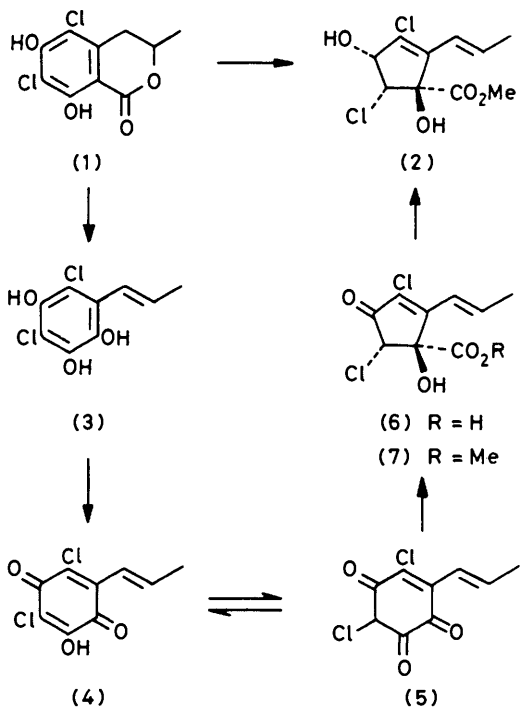
The Synthesis and Ring-contraction of Halogenated Hydroxyquinones; a New Synthesis of Cryptosporiopsin

Graeme B. Henderson and Robert A. Hill *
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

Syntheses of 2,6-dichloro- and 2,6-dibromo-3-hydroxy-5-alkyl-1,4-benzoquinones have been developed involving oxidation of trihalogenoresorcinol derivatives with Fremy's salt. The reactions of these quinones have been studied and their ring-contraction to cyclopentenoid structures on treatment with *N*-halogenosuccinimides is reported. This sequence of reactions has been used in an efficient synthesis of the fungal metabolite cryptosporiopsin.

The dihydroisocoumarin (1) has recently been shown [1] to be a biosynthetic intermediate on the pathway to cryptosporiopsinol (2), a metabolite of *Periconia macrospinosa*. A plausible mechanism for the biosynthetic conversion (Scheme 1) involves oxidative decarboxylation of (1) to the trihydroxyphenylpropene (3). Similar oxidative decarboxylations have been proposed in the biosyntheses of terrein,[2] furasterin,[3] and multicolic acid.[4] The trihydroxyphenylpropene (3) may then be oxidised to the quinone (4) whose tautomer (5) may undergo a benzylic acid-type rearrangement [5] to the cyclopentenone (6). Biological methylation would then give cryptosporiopsin (7) which may then be reduced to cryptosporiopsinol (2). In order to test these biosynthetic proposals we required efficient syntheses of the potential intermediates (3) and (4).

In this paper we report a general synthetic route to 2-alkyl-6-hydroxy-1,4-benzoquinones and describe some of the chemical properties of these compounds including their ring-contraction on treatment with *N*-halogenosuccinimides. This ring-contraction is used in an efficient synthesis of cryptosporiopsin (7).



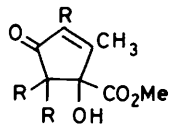
Scheme 1.

Results and Discussion

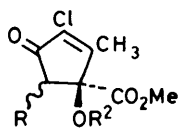
Our synthetic approach to the hydroxyquinones is based on the oxidation of suitably substituted resorcinols with Fremy's salt [6] (potassium nitrosodisulphonate). Oxidation of resorcinols with Fremy's salt frequently leads to unsatisfactory results as the 2-hydroxyquinone produced can undergo polymerisation reactions under the reaction conditions. We find that polymerisation is inhibited by the presence of a halogen atom at the 2-position of the resorcinol. Initial experiments were performed on the chlorinated orcinols † (8) and (9) which were themselves prepared by hydrolysis and decarboxylation of the corresponding orsellinic esters (13) [7] and (14).[8]

Oxidation of 2-chloro-orcinol (8) gave the quinone (15) in high yield. However, when the reaction was carried out on 2,4-dichloro-orcinol (9) two products were obtained: the dichloroquinone (16) and the monochloroquinone (15) in the ratio *ca.* 4 : 1 respectively. Attempted separation of the unstable quinones (15) and (16) resulted in low yields. Oxidative dehalogenation by Fremy's salt has been observed previously [6] in its reactions with compounds in which this is the only available reaction mode; however, in the case of the dichloro-orcinol it was expected that the nitrosyl radical would attack the unsubstituted position in preference. In view of this expectation, oxidation of 2,4,6-trichloro-orcinol (10), which is readily prepared by chlorination of orcinol (11), was performed. The oxidation yielded the dichloroquinone (16) as the sole product in excellent yield.

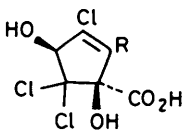
† Orcinol is 3,5-dihydroxytoluene.



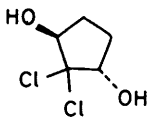
(19) R = Cl
(20) R = Br



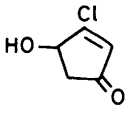
(21) R^1 = αCl, R^2 = H
(22) R^1 = βCl, R^2 = H
(23) R^1 = αCl, R^2 = Ac



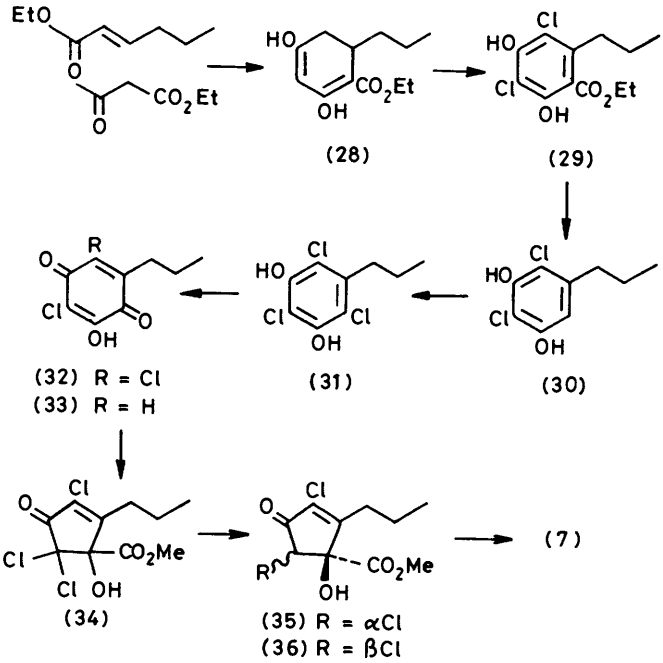
(24) R = CH_3
(25) R = H



(26)



(27)



(28) (29) (30) (31) (32) R = Cl, (33) R = H (34) (35) R = αCl, (36) R = βCl (7)

Scheme 2.

The structural similarity of the dichloroquinone (16) to the proposed biosynthetic quinone intermediate (4) prompted us to investigate the reactions of (16) and in particular to attempt to bring about a benzylic acid-type rearrangement on this compound. The quinone (16) was found to be quite stable under acid conditions and only underwent slow polymerisation with strong acids. Treatment of the quinone (16) with base (aqueous sodium hydroxide) produced a mixture of compounds from which the dihydroxyquinone (17) was obtained. Such quinones are known to undergo fairly rapid decomposition [9] in basic solution and this accounts for the low yield of the reaction. The dihydroxyquinone (17) is the result of nucleophilic substitution at the 6-position * in the dichloroquinone (16) and its structure was verified by reduction and acetylation to the symmetrical tetra-acetate (18).

Although we could not effect ring-contraction of the dichloroquinone (16) under hydrolytic conditions subsequent studies on the compound led to the observation that it can be converted in high yield into a rearranged product on treatment with *N*-chlorosuccinimide (NCS) in methanol. This reaction occurred rapidly at room temperature and the product was identified as the cyclopentenone (19).

The structure of the cyclopentenone (19) was assigned on the basis of its spectroscopic properties and by its conversion, by catalytic hydrogenation, into a mixture of diastereoisomeric cyclopentenones (21) and (22) in a 4 : 1 ratio respectively. Only the acetate (23) of the major isomer (21) was isolated after treatment with acetic anhydride and 4-dimethylaminopyridine. The C-5 proton of the acetate (23) showed a large downfield shift in its proton n.m.r. spectrum compared with its value in the n.m.r. spectrum of the alcohol (21), and this is consistent with the alcoholic group and the C-5 proton being on the same side of the molecule. The spectroscopic properties of the alcohol (21) and its acetate (23) are identical with the known compounds [10] produced from *m*-cresol.

The cyclopentenone (21) has been previously prepared from the cyclopentenol (24) which is itself formed by the action of alkaline chlorine on *m*-cresol.[11] The reaction of phenol with chlorine in alkaline solution to give the cyclopentenol (25) was described almost a century ago by Hantzsch.[12] More recently the structure [13,14] and stereochemistry [15] of the 'Hantzsch acid' (25) have been studied. The Hantzsch acid (25) has been used as an intermediate in the synthesis of caldariomycin (26) [14] and the demonstration [10] that *meta*-alkylphenols produce the corresponding alkyl-substituted acids [*e.g.* (24)] led to the synthesis of cryptosporiopsin (7) from *m*-propylphenol.[11] The Hantzsch acid (25) has recently been converted into the cyclopentenone (27) [16] and this compound has been further elaborated to give prostanoids.[17] However, the unreliable nature [13,14] of the Hantzsch reaction, the low yield (< 10% [10]) when using alkylphenols, and the severe conditions of the reaction limit its use to simple phenols. In contrast, our ring-contraction can be carried out under very mild conditions in high yield. The reaction also worked well with the corresponding bromo compounds; thus tribromo-orcinol (12) was converted into the tribromocyclopentenone (20) in a similar way.

The ring-contraction was used in a new, efficient synthesis of cryptosporiopsin (7) using the propylquinone (32). The synthesis of the propylquinone (32) is based on the aceto-acetate-condensation route to 5-substituted resorcylic acids [18] and is shown in Scheme 2. Ethyl hex-2-enoate was condensed with ethyl acetoacetate to give ethyl 6-propyl-5,6-dihydro-β-resorcylate (28). Chlorination and aromatisation of (28) gave the resorcylic ester (29) which was hydrolysed and decarboxylated to 2,4-dichloro-5-propylresorcinol (30). Treatment of the resorcinol (30) with Fremy's salt gave the quinones (32) and (33) in a *ca.* 4 : 1 ratio respectively. The quinone (32) could also be obtained by oxidation of the trichlororesorcinol (31) which was obtained by further chlorination of (30) with sulphuryl chloride. The ring-contraction of the quinone (32) was effected with NCS in methanol to give the cyclopentenone (34) in high yield. The cyclopentenone (34) was dechlorinated by catalytic reduction to a 4 : 1 mixture of dihydrocryptosporiopsin (35) and *epi*-dihydrocryptosporiopsin (36). Dihydrocryptosporiopsin can be converted into cryptosporiopsin (7) by standard procedures.[11]

In conclusion, the ring-contraction of halogenated hydroxy-

* Systematic-nomenclature numbering.

benzoquinones has been shown to be an efficient process which might be generally useful in the preparation of cyclopentenoid compounds.

Experimental

For general directions see reference 8.

4-*Chloro*-3,5-*dihydroxytoluene* (8).—A solution of ethyl 3-chloro-2,4-dihydroxy-6-methylbenzoate [7] (13) (1.5 g) in 5% aqueous sodium hydroxide (80 ml) was heated under reflux for 3 h. After being cooled the solution was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 50 ml). The organic solution was dried and evaporated to leave an oily residue which crystallised with time. The residue was dissolved in benzene and decolourised by boiling with animal charcoal for 1 h. After being cooled the solution was filtered and evaporated to give crystals of 4-chloro-3,5-dihydroxytoluene (8) (830 mg, 81%), m.p. 136—138 °C (from benzene) (lit.,[7] 137—138 °C); $\nu_{max.}$ 3 320, 1 610, and 1 590 cm^{-1}; δ_H ($CDCl_3$) 6.44 (2 H, s, ArH), 5.32 (2 H, br s, exchangeable with D_2O, OH), and 2.24 (3 H, s, Me).

2,4-*Dichloro*-3,5-*dihydroxytoluene* (9).—Prepared from ethyl 3,5-dichloro-2,4-dihydroxy-6-methylbenzoate [8] (14) by the above method, (85%), m.p. 118 °C (lit.,[19] 121 °C); $\nu_{max.}$ 3 400, 3 360, 1 610, and 1 580 cm^{-1}; δ_H ($CDCl_3$) 6.53 (1 H, s, ArH), 5.70 (1 H, br s, exchangeable with D_2O, OH), 5.35 (1 H, br s, exchangeable with D_2O, OH), and 2.28 (3 H, s, Me).

2,4,6-*Trichloro*-3,5-*dihydroxytoluene* (10).—Sulphuryl chloride (12 ml) was added to a solution of orcinol (11) (5 g) in acetic acid (50 ml). The mixture was kept at room temperature for 3 h. After partial evaporation of the solvent and addition of hexane, the product crystallised (8.2 g, 92%), m.p. 123 °C (from benzene–hexane) (lit.,[20] 127 °C); $\nu_{max.}$ 3 500 and 1 710 cm^{-1}; δ_H ($CDCl_3$) 2.45 (3 H, s, Me).

2-*Chloro*-3-*hydroxy*-5-*methyl*-1,4-*benzoquinone* (15).—A solution of Fremy's salt [6] (800 mg) and dipotassium hydrogen phosphate (150 mg) in water (25 ml) was added to a solution of 4-chloro-3,5-dihydroxytoluene (8) (250 mg) and dipotassium hydrogen phosphate (150 mg) in water (15 ml). The mixture (which became deep red) was stirred at room temperature for 75 min then acidified to congo red with dilute hydrochloric acid. The acidic solution was extracted with chloroform (4 × 25 ml). The combined extract was dried (sodium sulphate) and evaporated (at room temperature) to give 2-*chloro*-3-*hydroxy*-5-*methyl*-1,4-*benzoquinone* (15) as orange crystals (235 mg, 86%), m.p. 150—153 °C (from benzene–hexane) (Found: C, 48.7; H, 2.9; Cl, 20.4. $C_7H_5ClO_3$ requires C, 48.7; H, 2.9; Cl, 20.6%); $\lambda_{max.}$ (EtOH) 510, 268, and 210 nm; $\nu_{max.}$ 3 250, 1 680, 1 650, and 1 610 cm^{-1}; δ_H ($CDCl_3$) 6.67 (1 H, d, *J* 2 Hz, 5-H) and 2.12 (3 H, d, *J* 2 Hz, Me).

2,6-*Dichloro*-3-*hydroxy*-5-*methyl*-1,4-*benzoquinone* (16).—A solution of Fremy's salt (3 g) and dipotassium hydrogen phosphate (750 mg) in water (80 ml) was added to a suspension of 2,4,6-trichloro-3,5-dihydroxytoluene (10) (1 g) in a solution of dipotassium hydrogen phosphate (750 mg) in water (15 ml). The mixture was stirred at room temperature for 24 h then acidified to congo red with dilute hydrochloric acid and extracted with chloroform (4 × 50 ml). The combined extracts were dried (sodium sulphate) and evaporated to give 2,6-*dichloro*-3-*hydroxy*-5-*methyl*-1,4-*benzoquinone* (16) as red crystals (760 mg, 83%), m.p. 161—162 °C (from benzene–hexane) (Found: C, 41.0; H, 1.7; Cl, 34.0. $C_7H_4Cl_2O_3$ requires C, 40.8; H, 1.9; Cl, 34.0%); $\lambda_{max.}$ (EtOH) 530, 282, and 222 nm; $\nu_{max.}$ 3 400, 3 360, 1 680, 1 665, 1650, and 1 610 cm^{-1}; δ_H ($CDCl_3$) 2.22 (3 H, s, Me). Oxidation of 2,4-dichloro-3,5-dihydroxytoluene (9) by the same procedure gave a 4 : 1 mixture of (16) and (15).

2,3,5,6-*Tetra-acetoxy*-4-*chlorotoluene* (18).—A solution of 2,6-dichloro-3-hydroxy-5-methyl-1,4-benzoquinone (16) (250 mg) in aqueous sodium hydroxide (0.2M; 50 ml) was heated under reflux for 2 h. After being cooled the solution was filtered and the filtrate was acidified with dilute hydrochloric acid. The acidified solution was extracted with diethyl ether (2 × 50 ml). The combined extracts were dried and evaporated to give 2-chloro-3,6-dihydroxy-5-methyl-1,4-benzoquinone (17) as an unstable dark red residue (90 mg, 39%), $\lambda_{max.}$ (EtOH) 530 and 302 nm; $\nu_{max.}$ 1 675, 1 655, and 1 625 cm^{-1}; δ_H [$(CD_3)_2CO$] 1.85 (3 H, s, Me).

A solution of (17) (20 mg) in ethyl acetate (50 ml) containing palladium–carbon (10%; 5 mg) was stirred under hydrogen for 1 h. The catalyst was filtered off and the filtrate was evaporated to give an oil. Acetic anhydride (2 ml) and sodium acetate (10 mg) were added and the mixture was heated at 100 °C (steam bath) for 15 min. The solution was poured onto ice–water, from which 2,3,5,6-*tetra-acetoxy*-4-*chlorotoluene* (18) crystallised (23 mg, 60%), m.p. 120—121 °C (sub.) (Found: C, 50.3; H, 4.2; Cl, 9.8. $C_{15}H_{15}ClO_8$ requires C, 50.2; H, 4.2; Cl, 9.9%); $\nu_{max.}$ 1 780 cm^{-1}; δ_H ($CDCl_3$) 2.29 (6 H, s, COMe), 2.28 (6 H, s, COMe), and 1.96 (3 H, s, Me).

Methyl 3,5,5-*Trichloro*-1-*hydroxy*-2-*methyl*-4-*oxocyclopent*-2-*enecarboxylate* (19).—NCS (35 mg) was added to a solution of 2,6-dichloro-3-hydroxy-5-methyl-1,4-benzoquinone (16) (50 mg) in dry methanol (30 ml). The mixture was stirred at room temperature for 15 min during which time the initially deep red solution became pale yellow. The solvent was evaporated off and the residue was purified by preparative layer chromatography (p.l.c.) on silica gel using ethyl acetate as eluant to yield the *cyclopentenecarboxylate* (19) as plates (58 mg, 88%), m.p. 102—103 °C (from dichloromethane) (Found: C, 35.5; H, 2.3; Cl, 38.1. $C_8H_7Cl_3O_4$ requires C, 35.13; H, 2.6; Cl, 38.9%); $\lambda_{max.}$ 250 nm; $\nu_{max.}$ 3 450, 1 755, 1 748, and 1 628 cm^{-1}; δ_H ($CDCl_3$) 3.83 (3 H, s, OMe) and 2.07 (3 H, s, Me); δ_C ($CDCl_3$) 13.0, 55.0, 84.6, 85.3, 131.6, 162.2, 168.9, and 183.8 p.p.m.

Methyl 1-*Acetoxy*-3,5-*dichloro*-2-*methyl*-4-*oxocyclopent*-2-*enecarboxylate* (23).—A mixture of the cyclopentenecarboxylate (19) (50 mg), sodium acetate (13 mg), and palladium–carbon (5%; 5 mg) in acetic acid (5 ml) was stirred under hydrogen at room temperature for 1 h. The catalyst was filtered off and the solvent was evaporated off. The residue was a mixture of the two cyclopentenecarboxylates (21) and (22) as a pale yellow oil. These isomers could not be separated but were shown to be present in the ratio 4 : 1 [(21) : (22)]; for (21), δ_H ($CDCl_3$) 4.68 (1 H, s, 5-H), 3.93 (3 H, s, OMe), and 2.12 (3 H, s, Me); for (22), δ_H ($CDCl_3$) 4.59 (1 H, s, 5-H), 3.86 (3 H, s, 5-H), and 2.10 (3 H, s, Me). The mixture of isomers (21) and (22) (25 mg) was dissolved in acetic anhydride containing 4-dimethylaminopyridine (2 mg) and the mixture was heated at 50 °C for 1 h. The solution was concentrated and the residue was purified by p.l.c. on silica gel using dichloromethane as eluant. The cyclopentenecarboxylate (23) was the only product; its properties were identical with those reported.[10]

2,6-*Dibromo*-3-*hydroxy*-5-*methyl*-1,4-*benzoquinone* (16; Br instead of Cl).—A solution of Fremy's salt (2.7 g) and dipotassium hydrogen phosphate (700 mg) in water (35 ml)

was added to a solution of 2,4,6-tribromo-3,5-dihydroxytoluene [21] (12) (1 g) and dipotassium hydrogen phosphate (700 mg) in water (15 ml). The mixture was stirred at room temperature for 3 h then acidified to Congo Red with dilute hydrochloric acid. The acidic solution was extracted with chloroform (3 × 25 ml) and the combined extracts were dried (sodium sulphate) and evaporated at room temperature to give 2,6-*dibromo*-3-*hydroxy*-5-*methyl*-1,4-*benzoquinone* as orange crystals (780 mg, 96%), m.p. 185 °C (decomp.) (Found: C, 28.3; H, 1.4; Br, 54.2. $C_7H_4Br_2O_3$ requires C, 28.4; H, 1.36; Br, 54.1%); $\nu_{max.}$ 3 390, 1 662, 1 648, and 1 603 cm^{-1}; δ_H ($CDCl_3$) 7.45 (1 H, br s, exchangeable with D_2O, OH) and 2.27 (3 H, s, Me).

2,4,6-*Tribromo*-3,5-*dihydroxytoluene* (12).—Bromine (19 ml) was added to a solution of orcinol (11) (5 g) in acetic acid (55 ml) and the mixture was stirred for 2 h. The precipitate of 2,4,6-tribromo-orcinol (12) was collected and recrystallised from ethanol (12 g, 83%), m.p. 104—105 °C (lit.,[24] 105 °C); δ_H ($CDCl_3$) 2.18 (3 H, s, Me).

Methyl 3,5,5-*Tribromo*-1-*hydroxy*-2-*methyl*-4-*oxocyclopent*-2-*enecarboxylate* (20).—*N*-Bromosuccinimide (40 mg) was added to a solution of 2,6-dibromo-3-hydroxy-5-methyl-1,4-benzoquinone (66 mg) in dry methanol (15 ml) and the mixture was stirred at room temperature for 5 min by which time the initially deep red solution had become almost colourless. The solution was evaporated and the residue was purified by p.l.c. on silica gel using dichloromethane as eluant. The *cyclopentenecarboxylate* (20) was recrystallised from dichloromethane (75 mg, 91%), m.p. 110—114 °C (Found: C, 23.5; H, 1.7; Br, 59.0. $C_8H_7Br_3O_4$ requires C, 23.6; H, 1.7; Br, 15.7%); $\lambda_{max.}$ (EtOH) 264 nm; $\nu_{max.}$ 3 400, 1 755, 1 735, and 1 615 cm^{-1}; δ_H ($CDCl_3$) 4.67 (1 H, br s, exchangeable with D_2O, OH), 3.83 (3 H, s, OMe), and 2.05 (3 H, s, Me).

Ethyl 6-*Propyl*-5,6-*dihydro*-β-*resorcylate* (28).*—Ethyl diethoxyphosphorylacetate [22] (50 g) was added during 1 h to sodium hydride (9 g; 62% mineral oil dispersion) in dry diethyl ether (300 ml) at 0 °C. The mixture was allowed to warm up to room temperature and was then heated at reflux for 1 h. The solution was cooled to −10 °C (ice–salt-bath) and freshly distilled butyraldehyde (16 g) was added to the vigorously stirred solution during 45 min. The solution became increasingly viscous as the reaction proceeded. After the mixture had been stirred for a further 1 h, the cooling bath was removed and the mixture was allowed to come to room temperature and was then brought slowly to reflux. A thick gummy precipitate of sodium diethyl phosphate separated on cooling. The clear solution was separated and washed in turn with saturated aqueous sodium hydrogen carbonate and water. The ether solution was dried and evaporated to give ethyl hex-2-enoate as an oil (28 g, 80%); δ_H ($CDCl_3$) 6.98 (1 H, dt, *J* 7 and 15 Hz, 3-H), 5.82 (1 H, dt, *J* 1 and 15 Hz, 2-H), 4.20 (2 H, q, *J* 7 Hz, OCH_2), 2.19 (2 H, q, *J* 7 Hz, 4-H_2), 1.48 (2 H, m, 5-H_2), 1.28 (3 H, t, *J* 7 Hz, OCH_2CH_3), and 0.93 (3 H, t, *J* 6 Hz, 6-H_3).

Ethyl acetoacetate (18.3 g) was added dropwise to a stirred solution of sodium (3.56 g) in ethanol (100 ml) at a rate which maintained a gentle reflux. The solution was heated at reflux for a further 30 min then ethyl hex-2-enoate (20 g) was added dropwise during 15 min. The mixture was heated at reflux for 8 h, then stirred at room temperature for a further 16 h. The sodium salt of the enolate was filtered off and washed with dry diethyl ether and was then air-dried. The dried salt was dissolved in water, washed with diethyl ether, acidified with dilute hydrochloric acid, and the aqueous solution extracted with diethyl ether. The extract was dried and evaporated to give *ethyl* 6-*propyl*-5,6-*dihydro*-β-*resorcylate* (28) as an oil which slowly crystallised (12 g, 35%), m.p. 80 °C (Found: C, 63.3; H, 7.5; $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%); $\nu_{max.}$ 1 735, 1 610, and 1 505 cm^{-1}; δ_H ($CDCl_3$) 5.75 (1 H, br s, exchangeable with D_2O, OH), 5.50 (1 H, s, 3-H), 4.22 (2 H, q, *J* 7 Hz, OCH_2), 3.55 (2 H, m, 5-H_2), 3.15 (1 H, d, *J* 10 Hz, 6-H), 2.35 (3 H, m, $CHCH_2$), 1.30 (2 H, m, $CH_2CH_2CH_3$), 1.25 (3 H, t, *J* 7 Hz, OCH_2CH_3), and 0.88 (3 H, m, $CH_2CH_2CH_3$).

Ethyl 3,5-*Dichloro*-6-*propyl*-β-*resorcylate* (29).†—A solution of chlorine (2.2 g) in acetic acid (30 ml) was added to a stirred solution of ethyl 6-propyl-5,6-dihydro-β-resorcylate (28) (3.3 g) in glacial acetic acid (20 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min, at room temperature for 30 min, and then at 60 °C for 4 h. Nitrogen was passed through the solution to remove hydrogen chloride, then a further quantity of chlorine (1.5 g) in acetic acid (20 ml) was added to the stirred mixture at 0 °C. The mixture was stirred for 30 min, then poured onto ice–water, from which the product precipitated from solution. *Ethyl* 3,5-*dichloro*-6-*propyl*-β-*resorcylate* (29) was recrystallised from diethyl ether–hexane (4.1 g, 95%), m.p. 86—88 °C (Found: C, 49.1; H, 4.8; Cl, 24.0. $C_{12}H_{14}Cl_2O_4$ requires C, 49.15; H, 4.8; Cl, 24.2%); $\nu_{max.}$ 3 400, 1 640, and 1 585 cm^{-1}; δ_H ($CDCl_3$) 6.40 (2 H, br s, exchangeable with D_2O, OH), 4.45 (2 H, q, *J* 7 Hz, OCH_2CH_3), 3.03 (2 H, m, $CH_2CH_2CH_3$), 1.50 (2 H, m, $CH_2CH_2CH_3$), 1.40 (3 H, t, *J* 7 Hz, OCH_2CH_3), and 0.98 (3 H, t, *J* 6 Hz, $CH_2CH_2CH_3$).

2,4-*Dichloro*-5-*propylresorcinol* (30).—Ethyl 3,5-dichloro-6-propyl-β-resorcylate (29) (3 g) in aqueous sodium hydroxide solution (5%; 50 ml) was heated at reflux under nitrogen for 5 h. After being cooled the solution was acidified with concentrated hydrochloric acid, then extracted with ethyl acetate (3 × 50 ml). The organic solution was dried and evaporated to leave a brown gummy residue which was purified by chromatography on silica gel using dichloromethane as eluant to give 2,4-*dichloro*-5-*propylresorcinol* (30) (2 g, 88%), m.p. 56—58 °C (Found: C, 49.0; H, 4.5; Cl, 32.3. $C_9H_{10}Cl_2O_2$ requires C, 48.9; H, 4.6; Cl, 32.1%); $\nu_{max.}$ 3 400, 1 570, and 1 465 cm^{-1}; δ_H ($CDCl_3$) 6.55 (1 H, s, ArH), 5.08 (2 H, br s, exchangeable with D_2O, OH), 2.64 (2 H, t, *J* 8 Hz, $ArCH_2$), 1.62 (2 H, m, $CH_2CH_2CH_3$), and 0.95 (3 H, t, *J* 8 Hz, Me).

2,4,6-*Trichloro*-5-*propylresorcinol* (31).—Sulphuryl chloride (0.3 ml) was added to a solution of 2,4-dichloro-5-propylresorcinol (30) (250 mg) in diethyl ether (20 ml) and the mixture was kept at room temperature for 2 h. The excess of sulphuryl chloride was destroyed carefully with water. The ether layer was separated, dried, and evaporated to give 2,4,6-*trichloro*-5-*propylresorcinol* (31) (260 mg, 90%), m.p. 114 °C (from diethyl ether) (Found: C, 42.3; H, 3.4; Cl, 41.5. $C_9H_9Cl_3O$ requires C, 42.3; H, 3.6; Cl, 41.6%); $\nu_{max.}$ 1 595 cm^{-1}; δ_H ($CDCl_3$) 2.86 (2 H, t, *J* 8 Hz, $ArCH_2$), 1.90 (2 H, m, $CH_2CH_2CH_3$), and 1.12 (3 H, t, *J* 7 Hz, Me).

2,6-*Dichloro*-3-*hydroxy*-5-*propyl*-1,4-*benzoquinone* (32).—A solution of Fremy's salt (600 mg) and dipotassium hydrogen phosphate (140 mg) in water (30 ml) was added to a solution of 2,4,6-trichloro-5-propylresorcinol (31) (160 mg) and dipotassium hydrogen phosphate (140 mg) in water (5 ml). The mixture was stirred at room temperature for 20 h, then

* Ethyl 2,4-dihydroxy-6-propylcyclohexa-1,3-dienecarboxylate.

† Ethyl 3,5-dichloro-2,4-dihydroxy-6-propylbenzoate.

acidified to congo red with dilute hydrochloric acid. The acidic solution was extracted with chloroform (3 × 30 ml) and the combined extracts were dried (sodium sulphate) and evaporated at room temperature to give the *benzoquinone* (32) as orange needles (from chloroform–hexane) (130 mg, 91%), m.p. 91—93 °C (Found: C, 45.9; H, 3.3; Cl, 30.4. $C_9H_8Cl_2O_3$ requires C, 46.0; H, 3.4; Cl, 30.2%); $\nu_{max.}$ (Et_2O) 225, 288, and 418 nm; δ_H ($CDCl_3$) 1.68 (2 H, t, *J* 7 Hz, $ArCH_2$), 1.55 (2 H, m, CH_2Me), and 0.99 (3 H, t, *J* 7 Hz, Me).

Methyl 3,5,5-*Trichloro*-1-*hydroxy*-4-*oxo*-2-*propylcyclopent*-2-*enecarboxylate* (34).—A mixture of the quinone (32) (250 mg) and NCS (150 mg) in dry methanol (30 ml) was stirred at room temperature for 30 min and then evaporated to dryness. The resulting residue was dissolved in tetrachloromethane (15 ml) from which succinimide precipitated. The succinimide was removed by filtration and the filtrate was evaporated to give a crystalline residue which was purified by p.l.c. on silica gel using dichloromethane as eluant to give the *cyclopentenecarboxylate* (34) (260 mg, 81%), m.p. 55—57 °C (Found: C, 39.3; H, 3.5; Cl, 34.9. $C_{10}H_{11}Cl_3O_4$ requires C, 39.8; H, 3.7; Cl, 35.3%); $\nu_{max.}$ (CCl_4) 3 490, 1 765, 1 750, and 1 620 cm^{-1}; δ_H ($CDCl_3$) 4.64 (1 H, br s, exchangeable with D_2O, OH), 3.84 (3 H, s, OMe), 2.50 (2 H, m, $CH_2CH_2CH_3$), 1.55 (2 H, m, $CH_2CH_2CH_3$), and 0.98 (3 H, t, *J* 7 Hz, Me).

Methyl 3,5-*Dichloro*-1-*hydroxy*-4-*oxo*-2-*propylcyclopent*-2-*enecarboxylate* (*Dihydrocryptosporiopsin*) (35).—A mixture of the cyclopentenecarboxylate (34) (72 mg), anhydrous sodium acetate (22 mg), and palladium–carbon (10%; 15 mg) in acetic acid (30 ml) was stirred at room temperature for 1.25 h under hydrogen. The catalyst was removed by filtration and the acetic acid was removed by evaporation. The residue was dissolved in chloroform and the solid sodium acetate removed by filtration. The chloroform filtrate was evaporated to give an oil which crystallised with time; the dihydrocryptosporiopsin (35) was recrystallised from cyclohexane (45 mg, 70%), m.p. 98—102 °C (lit.,[11] 101—103 °C) (Found: C, 45.2; H, 4.2; Cl, 26.9%; M^+, 266. Calc. for $C_{10}H_{12}Cl_4O_2$: C, 45.0; H, 4.53; Cl, 26.5%; *M*, 266). The spectra were identical with hose reported in the literature.[11]

Acknowledgements

We thank the S.E.R.C. for financial support.

References

1 G. B. Henderson and R. A. Hill, *J. Chem. Soc., Perkin Trans. 1*, 1982, 3037.
2 R. A. Hill, R. H. Carter, and J. Staunton, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2570.
3 R. J. J. Lousberg and Y. Tirilly, *Experientia*, 1976, **32**, 1394.
4 J. A. Gudgeon, J. S. E. Holker, T. J. Simpson, and K. Young, *Bioorg. Chem.*, 1979, **8**, 311.
5 S. Selman and J. F. Eastham, *Quart. Rev.*, 1960, **14**, 221.
6 H. Zimmer, D. C. Lankin, and S. W. Morgan, *Chem. Rev.*, 1971, **71**, 229.
7 L. Fitzpatrick, T. Sala, and M. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1980, 85.
8 G. B. Henderson and R. A. Hill, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1111.
9 P. Hodge, in 'The Chemistry of the Quinonoid Compounds,' ed. S. Patai, Wiley, London, 1974, part 1, p. 580.
10 G. M. Strunz, A. S. Court, and J. Komlossy, *Tetrahedron Lett.*, 1969, 3613.
11 G. M. Strunz and A. S. Court, *J. Am. Chem. Soc.*, 1973, **95**, 3000.
12 A. Hantzsch, *Chem. Ber.*, 1887, **20**, 2780; 1889, **22**, 1238.
13 C. J. Moye and S. Sternhell, *Aust. J. Chem.*, 1966, **19**, 2107.
14 A. W. Burgstahler, T. B. Lewis, and M. O. Abdel-Rahman, *J. Org. Chem.*, 1966, **31**, 3516.
15 R. M. Christie, R. W. Rickards, K. J. Schmalzl, and D. Taylor, *Aust. J. Chem.*, 1977, **30**, 2195.
16 R. M. Christie, M. Gill, and R. W. Rickards, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1782.
17 M. Gill and R. W. Rickards, *J. Chem. Soc., Perkin Trans. 1*, 1981, 599.
18 C. R. Smith, *J. Org. Chem.*, 1960, **25**, 588.
19 T. J. Nolan and D. Murphy, *Sci. Proc. R. Dublin Soc.*, 1940, **22**, 315.
20 T. Zincke and A. von der Linde, *Chem. Ber.*, 1893, **26**, 318.
21 L. Cleaver, J. A. Croft, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, 1976, **29**, 1989.
22 R. S. Marmor, *J. Org. Chem.*, 1972, **37**, 2901.

Received 16*th May* 1983; *Paper* 3/768