# Experiments on the Synthesis of Tetracycline. Part 15.[1] Oxidation of Phenols and Ring A Model Phenols to o-Hydroxy-dienones with Benzene-seleninic Anhydride

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Benzeneseleninic anhydride has been used to oxidise simple alkylphenols and tetracycline ring A model phenols to hydroxy-dienones. The corresponding phenolate salts with benzeneseleninic anhydride give increased yields of o-hydroxylated products

IMPORTANT to the Imperial College approach to the total synthesis of tetracycline (1) is the introduction of a 12a-hydroxy-function into an aromatic ring A precursor.[2]

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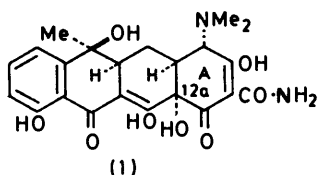
A variety of reagents will oxidise alkylphenols to hydroxy-dienones with a varying degree of *ortho*-selectivity. For example, lead tetra-acetate,[3] acyl per-oxides,[4] peroxy-acids,[4] metal ions (oxides) in the presence of hydrogen peroxide,[2,5] sodium periodate,[6] periodic or iodic acid,[7] sodium bismuthate,[8] and selenium dioxide–hydrogen peroxide [5,9] will readily effect this transformation.

We have consistently [4] sought a reagent which, because of prior reaction at the phenolate oxygen, would necessarily deliver oxygen into the *ortho*-position. The present paper describes a readily available compound which we consider to fulfil these conditions.

Initial experiments with selenium dioxide [9] were not promising. However, perusal of a well known text book [10] showed that benzeneseleninic anhydride [11] (2) was monomeric and, therefore, should be more reactive. We report here a study of its reactions with simple phenols and tetracycline ring A model phenols.

Benzeneseleninic anhydride (2), first prepared by Doughty,[12] can be conveniently obtained by oxidation of diphenyl diselenide with ozone,[13] or by heating *in vacuo* the nitric acid complex of benzeneselenic acid, itself formed by oxidation of diphenyl diselenide with concentrated nitric acid.[14] Benzeneseleninic anhydride is a fairly stable white solid, m.p. 164°, which is hydrolysed slowly in a moist atmosphere.

Initial experiments indicated little regioselectivity of

attack. Thus 2,4-xylenol with the reagent (2) in dimethylformamide at room temperature gave, in addition to diphenyl diselenide, the *p*-hydroxy-dienone (3) (15%) and the *o*-hydroxy-dienone dimer (4) (40%). Similarly 2,6-xylenol gave the quinone (5), the biphenylquinone (6), and only a small amount (5%) of the *o*-hydroxy-dienone (7).

When mesitol was treated with benzeneseleninic anhydride in dichloromethane the isolated products were the *p*-hydroxy-dienone (8) (30%) and the *o*-hydroxy-dienone dimer (9) (48%). With more hindered phenols,

(2)   (3)   (4)

(5)   (6)

(7)   (8)   (9)
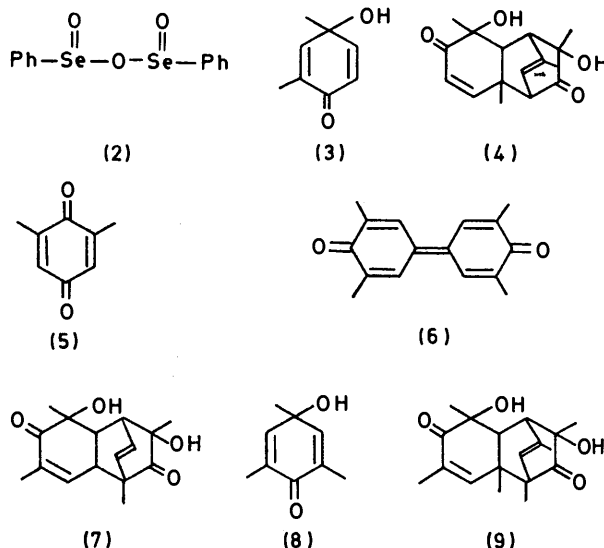
such as 2,6-di-t-butyl-4-methylphenol, no reaction occurred after 48 h at room temperature. Although the levels of *ortho*-hydroxylation were disappointingly low in these experiments, the oxidation of the ring A model phenols (10; R = OMe or NH$_2$) were studied, as previous attempts to effect their oxidation in these laboratories met with only limited success.[2]

[1] Part 14, D. H. R. Barton, J. H. Bateson, S. C. Datta, and P. D. Magnus, *J.C.S. Perkin I*, 1976, 503.

[2] D. H. R. Barton, P. D. Magnus, and J. C. Quinney, *J.C.S. Perkin I*, 1975, 1610.

[3] (a) F. Wessely and F. Sinwell, *Monatsh.*, 1950, **81**, 1055; (b) A. J. Waring, *Adv. Alicyclic Chem.*, 1966, vol. 1.

[4] D. H. R. Barton, P. D. Magnus, and M. J. Pearson, *J. Chem. Soc. (C)*, 1971, 2231, and references therein.

[5] For a comparative study, see R. G. R. Bacon and A. R. Izzat, *J. Chem. Soc. (C)*, 1966, 791.

[6] (a) E. Adler, *Angew. Chem.*, 1957, **69**, 272; (b) E. Adler, J. Dahlen, and G. Westin, *Acta Chem. Scand.*, 1960, **14**, 512; (c) E. Adler, L. Junghahn, U. Lindberg, B. Berggren, and G. Westin, *ibid.*, p. 1261.

[7] E. Adler, G. Andersson, and E. Edman, *Acta Chem. Scand.* (B), 1975, **29**, 909.

[8] E. Kon, *J. Org. Chem.*, 1976, **41**, 1646.

[9] D. H. Davies, Ph.D. Thesis, London, 1972.

[10] D. L. Klayman and W. H. H. Günther, 'Organic Selenium Compounds: their Chemistry and Biology,' Wiley, New York, 1973.

[11] D. H. R. Barton, P. D. Magnus, and M. N. Rosenfeld, *J.C.S. Chem. Comm.*, 1975, 301.

[12] H. W. Doughty, *Amer. Chem. J.*, 1909, **41**, 326.

[13] G. Ayrey, D. Barnard, and D. T. Woodridge, *J. Chem. Soc.*, 1962, 2089.

[14] M. Stoecker and F. Krafft, *Ber.*, 1906, **39**, 2197.

Treatment of the ester (10; R = OMe) with benzene-seleninic anhydride in dichloromethane at room temperature gave the desired hydroxy-dienone (11; R = OMe) in moderate yield, together with compound (12; R = OMe). The amide (10; R = NH$_2$) however, under similar conditions, afforded the hydroxy-dienone (11; R = NH$_2$), compound (12; R = NH$_2$), and the quinone (13) in yields of 24, 45, and 20%, respectively.

(10) (12)

(13) (14)

(15) (16)
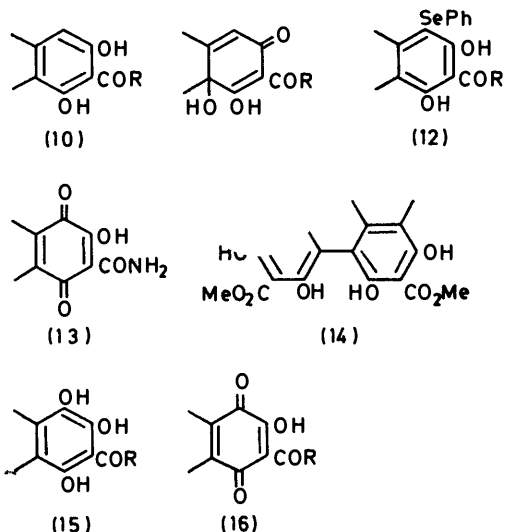
Attempts to oxidise the ester (10; R = OMe) by using Adlers' sodium periodate procedure gave 60% starting material, even after warming on a steam-bath for 6 h, and the only product isolated was the coupled compound (14) (12%); *ortho*-hydroxylation was not observed. Similar lack of reactivity was shown by selenium dioxide.

In the hope of improving *ortho*-selectivity, the series of phenols was converted into the corresponding anions prior to reaction with benzeneseleninic anhydride. In this manner, 2,4-xylenol gave an improved yield of the *o*-hydroxy-dienone dimer (4); however, more significant was the fact that the *p*-hydroxy-dienone (3) was not observed under these conditions.

2,6-Xylenol, after phenolate formation with sodium hydride in 1,2-dimethoxyethane, gave with benzeneseleninic anhydride, a good yield of the *o*-hydroxy-dienone dimer (7) and only traces of other products. Similarly the mesitate anion cleanly afforded the *o*-hydroxy-dienone dimer (9) without any apparent formation of the *p*-hydroxy-dienone (8).

Extension of this procedure to the ring A model phenols (10; R = OMe or NH$_2$) gave good results. The ester (10; R = OMe), after anion formation, was treated with benzeneseleninic anhydride and gave the hydroxy-dienone (11; R = OMe) in 75% yield together with only small quantities of the phenylseleno-species (12; R = OMe). The structural assignment for the hydroxy-dienone (11; R = OMe) readily follows from its spectral

15 D. H. R. Barton, L. Bould, D. L. J. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc. (C)*, 1971. 2204.

16 M. L. Wolfrom and J. Solms, *J. Org. Chem.*, 1956, **21**, 815.

and analytical data. For example the ^{1}H n.m.r. spectrum shows significant signals at τ 6.6 (3 H, s), 7.8 (3 H, d, *J* 1.6 Hz), 6.1 (3 H, s), and 4.0 (1 H, d, *J* 1.6 Hz); the i.r. spectrum has absorptions at 3 450 and 1 680 cm^{-1}.

The phenolate anion of the amide (10; R = NH$_2$) yielded the hydroxy-dienone (11; R = NH$_2$) in good yield after treatment with benzeneseleninic anhydride. The phenylseleno-amide (12; R = NH$_2$) and the quinone (13) were only formed in trace amounts (t.l.c. and ^{1}H n.m.r.). The hydroxy-dienone amide (11; R = NH$_2$) displayed characteristic ^{1}H n.m.r. signals at τ 8.55 (3 H, s), 7.85 (3 H, d, *J* 1.5 Hz), and 3.7 (1 H, d, *J* 1.5 Hz).

Attempted *o*-hydroxylation of other possible ring A model phenols (15; R = OMe or NH$_2$) gave the quinones (16; R = OMe or NH$_2$) in 98 and 85% yield, respectively. It was reasoned that if the triphenols (15; R = OMe or NH$_2$) were converted into the cyclic carbonates (17) or their phenylboronates (18) hydroxylation might then be possible. These carbonates (17) [15] and boronates (18) [16] were prepared by standard methods and the corresponding anions were subjected to oxidation by benzenesel-enic anhydride. However, hydroxylated derivatives were not obtained and the products isolated were again the quinones (16). For example when the sodium phenolate of the ester carbonate (17; R = OMe) or the phenyl-boronate (18; R = OMe) was treated with benzene-seleninic anhydride the quinone (16; R = OMe) was formed in 78 or 88% yield, respectively.

Lastly it was of interest to investigate the *ortho*-hydroxylation of the aryl ethyl carbonate (19; R^1 = H, R^2 = CO$_2$Et) as an example of a phenol containing a sensitive functionality (O·CO·OEt) but of potential

(17) (18)

(19) (20)

(21) (22)
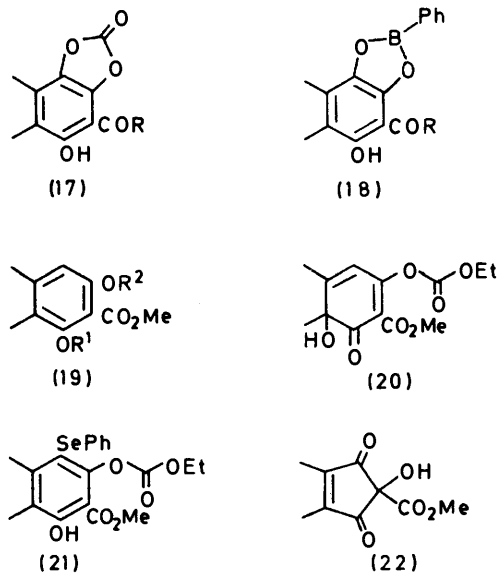
application in tetracycline chemistry. Compound (19; R^1 = H, R^2 = CO$_2$Et) was prepared by partial hydrolysis of the bis-carbonate (19; R^1 = R^2 = CO$_2$Et) with sodium methoxide. The other isomer (19; R^1 = CO$_2$Et, R^2 = H) was not formed, nor could it be ob-

tained by treatment of the diphenol (10; R = OMe) with 1 equiv. of ethyl chloroformate. Assignment of constitution to the aryl ethyl carbonates was based mainly on ^{13}C n.m.r. data and comparison with a number of model compounds.* Surprisingly the carbonate (19; R^1 = H, R^2 = CO_2Et) did not react with benzeneseleninic anhydride under the usual conditions. This we attribute to increased hydrogen bonding in comparison with the ester (10; R = OMe). However, if the anion of the carbonate (19; R^1 = H, R^2 = CO_2Et) was formed and subsequently treated with benzeneseleninic anhydride at room temperature, the o-hydroxy-dienone (20) was formed, albeit in low yield. Increasing the temperature of the reaction to 55 °C afforded the o-hydroxy-dienone (20) in 56% yield. That the carbonate groups remained intact in the product was readily seen from the ^{1}H n.m.r. spectrum [τ 8.72 (3 H, t, J 7.4 Hz) and 6.77 (2 H, q, J 7.4 Hz)]. The position of hydroxylation was revealed by the characteristic methyl signals at τ 8.45 and 7.8.

· If the carbonate (19; R^1 = H, R^2 = CO_2Et) was treated under more vigorous conditions (3 h; tetrahydrofuran at reflux) with benzeneseleninic anhydride, reaction took place to yield the o-hydroxy-dienone (20) (46%) together with other products. These included the phenylseleno-species (21), a pure sample of which was not isolated. Also formed in small amounts was a compound to which structure (22) was assigned on the basis of spectral and analytical properties. Its ^{1}H n.m.r. spectrum shows a six-proton singlet at τ 7.9 and a three-proton singlet at τ 6.3 (CO_2Me). The formation of compounds similar to (22) by ring contraction of ring A models has been observed previously.[15]

Hydroxylation of alkylphenols by benzeneseleninic anhydride can be interpreted mechanistically in a variety of ways. In all the reactions studied so far diphenyl diselenide was the principal by-product; other partially reduced forms of benzeneseleninic anhydride were never detected. Also, in most cases 1 mol. equiv. of the anhydride was required to convert all the starting material, although in one example, compound (10; R = OMe), only 0.33 mol. equiv. was required. All three oxygen atoms can in principle be used in the oxidation process. Unchanged benzeneseleninic acid was, in many of the oxidations, observed as the t.l.c. base-line product.

The high degree of ortho-selectivity during oxidation of phenolate anions supports our original conception (see Scheme) of the course of this reaction. The intermediate selenenic ester (23) could be responsible for the phenylselenation of unchanged phenol (or phenolate). Also the first step of the proposed scheme generates benzeneseleninate ion, which conceivably could react with benzeneseleninic anhydride to generate the species PhSe·O·Se(O)Ph; this could effect phenylselenation or further ortho-hydroxylation. We intend addressing the problem of phenylselenation and quinone formation in more detail in another communication.[17]

In summary, benzeneseleninic anhydride can be used

* We thank Drs. L. Phillips and P. Mitchell for these measurements.

effectively to convert alkylphenolates into the corresponding ortho-hydroxylated derivatives.

The oxidations of phenols themselves, which afford p-hydroxylated or other derivatives, clearly proceed by a different mechanism. The reagent may act as an ordinary electrophilic oxidant towards carbon or, by an
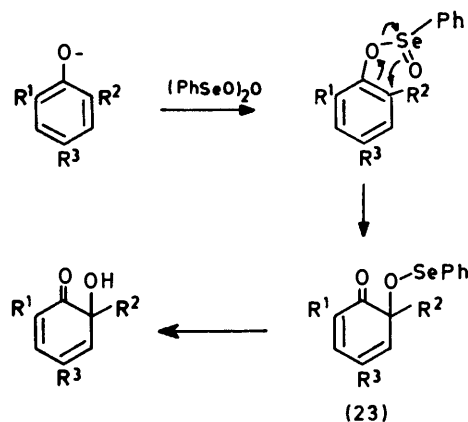
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electron-transfer process, a radical mechanism may be initiated.

We have naturally considered whether benzeneseleninic anhydride could be really the compound PhSe(O)·Se(O$_2$)Ph. There is good evidence against this structure in the literature.[13] Proton and (especially) carbon-13 n.m.r. measurements † confirm that the reagent is symmetrical and therefore has formula (2). We also attempted to oxidise phenols with benzenetellurinic anhydride and benzenetellurinyl chloride in a similar manner, but no oxidation was effected.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Unicam SP 1800 or a Perkin-Elmer 157 spectrophotometer for liquid films or Nujol mulls. U.v. spectra were recorded for solutions in ethanol with a Unicam SP 800 spectrophotometer. ^{1}H N.m.r. spectra were taken for solutions in CDCl$_3$ (Me$_4$Si as internal standard) with a Varian T60 spectrometer. Mass spectra were obtained at 70 eV with an A.E.I. MS9 spectrometer. Both thin-layer and plate chromatography were carried out on silica gel (Merck G 254); isolated products are listed in order of decreasing R_F values. Light petroleum refers to the fraction b.p. 40—60 °C. Solutions were dried over magnesium sulphate and solvents dried by standard techniques.

Benzeneseleninic Anhydride (2).—(a)[13] Ozonolysis of diphenyl diselenide at −10 °C in carbon tetrachloride gave the anhydride (2), m.p. 164—165° (lit.,[12] 165°).

(b) A stirred suspension of diphenyl diselenide (10 g) in water (10 ml) at 60 °C was treated cautiously with concentrated nitric acid (ca. 10 ml) in 1 ml portions until evolution of the oxides of nitrogen had ceased. After cooling at 4 °C overnight the white crystals of the nitric acid complex of benzeneseleninic acid, m.p. 112°,[14] were isolated by filtration,

[17] D. H. R. Barton, A. G. Brewster, S. V. Ley, and M. N. Rosenfeld, J.C.S. Chem. Comm., 1976, 985.

washed with water, and dried in air. The complex was heated *in vacuo* at 120 °C for 72 h to give the anhydride (*ca.* 90%) as a white powder, m.p. 164°.

Preparation of Ring A *Model Phenols.*—The diphenol ester (10; R = OMe),[15] the amide (10; R = NH₂),[2] and the triphenol ester (15; R = OMe)[15] were prepared according to literature methods. The triphenol amide (15; R = NH₂) was prepared by reduction of the known quinone (16; R = NH₂).[2] Thus, the quinone (16; R = NH₂) (195 mg, 1 mmol) was dissolved in ethyl acetate and hydrogenated over 10% palladium–barium sulphate until uptake ceased. Removal of the catalyst followed by evaporation under reduced pressure gave 2,3,6-*trihydroxy*-4,5-*dimethylbenzamide* (15; R = NH₂) (183 mg, 93%), m.p. 110° (decomp.), sublimed at 120° and 10⁻⁴ mmHg, $\nu_{max.}$ 3 450, 3 250, 1 680, and 1 630 cm⁻¹, τ 7.85br (s) (Found: C, 54.8; H, 5.5; N, 6.9%; *m/e*, 197. C₉H₁₁NO₄ requires C, 54.8; H, 5.6; N, 7.1%; *M*, 197).

2,4-Dimethylphenol with Benzeneseleninic Anhydride.—2,4-Dimethylphenol (100 mg, 0.82 mmol) in dimethylformamide (2 ml) was treated with benzeneseleninic anhydride (286 mg, 0.8 mmol) for 2 h at room temperature. P.l.c. (7 : 3 light petroleum–ethyl acetate) gave (i) diphenyl diselenide (115 mg); (ii) starting material; (iii) the *o*-hydroxy-dienone dimer (4) (46 mg, 40%), m.p. 236° (lit.,[18] 237—238°), *m/e* 276 (*M*⁺); and (iv) the *p*-hydroxy-dienone (3) (17 mg, 15%) as prisms, m.p. 73° (lit.,[18] 73—74°), $\lambda_{max.}$ 225, 270, and 315 nm.

2,6-Dimethylphenol with Benzeneseleninic Anhydride.—2,6-Dimethylphenol (106 mg, 0.86 mmol) in dimethylformamide (2 ml) was treated with benzeneseleninic anhydride (292 mg, 0.81 mmol) for 2 h at room temperature. P.l.c. (7 : 3 light petroleum–ethyl acetate) gave (i) the quinone (5) as red needles (30 mg, 25%), m.p. 72° (from light petroleum) (lit.,[19] 73°), $\nu_{max.}$ 1 655 cm⁻¹, τ 3.3 (2 H, s) and 7.75 (6 H, s); (ii) the tetramethylbiphenylquinone (6) as a red solid (42 mg, 40%), m.p. 211—214° (from AcOH) (lit.,[20] 212—215°), $\lambda_{max.}$ 254, 269sh, and 415 nm (ε 18 500 for 415 nm); and (iii) the *o*-hydroxy-dienone dimer (7) (13 mg, 5%), m.p. 183°, identical with an authentic sample.[18]

2,4,6-Trimethylphenol with Benzeneseleninic Anhydride.—To a stirred solution of 2,4,6-trimethylphenol (100 mg, 0.72 mmol) in dry dichloromethane (5 ml) was added benzeneseleninic anhydride (180 mg, 0.5 mmol). After 2 h at room temperature p.l.c. (9 : 1 light petroleum–ethyl acetate) gave (i) the *p*-hydroxy-dienone (8) (33 mg, 30%), m.p. 123° (lit.,[6a] 123—124°), *m/e* 152 (*M*⁺); and (ii) the *o*-hydroxy-dienone dimer (9) (54 mg, 48%), m.p. 181° (lit.,[21] 181—183°), *m/e* 304 (*M*⁺).

Methyl 2,6-Dihydroxy-3,4-dimethylbenzoate (10; R = OMe) *with Benzeneseleninic Anhydride.*—To a stirred solution of the benzoate (10; R = OMe) (100 mg, 0.5 mmol) in dry dichloromethane (5 ml) at room temperature was added benzeneseleninic anhydride (195 mg, 0.54 mmol). After 15 min the reaction was quenched by addition of aqueous sodium hydrogen carbonate (10%; 10 ml) and the mixture extracted with dichloromethane (3 × 25 ml). Evaporation of the dried extracts gave a residue which after p.l.c. (7 : 3 light petroleum–ethyl acetate) afforded (i) diphenyl diselenide (146 mg, 86% based on benzeneseleninic anhydride); and (ii) *methyl 2,6-dihydroxy-3,4-dimethyl-5-phenylseleno-*

benzoate (12; R = OMe) (99 mg, 55%), m.p. 118—119° (from methanol), $\nu_{max.}$ 3 450, 1 690, and 1 620 cm⁻¹, $\lambda_{max.}$ 221, 238, 258, 270sh, and 338 nm (ε 21 500, 17 560, 18 720, 12 650, and 3 600), τ 7.9 (3 H, s), 7.5 (3 H, s), 5.9 (3 H, s), 2.8 (5 H, m), 0.3 (1 H, s, exchanged by D₂O), and −0.6 (1 H, s, exchanged by D₂O) (Found: C, 54.35; H, 4.5%; *m/e*, 352. C₁₆H₁₆O₄ requires C, 54.65; H, 4.6%; *M*, 352).

The aqueous layer was acidified with 0.1N-hydrochloric acid and extracted with dichloromethane (3 × 25 ml). Evaporation of the dried extracts gave *methyl 2,3-dihydroxy-3,4-dimethyl-6-oxocyclohexa-1,4-dienecarboxylate* (11; R = OMe) (38 mg, 35%), m.p. 111° (from light petroleum–diethyl ether at 0°), $\nu_{max.}$ 3 450 and 1 680 cm⁻¹, $\lambda_{max.}$ 224, 278, and 284 nm (ε 11 200, 2 450, and 2 000), τ 8.6 (3 H, s), 7.8 (3 H, d, *J* 1.6 Hz), 6.1 (3 H, s), and 4.0 (1 H, d, *J* 1.6 Hz) (Found: C, 56.9; H, 5.79%; *m/e*, 212. C₁₀H₁₂O₅ requires C, 56.6; H, 5.7%; *M*, 212).

2,6-Dihydroxy-3,4-dimethylbenzamide (10; R = NH₂) *with Benzeneseleninic Anhydride.*—The amide (10; R = NH₂) (115 mg, 0.64 mmol) in dry chloroform (4 ml) was treated with benzeneseleninic anhydride (200 mg, 0.55 mmol) with stirring at room temperature. Work-up, after 35 min, as in the previous experiment gave [from the organic fraction after p.l.c. (chloroform)] (i) diphenyl diselenide (152 mg); (ii) 2,6-*dihydroxy*-3,4-*dimethyl*-5-*phenylselenobenzamide* (12; R = NH₂) (96 mg, 45%), m.p. 175° (from ethanol), $\nu_{max.}$ 3 380, 3 200, 1 635, and 1 595 cm⁻¹, $\lambda_{max.}$ 222, 245, and 322 nm (ε 23 380, 19 700, and 3 490), τ 7.85 (3 H, s), 7.55 (3 H, s), and 2.8 (5 H, m) (Found: C, 53.55; H, 4.25; N, 4.15%; *m/e*, 337. C₁₅H₁₅NO₃Se requires C, 53.6; H, 4.5; N, 4.15%; *M*, 337); and (iii) 2-carbamoyl-3-hydroxy-5,6-dimethylbenzoquinone (13) (25 mg, 20%), m.p. 165—166° (lit.,[2] 163—166°), $\nu_{max.}$ 3 400, 3 310, and 1 650 cm⁻¹, $\lambda_{max.}$ 272 and 412 nm (ε 21 800 and 770), *m/e* 195 (*M*⁺).

The aqueous layer, upon acidification, gave 2,3-dihydroxy-3,4-dimethyl-6-oxocyclohexa-1,4-dienecarboxamide (11; R = NH₂) (32 mg, 25%) as a yellow solid, m.p. 146—147° (lit.,[2] 145—147°), $\nu_{max.}$ 3 450, 3380, 3 200, and 1 685 cm⁻¹, *m/e* 197 (*M*⁺).

Methyl 2,6-Dihydroxy-3,4-dimethylbenzoate (10; R = OMe) *with Sodium Periodate.*—To a solution of the benzoate (10; R = OMe) (196 mg, 1 mmol) in methanol–water (15 ml) was added sodium periodate (300 mg) in water (2 ml). The mixture was warmed on a steam-bath for 6 h, cooled, and extracted with dichloromethane (3 × 50 ml). Evaporation of the dried extracts left a yellow oil which after p.l.c. (7 : 3 light petroleum–ethyl acetate) gave starting material (118 mg, 60%), and *dimethyl 2,2′,4,4′-tetrahydroxy-5,5′,6,6′-tetramethylbiphenyl-3,3′-dicarboxylate* (14) (12 mg, 12%), m.p. 214—215°, $\nu_{max.}$ 3 400, 1 660, and 1 630 cm⁻¹, τ 7.95 (6 H, s), 7.75 (6 H, s), 5.95 (6 H, s), 0.9 (2 H, s), and −0.8 (2 H, s, exchanged by D₂O) (Found: C, 61.3; H, 5.9%; *m/e*, 390. C₂₀H₂₂O₈ requires C, 61.55; H, 5.7%; *M*, 390).

General Method for Phenolate Formation.—The phenolate anions used in subsequent experiments were generated from the phenol (100—200 mg) in *dry* 1,2-dimethoxyethane or tetrahydrofuran (5 ml) by treatment, at room temperature under nitrogen, with sodium hydride (1 mol. equiv.; oil-free). The mixture was stirred vigorously for 15 min before being oxidised *in situ* at room temperature with benzeneseleninic anhydride.

Sodium 2,4-Dimethylphenolate with Benzeneseleninic

[18] E. Alder, L. Junghahn, U. Lindberg, B. Berggren, and G. Westin, *Acta Chem. Scand.*, 1960, **14**, 1261.
[19] W. T. Summerford and D. N. Dalton, *J. Amer. Chem. Soc.*, 1944, **66**, 1330.

[20] K. Auwers and Th. v. Markovits, *Ber.*, 1905, **38**, 226.
[21] A. Siegel, F. Wessely, P. Stockhammer, F. Antony, and P. Klezl, *Tetrahedron*, 1958, **4**, 49.

Anhydride.—Sodium 2,4-dimethylphenolate [from 2,4-xylenol (106 mg, 0.87 mmol) and sodium hydride (25 mg; 80% suspension in oil)] in benzene (10 ml) was treated with benzeneseleninic anhydride (350 mg, 0.97 mmol) at room temperature in a nitrogen atmosphere. After 2 h the mixture was quenched by addition of aqueous potassium dihydrogen phosphate (5 ml, 10%). Extraction with chloroform (3 × 25 ml) followed by p.l.c. (3 : 1 light petroleum–ether) gave diphenyl diselenide (280 mg) and the *o*-hydroxy-dienone dimer (4) (53 mg, 45%), m.p. 235—237° (lit.,[18] 237—238°).

Sodium 2,6-Dimethylphenolate with Benzeneseleninic Anhydride.—Sodium 2,6-dimethylphenolate [from 2,6-xylenol (122 mg, 1 mmol) and sodium hydride (31 mg; 80% suspension in oil)] in tetrahydrofuran (6 ml) and benzeneseleninic anhydride (360 mg, 1 mmol) were stirred at room temperature under nitrogen for 2 h. Work-up gave the *o*-hydroxy-dienone dimer (7) as white prisms (61 mg, 44%), m.p. 183° (lit.,[18] 183—184°).

Sodium 2,4,6-Trimethylphenolate with Benzeneseleninic Anhydride.—Sodium 2,4,6-trimethylphenolate [from mesitol (136 mg, 1 mmol) and sodium hydride (32 mg; 80% suspension in oil)] in tetrahydrofuran (5 ml) and benzeneseleninic anhydride (365 mg, 1.03 mmol) were stirred at room temperature under nitrogen for 2 h. Work-up gave diphenyl diselenide (291 mg) and the *o*-hydroxy-dienone dimer (9) (84 mg, 55%), m.p. 182° (lit.,[21] 181—183°), mixed m.p. 182°.

Phenolate of the Ring A *Ester* (10; R = OMe) *with Benzeneseleninic Anhydride.*—Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (10; R = OMe) in 1,2-dimethoxyethane (5 ml) was treated with sodium hydride (24 mg; 80% suspension in oil) to form ·the anion in the usual manner. Subsequent treatment with benzeneseleninic anhydride (280 mg, 0.78 mmol) for 30 min followed by quenching with aqueous potassium dihydrogen phosphate (10 ml; 10%) and extraction with chloroform (3 × 25 ml) gave, after work-up by the sodium hydrogen carbonate extraction procedure, from the organic layer, diphenyl diselenide (215 mg) and compound (12; R = OMe) as pale yellow needles (46 mg, 17%), m.p. and mixed m.p. 118°. The aqueous layer on acidification gave the hydroxy-dienone (11; R = OMe) (119 mg, 75%), m.p. and mixed m.p. 111°.

Phenolate of the Ring A *Amide* (10; R = NH₂) *with Benzeneseleninic Anhydride.*—2,6-Dihydroxy-3,4-dimethylbenzamide (10; R = NH₂) (108 mg, 0.6 mmol) in 1,2-dimethoxyethane (5 ml) was treated with sodium hydride (18 mg; 80% suspension in oil) to form the anion. Benzeneseleninic anhydride (216 mg, 0.6 mmol) was added and the mixture stirred at room temperature for 12 h. Work-up in the usual manner gave, from the organic extract, only traces of the phenylseleno-derivative (12; R = NH₂) (t.l.c. and ¹H n.m.r.). The aqueous layer afforded the hydroxy-dienone (11; R = NH₂) (81 mg, 68%), m.p. 146—147° (lit.,[2] 145°), mixed m.p. 145—147°.

Methyl 2,3,6-Trihydroxy-4,5-dimethylbenzoate (15; R = OMe) *with Benzeneseleninic Anhydride.*—To a stirred solution of the triphenol (15; R = OMe) (110 mg, 0.52 mmol) in tetrahydrofuran at room temperature was added benzeneseleninic anhydride (180 mg, 0.5 mmol). After 10 min, water (10 ml) was added and the products were extracted with dichloromethane (3 × 20 ml). Evaporation of the dried extract gave a residue which was crystallised from light petroleum to furnish the quinone (16; R = OMe) as red prisms (105 mg, 98%), m.p. 68° (lit.,[15] 68°).

2,3,6-*Trihydroxy*-4,5-*dimethylbenzamide* (15; R = NH₂)

with Benzeneseleninic Anhydride.—The triphenol (15; R = NH₂) (125 mg, 0.63 mmol) in tetrahydrofuran (5 ml) and benzeneseleninic anhydride (185 mg, 0.52 mmol) were stirred at room temperature under nitrogen for 10 min. Water (10 ml) was added and work-up gave the quinone (16; R = NH₂) (112 mg, 85%), m.p. 165° (lit.,[2] 163—166°), mixed m.p. 165—166°.

Preparation of the Carbonate (17; R = OMe).—The literature [15] method gave the carbonate (17; R = OMe) in 89% yield, m.p. 167°.

Preparation of the Carbonate (17; R = NH₂).—The triphenol (15; R = NH₂) (82 mg, 0.42 mmol) in tetrahydrofuran (5 ml) was treated with *NN'*-carbonyldi-imidazole [22] (80 mg, 0.48 mmol) in tetrahydrofuran (2 ml) at 0 °C. After 1 h 0.02N-hydrochloric acid (15 ml) was added and the mixture was extracted with chloroform (3 × 50 ml). Removal of the solvent from the dried extracts under reduced pressure gave 3-*carbamoyl*-4-*hydroxy*-5,6-*dimethyl*-1,2-*phenylene carbonate* (17; R = NH₂) as a yellow solid (72 mg, 80%), m.p. 248° (from CH₂Cl₂–CHCl₃), ν_max. 3 400, 3 250, 1 810, and 1 635 cm⁻¹, λ_max. 233, 268, and 344 nm (ε 22 300, 21 200, and 6 800), τ 7.9 (6 H, s) and 1.9 (1 H, s, exchanged with D₂O) (Found: C, 53.75; H, 4.1; N, 6.15%; *m/e*, 223. C₁₀H₉NO₅ requires C, 53.8; H, 4.05; N, 6.3%; *M*, 223).

Preparation of the Phenylboronate (18; R = OMe).—To the triphenol (15; R = OMe) (60 mg, 0.28 mmol) in ethanol (5 ml) was added phenylboronic acid (34 mg, 0.28 mmol) with stirring at room temperature. After 2 h solvent was removed under reduced pressure to leave 4-*hydroxy*-3-*methoxycarbonyl*-5,6-*dimethyl*-1,2-*phenylene phenylboronate* (18; R = OMe) as a pale yellow solid (59 mg, 71%), m.p. 136—136° (from dichloromethane), ν_max. 3 180, 1 675, 1 650, 1 440, and 1 320 cm⁻¹, τ 7.9 (3 H, s), 7.75br (3 H, s), 5.95 (3 H, s), 2.7 (5 H, s), and (1 H, s) (Found: C, 64.35; H, 5.15%; *m/e*, 298. C₁₆H₁₅BO₅ requires C, 64.45; H, 5.05%; *M*, 298).

Preparation of the Phenylboronate (18; R = NH₂).—A procedure similar to that in the previous experiment gave 3-*carbamoyl*-4-*hydroxy*-5,6-*dimethyl*-1,2-*phenylene phenylboronate* (18; R = NH₂) (67%), m.p. 266—268° (from benzene), ν_max. 3 300, 3 150, 1 730, 1 440, and 1 320 cm⁻¹, λ_max. 220, 272, and 405 nm (ε 13 000, 17 000, and 800), τ 7.9 (6 H, s), 2.65 (5 H, m), and 1.9 (1 H, s, exchanged by D₂O) (Found: C, 63.65; H, 5.1; N, 4.75%; *m/e*, 283. C₁₅H₁₄BNO₄ requires C, 63.6; H, 5.0; N, 4.95%; *M*, 283).

The Carbonate (17; R = OMe) *with Benzeneseleninic Anhydride.*—The carbonate (17; R = OMe) (103 mg, 0.43 mmol) in 1,2-dimethoxyethane (5 ml) was treated with sodium hydride (20 mg; 80% suspension in oil) under nitrogen at room temperature. Benzeneseleninic anhydride (180 mg, 0.5 mmol) was added and after complete reaction (t.l.c.) the mixture was worked up in the usual way and gave the quinone (16; R = OMe) (63 mg, 78%), m.p. 68°.

The Phenylboronate (18; R = OMe) *with Benzeneseleninic Anhydride.*—The boronate (18; R = OMe) (95 mg, 0.34 mmol) in 1,2-dimethoxyethane (3 ml) was treated with sodium hydride (15 mg; 80% suspension in oil) under nitrogen at room temperature. Benzeneseleninic anhydride (160 mg, 0.44 mmol) was added. After 25 min the reaction was worked up in the usual way and gave the quinone (16; R = OMe) (63 mg, 88%), m.p. 68°, mixed m.p. 66—68°. Other, minor products were observed by t.l.c. but not isolated.

Preparation of the Bis(ethyl carbonate) (19; R¹ = R² = CO₂Et).—Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (10;

[22] H. Staab, *Angew. Chem. Internat. Edn.*, 1962, **1**, 351.

R = OMe) (392 mg, 2 mmol) in chloroform (10 ml) (dried by passage through an alumina column) and pyridine (1 ml) was treated with ethyl chloroformate (434 mg, 4 mmol) at room temperature. After 1 h cold 0.1N-hydrochloric acid (15 ml) was added and the product extracted with chloroform (2 × 50 ml). Removal of the solvent from the extracts under reduced pressure gave the *bis(ethyl carbonate)* (19; $R^1 = R^2 = CO_2Et$) as prisms (612 mg, 89%), m.p. 61° (from light petroleum–ether), $v_{max.}$ 1 775, 1 735, and 1 635 cm^{-1}, $\lambda_{max.}$ 215, 256, and 316 nm (ε 27 200, 7 620, and 4 200), τ 8.7—8.4 (6 H, t, J 7.6 Hz), 7.85 (3 H, s), 7.65 (3 H, s), 6.15 (3 H, s), 5.85—5.4 (4 H, q, J 7.6 Hz), and 3.0 (1 H, s) (Found: C, 56.7; H, 5.85; m/e, 340. $C_{16}H_{20}O_8$ requires C, 56.45; H, 5.9%; M, 340),

Preparation of the Mono(ethyl carbonate) (19; $R^1 = H$, $R^2 = CO_2Et$).—Sodium (11 mg, 0.48 g atom) was dissolved in dry methanol (3 ml) at 0 °C. To this solution was added the bis(ethyl carbonate) (19; $R^1 = R^2 = CO_2Et$) (258 mg, 0.96 mmol) in methanol (9 ml). Work-up after 5 min by the addition of 0.1N-hydrochloric acid (15 ml) followed by extraction with dichloromethane (3 × 25 ml) gave *ethyl 3-hydroxy-2-methoxycarbonyl-4,5-dimethylphenyl carbonate* (19; $R^1 = H$, $R^2 = CO_2Et$) (192 mg, 96%), m.p. 90° (from light petroleum–ether at 0 °C), $v_{max.}$ 3 300, 1 765, 1 675, and 1 630 cm^{-1}, $\lambda_{max.}$ 213, 254, and 312 nm (ε 27 800, 7 850, and 4 220), τ 8.7—8.8 (3 H, t, J 7 Hz), 7.95 (3 H, s), 7.8 (3 H, s), 6.05 (3 H, s), 5.85—5.45 (2 H, q, J 7 Hz), 3.25 (1 H, s), and −1.0 (1 H, s, exchanged by D_2O) (Found: C, 58.2; H, 6.05%; m/e, 268. $C_{13}H_{16}O_3$ requires C, 58.2; H, 6.0%; M, 268).

The Mono(ethyl carbonate) (19; $R^1 = H$, $R^2 = CO_2Et$) *with Benzeneseleninic Anhydride.*—A mixture of the mono-(ethyl carbonate) (19; $R^1 = H$, $R^2 = CO_2Et$) (117 mg, 0.44 mmol) and benzeneseleninic anhydride (180 mg, 0.5 mmol) was stirred in dichloromethane (3 ml) at room temperature for 3 h; t.l.c. indicated that no reaction took place.

The Mono(ethyl carbonate) (19; $R^1 = H$, $R^2 = CO_2Et$) *with Sodium Hydride–Benzeneseleninic Anhydride.*—The mono(ethyl carbonate) (19; $R^1 = H$, $R^2 = CO_2Et$) (107 mg,

0.4 mmol) in tetrahydrofuran (2 ml) was treated with sodium hydride (10 mg; 80% suspension in oil) under nitrogen. Benzeneseleninic anhydride (160 mg, 0.45 mmol) was added and the temperature of the mixture was raised to 55 °C for 2 h. Work-up by the sodium hydrogen carbonate extraction method gave, from the organic layer, diphenyl diselenide (83 mg) and a mixture of starting material and phenylseleno-compound (21) which resisted all attempts at separation; the mass spectrum showed m/e 268 and 424.

The aqueous layer on acidification and extraction gave *ethyl 4-hydroxy-2-methoxycarbonyl-4,5-dimethyl-3-oxocyclo-hexa-1(6),2-dienyl carbonate* (20) (30 mg, 55% based on converted starting material), m.p. 98° (from light petroleum), $v_{max.}$ 3 450, 1 770, 1 680, and 1 630 cm^{-1}, $\lambda_{max.}$ 226, 276, 283, and 314 nm (ε 11 350, 2 600, 2 180, and 4 490), τ 8.8—8.55 (3 H, t, J 4.4 Hz), 8.45 (3 H, s), 7.8 (3 H, m), 6.05 (3 H, s), 6.0—5.55 (2 H, q, J 7.4 Hz), and 3.8 (1 H, d) (Found: C, 54.9; H, 5.75%; m/e, 284. $C_{13}H_{16}O_7$ requires C, 54.95; H, 5.65%; M, 284).

The Mono(ethyl carbonate) (19; $R^1 = H$, $R^2 = CO_2Et$) *with Benzeneseleninic Anhydride at Elevated Temperature.*—The mono(ethyl carbonate) (19; $R^1 = H$, $R^2 = CO_2Et$) (139 mg, 0.52 mmol) and benzeneseleninic anhydride (180 mg, 0.5 mmol) in tetrahydrofuran (5 ml) were heated under reflux for 3 h. The cooled mixture was worked up by the sodium hydrogen carbonate extraction procedure, and gave (from the organic layer) an inseparable mixture of starting material and compound (21) together with *methyl 1-hydroxy-3,4-dimethyl-2,5-dioxocyclopent-3-enecarboxylate* (22) (10 mg, 10%), m.p. 126—127°, $v_{max.}$ 1660—1680 cm^{-1}, $\lambda_{max.}$ 255 nm (ε 22 000), τ 7.9 (6 H, s) and 6.3 (3 H, s) [Found: C, 54.35; H, 5.1%; m/e, 200 ($M + 2$). $C_9H_{10}O_5$ requires C, 54.55; H, 5.1%; M, 198].