonitrile (17 ml), and water (37 ml) was added ammonium

* Evaporation to dryness caused decomposition.

peroxodisulfate (2.96 g, 0.013 mol) in water (15 ml). The reaction mixture was extracted with cyclohexane and the extract washed with 10 % NaHCO₃ until neutral, dried, and evaporated. The crude product was chromatographed on silica gel (eluent: methylene chloride) to yield 400 mg of naphthoquinone and 1300 mg of *11* (58 % based on naphthoquinone), m.p. 60–61°C (from light petroleum) (lit. 62°).⁵ UV (EtOH): λ_{\max} nm (log ϵ) 247 (4.2), 252 (4.2), 264 (4.1), 334 (3.4). IR (KBr): cm⁻¹ 1660(s), 1610(m), 1595(m). NMR (CDCl₃): δ 1.69 (3 H, broad s), 1.79 (3 H, broad s), 3.3 (2 H, broad d, $J=7.5$), 5.2 (1 H, t, m, $J=7.5$), 6.8 (1 H, t, $J=1.5$), 7.5–8.3 (4H, m).

2-Methyl-(γ,γ -dimethylallyl)-1,4-naphthoquinone (menaquinone-1) 12. The general procedure was followed. To 2-methyl-1,4-naphthoquinone (0.86 g, 0.005 mol), *9* (0.74 g, 0.065 mol), silver nitrate (0.5 g) in acetonitrile (20 ml), and water (20 ml) was added ammonium peroxydisulfate (2.28 g, 0.1 mol) in water (10 ml). The mixture was neutralized with solid sodium bicarbonate and extracted with ether. The extract was dried and evaporated to give a yellow oil, which after TLC on silica gel (eluent 15 % ether in light petroleum) yielded 845 mg (70 % based on the 2-methyl-1,4-naphthoquinone) of *12* as a yellow oil. UV (EtOH): λ_{\max} nm (log ϵ) 245 (4.2), 249 (4.2), 264 (4.1), 272 (4.1), 334 (3.4). IR (film): cm⁻¹ 1665(s), 1630(m), 1610(m). NMR (CCl₄): δ 1.69 (3 H, broad s), 1.75 (3 H, broad s), 2.1 (3 H, s), 3.3 (2 H, broad d, $J=7$), 5.0 (1 H, t, m, $J=7$), 7.5–8.2 (4 H, m).

Lapachol acetate 13. The general procedure was followed. To 2-acetoxy-1,4-naphthoquinone (1.08 g, 0.005 mol), *7* (0.067 g, 85 %, 0.005 mol), silver nitrate (0.5 g) in acetonitrile (17 ml), and water (20 ml) was added ammonium peroxydisulfate (2.05 g, 0.009 mol) in water (10 ml). The reaction mixture was neutralized with solid sodium bicarbonate and extracted with ether. The extract was dried and evaporated to give 1.2 g of *13* containing about 10 % of 2-acetoxy-1,4-naphthoquinone (NMR). Recrystallization of the crude product from methanol gave 1.04 g *13* (73 %, m.p. 60–62°C (lit. 65–66°).⁶ Recrystallization from light petroleum raised the m.p. to 79–80°C. UV (EtOH): λ_{\max} nm (log ϵ) 245 (4.2), 251 (4.2), 264 (4.1), 269 (4.1), 336 (3.4). IR (CHCl₃): cm⁻¹ 1780(s), 1675(s), 1640(m), 1600(m). NMR (CCl₄): δ 1.69 (3 H, broad s), 1.73 (3 H, broad s), 2.3 (3 H, s), 3.2 (2 H, broad d, $J=7.5$), 5.1 (1 H, t, m, $J\sim 7.5$), 7.5–8.2 (4 H, m). By carrying out the same reaction using *9* (0.68 g, 0.006 mol) instead of *7* and ammonium peroxydisulfate (2.28 g, 0.01 mol) 1.12 g (79 %) of almost pure *13* was obtained as crude product.

Hydrolysis of 13. 200 mg of crude product from the synthesis of *13* using *7* was heated on a steam bath with 10 ml 1 M sodium carbonate for 30 min. The dark red solution was filtered, cooled in an ice bath, and acidified with concentrated HCl. After 1 h at 0°C, the yellow precipitate of lapachol *15* was filtered and dried *in vacuo* over anhydrous potassium carbonate. The yield was 143 mg, 83 %, m.p. (from CCl₄) 139–140°C (lit. 139–140°).¹² UV (EtOH): λ_{\max} nm (log ϵ) 253 (4.3), 279 (4.1), 333 (3.4). IR (KBr): cm⁻¹ 3320(s), 1660(s), 1640(s), 1590(m). NMR (CDCl₃): δ 1.68 (3 H, d, $J=1$), 1.80 (3 H, broad s), 3.3 (2 H, broad d, $J=7$), 5.2 (1 H, t, m, $J=7$), 7.5–8.3 (4 H, m).

2-Undecyl-1,4-benzoquinone 16. The general procedure was followed. To lauric acid (1.00 g, 0.005 mol), benzoquinone (2.16 g, 0.02 mol), and silver nitrate (0.5 g) in acetonitrile (40 ml) was added ammonium peroxydisulfate (2.51 g, 0.011 mol) in water (15 ml). The reaction mixture was cooled to 5° and 20 ml of cold water was added with vigorous stirring. The precipitate (1.12 g) was filtered and dried *in vacuo* over CaCl₂. TLC on silica (eluent 20 % ether in light petroleum) gave 490 mg of *16*, 37 % calculated on the lauric acid, m.p. (CH₃OH) 59–60°C (lit. 57–59°).⁷ UV (EtOH): λ_{\max} nm (log ϵ) 249 (3.8). IR (KBr): cm⁻¹ 1660(s), 1600(m), 717(m). NMR (CCl₄): δ 0.9 (3 H, distorted t, $J\sim 6$), 1.3 (18 H, m), 2.4 (2 H, distorted t, $J\sim 7$), 6.5 (1 H, m), 6.7 (2 H, m).

REFERENCES

1. Jacobsen, N. and Torssell, K. *Ann.* **763** (1972) 135.
2. Schildknecht, H. and Schmidt, H. *Z. Naturforsch.* **22b** (1967) 287.
3. Schildknecht, H., Bayer, I. and Schmidt, H. *Z. Naturforsch.* **22b** (1967) 36.
4. Bohlman, F. and Kleine, K. M. *Chem. Ber.* **99** (1966) 885.
5. Burnett, A. R. and Thomson, R. H. *J. Chem. Soc. C* **1967** 2100.
6. Cooke, R. G., Killen Macbeth, A. and Winzor, F. L. *J. Chem. Soc.* **1939** 878.

7. Asano, M. and Hase, Z. *J. Pharm. Soc. Japan* **60** (1940) 650.
8. Ultee Sr., A. J. *Rec. Trav. Chim.* **68** (1949) 495.
9. Reichstein, T. *Chem. Ber.* **63** (1930) 749.
10. Engel, P. S. and Schexsnayder, M. A. *J. Am. Chem. Soc.* **94** (1972) 4357.
11. Thiele, J. and Winther, E. *Ann.* **311** (1900) 341.
12. Burnett, A. R. and Thomson, R. H. *Chem. Ind. (London)* **1968** 1771.

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