Experiments on the Synthesis of Tetracycline. Part XIII.[1] Oxidation of Ring A Model Phenols to p-Hydroxycyclohexadienones

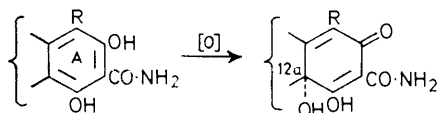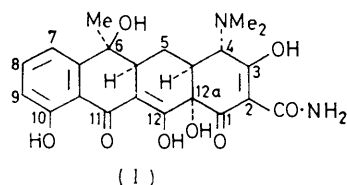By **Derek H. R. Barton, Philip D. Magnus,*** and **John C. Quinney,** Chemistry Department, Imperial College, Kensington, London SW7 2AY

The reaction of phenols with cerium(IV) oxide–hydrogen peroxide to give hydroperoxycyclohexadienones is described. In particular 2,6-dihydroxy-3,4-dimethylbenzamide (V) is converted into 3-hydroperoxy-2-hydroxy-3,4-dimethyl-6-oxocyclohexa-1,4-dienecarboxamide (VII). The reagent system is shown to be an *in situ* source of singlet oxygen.

IN previous papers we have described an approach towards the total synthesis of tetracycline (I).[2] In particular our strategy involves the dearomatisation of ring A with concomitant 12a-hydroxylation [3] (Scheme).

A number of reagents have been developed by other workers that oxidise simple alkylphenols to either *p*-hydroperoxycyclohexadienones or the corresponding

(I)

SCHEME

p-hydroxycyclohexadienones. In some cases *ortho*-hydroxylation is observed. 2,6-Xylenol has been oxidised by trifluoroperacetic acid to give the dimer (II), formed from the *ortho*-hydroxydienone by Diels–Alder

addition.[4] Transition metal ion–hydrogen peroxide systems have been employed for the oxidation of

(II)   (III)   (IV)
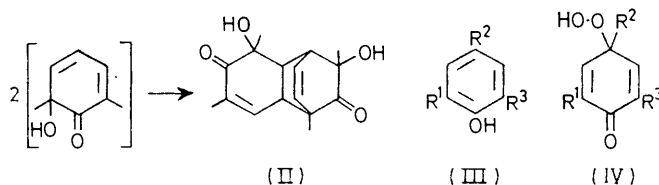
phenols. Thus the alkylphenols (III; $R^1 = R^2 = R^3 = $ Me or Bu^t) when treated with titanium tetrachloride or dichlorocyclopentadienyltitanium(IV) and hydrogen peroxide afford the corresponding *p*-hydroperoxycyclohexadienones (IV).[5] Molybdenum(VI) has also been shown to be an effective reagent for these reactions.[5,6] Decomposition of hydrogen peroxide by various transition metal ions (Co^{II}, Fe^{II}, Fe^{III}, Cu^I, and Cu^{II}) in the presence of the phenol (III; $R^1 = R^3 = $ Bu^t, $R^2 = $ Me) gave the *p*-hydroperoxycyclohexadienone (IV; $R^1 = R^3 = $ Bu^t, $R^2 = $ Me).[7] Similarly, a number of

[1] Part XII, D. H. R. Barton, P. D. Magnus, and J. I. Okogun, *J. Chem. Soc. (C)*, 1972, 1103.
[2] D. H. R. Barton and P. D. Magnus, *J. Chem. Soc. (C)*, 1971, 2164.
[3] D. H. R. Barton, L. Bould, D. L. J. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc. (C)*, 1971, 2204.

[4] D. Bryce-Smith and A. Gilbert, *J. Chem. Soc.*, 1964, 873; R. D. Chambers, P. Goggin, and W. K. R. Musgrave, *ibid.*, 1959, 1804, C. A. Buehler and H. Hart, *J. Amer. Chem. Soc.*, 1963, **85**, 2177; *J. Org. Chem.*, 1964, **29**, 2397; A. J. Waring and H. Hart, *J. Amer. Chem. Soc.*, 1964, **86**, 1454; J. D. McClure, *J. Org. Chem.*, 1963, **28**, 69.
[5] R. G. R. Bacon and Lai Ching Kuan, *Tetrahedron Letters*, 1971, 3397.
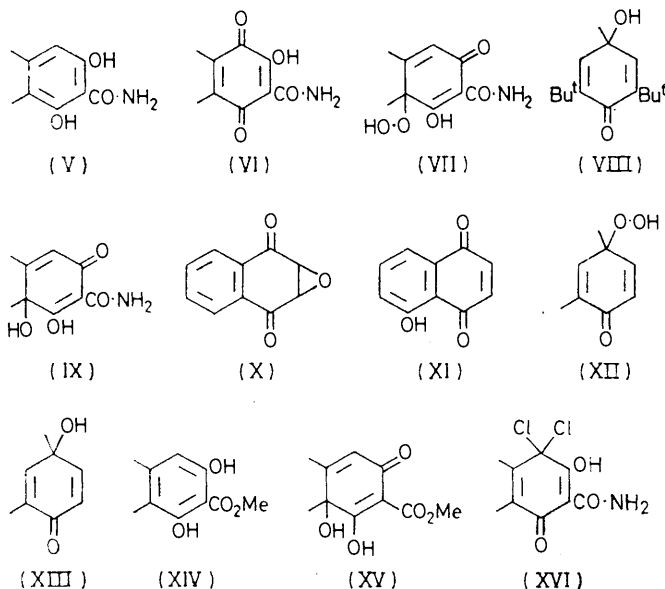[6] Y. Hayashi, S. Shiori, M. Togami, and T. Sakau, *Chem. Letters*, 1973, **7**, 651.
[7] G. M. Coppinger, *J. Amer. Chem. Soc.*, 1957, **79**, 2758.

metal ion–hydrogen peroxide systems have been employed in a comparative study of the oxidation of 2,6-xylenol.[8]

The dihydroxy-amide (V) was chosen as a model to test a number of metal ion–hydrogen peroxide systems. Treatment of the amide (V) with ammonium molybdate–hydrogen peroxide gave the quinone (VI), m.p. 145—147 °C, in fair yield. Sodium molybdate gave a solid, m.p. 163—166 °C, which proved to be an isomorphic form of the quinone (VI).

After preliminary studies of metal oxide–hydrogen peroxide systems, technical grade cerium(IV) oxide–hydrogen peroxide seemed promising. The phenol (III; $R^1 = R^3 = Bu^t$, $R^2 = Me$) was treated with this reagent in ethanol to give a pale yellow, light-sensitive solid (IV; $R^1 = R^3 = Bu^t$, $R^2 = Me$) in good yield. Similarly, mesitol (III; $R^1 = R^2 = R^3 = Me$) and p-cresol (III; $R^1 = R^3 = H$, $R^2 = Me$) were converted into the hydroperoxycyclohexadienones (IV; $R^1 = R^2 = R^3 = Me$) and (IV; $R^1 = R^3 = H$, $R^2 = Me$), respectively. The amide (V) was treated with cerium(IV) oxide–hydrogen peroxide in ethanol at 60 °C to give a pale yellow oil that slowly crystallised in good yield, showing $v_{max.}$ 3 400, 3 250, 1 720, 1 685, and 1 580 cm^{-1}, 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), with OH and $CONH_2$ signals as a broad envelope at low field. These facts, combined with mass spectral and microanalytical data, indicated that the

efficient procedure was to treat the hydroperoxides with dimethyl sulphide in tetrahydrofuran. Reduction to the corresponding hydroxycyclohexadienones proceeded in quantitative yield.

1-Naphthol reacted with cerium(IV) oxide–hydrogen peroxide to give a compound $v_{max.}$ 1 700, 1 600, and 1 300 cm^{-1}, τ 6.0 (2 H, s) and 2.4—1.9 (4 H, m), identified as the epoxide (X).[10] Naphthalene-1,5-diol was converted into juglone (XI) under similar conditions. 2,4-Xylenol (III; $R^1 = R^2 = Me$, $R^3 = H$) gave the hydroperoxycyclohexadienone (XII) in good yield. Its structure was established by reduction (Me$_2$S) to the known hydroxy-dienone (XIII).[11] The ester (XIV) did *not* react under the conditions used to produce the hydroperoxy-dienone (VII) from (V). This unexpected result has been reproduced by several workers in these laboratories. On the other hand the ester (XIV) did react with cobalt(II) acetate–hydrogen peroxide to give the hydroxy-dienone (XV), $v_{max.}$ 3 420, 1 680, and 1 580 cm^{-1}, τ 8.6 (3 H, s), 7.9 (3 H, d, J 1.5 Hz), 6.1 (3 H, s), 4.0 (1 H, d, J 1.5 Hz), and −4.2 (1 H, exchangeable s), identical with an authentic sample.[12] The amide (V) reacted with cobalt(II) acetate–hydrogen peroxide to give a green oil which upon treatment with the sodium salt of ethylenediaminetetra-acetic acid gave the hydroxy-dienone (IX) in low yield.

Uranyl salts and hydrogen peroxide react to form so-called peruranic acid $UO_4,2H_2O$.[13] Uranyl chloride–hydrogen peroxide converted mesitol (III; $R^1 = R^2 = R^3 = Me$) into (IV; $R^1 = R^2 = R^3 = Me$) along with traces of 2,6-dimethylbenzoquinone. Similarly the phenol (III; $R^1 = R^3 = Bu^t$, $R^2 = Me$) reacted to give the hydroperoxy-dienone (IV; $R^1 = R^3 = Bu^t$, $R^2 = Me$). In contrast the benzamide (V) gave a product whose spectral properties indicated it to be the dichloro-dienone (XVI). The same product (XVI) was formed from the benzamide (V) and cerium(V) oxide–hydrogen peroxide, if hydrochloric acid was present. Acid-free uranyl peroxide[13] did not react with the benzamide (V). In blank experiments the phenol (III; $R^1 = R^3 = Bu^t$, $R^2 = Me$) reacted with hydrogen peroxide–hydrochloric acid to give the dienone (IV; $R^1 = R^3 = Bu^t$, $R^2 = Me$), whereas (V) gave the dichloro-dienone (XVI).

Since the cerium(IV) oxide–hydrogen peroxide system was the most successful it was studied further. To ascertain whether or not singlet oxygen was the reactive species ergosterol acetate (XVII) was treated with technical cerium(IV) oxide–hydrogen peroxide (under nitrogen with light excluded). The 5α,8α-peroxide (XVIII) was isolated in 38% yield.[14] Similarly lumisterol

(V)　　(VI)　　(VII)　　(VIII)

(IX)　　(X)　　(XI)　　(XII)

(XIII)　　(XIV)　　(XV)　　(XVI)

required product (VII) was formed. Treatment of the hydroperoxycyclohexadienones (IV; $R^1 = R^3 = Bu^t$, $R^2 = Me$) and (VII) with aqueous potassium hydroxide–potassium iodide gave the corresponding hydroxycyclohexadienones (VIII)[9] and (IX). A simpler and more

[8] R. G. R. Bacon and A. R. Izzat, *J. Chem. Soc. (C)*, 1966, 791.
[9] A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 1953, 3211.
[10] L. F. Fieser, M. Tishler, and W. L. Sampson, *J. Amer. Chem. Soc.*, 1940, 62, 1628.
[11] E. Bamberger and F. Brady, *Chem. Ber.*, 1960, 33, 3650.

[12] D. H. R. Barton, P. D. Magnus, and M. N. Rosenfeld, unpublished observations.
[13] A. Rosenheim and H. Daehv, *Z. anorg. Chem.*, 1929, 181, 137; A. Sievents and E. L. Muller, *ibid.*, 1928, 173, 299; G. W. Watt, S. L. Achorn, and J. L. Marley, *J. Amer. Chem. Soc.*, 1950, 72, 3341; J. E. Boggs and M. El Chehabi, *ibid.*, 1957, 79, 4258.
[14] V. Prelog and P. Wieland, *Helv. Chim. Acta*, 1947, 30, 1028; D. H. R. Barton, G. Leclerc, P. D. Magnus, and I. D. Menzies, *J.C.S. Chem. Comm.*, 1972, 447; A. Windaus and J. Brunken, *Annalen*, 1927, 460, 225.
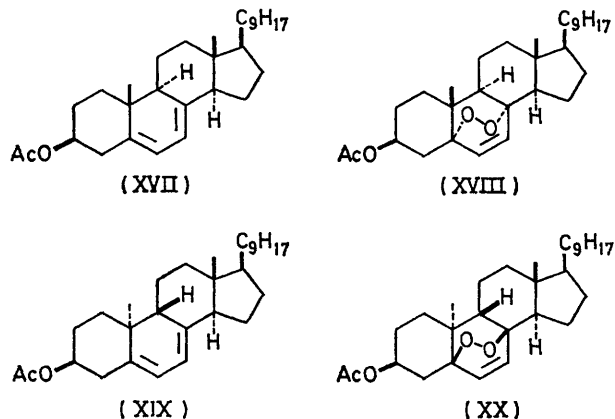
acetate (XIX) was converted into the corresponding 5β,8β-peroxide (XX) in 45% yield.[15] A direct rate comparison was made by treating equal amounts of the two dienes (XVII) and (XIX) in t-butyl alcohol in the

C_9H_{17}

(XVII)

C_9H_{17}

(XVIII)

C_9H_{17}

(XIX)

C_9H_{17}

(XX)

AcO (on all four structures)

same vessel with cerium(IV) oxide–hydrogen peroxide at 65 °C under nitrogen, with exclusion of light. The two peroxides (XVIII) and (XX) were isolated in the ratio 2.3 : 1, indicating that they are formed from singlet oxygen.[14] The reaction of singlet oxygen with various alkylphenols, none of them resorcinols, has been reported to give the corresponding p-hydroperoxycyclohexa-dienones.[16] Treatment of the benzamide (V) with singlet oxygen ($h\nu$, eosin–O_2 in ethanol) gave, after reduction (Me$_2$S), a mixture of two products, the hydroxy-dienone (IX) (major component) and the quinone (VI). Oxidation with cerium(IV) oxide–hydrogen peroxide gives no quinone (VI).

A series of control experiments on the reaction (V) → (VII) showed that both cerium(IV) oxide and hydrogen peroxide were needed, at an optimum temperature of 60—70 °C. Oxygen and light were not required. At pH 9 there was no reaction. The natural pH of the reaction system was 5.0—5.4. In the presence of hydrochloric acid the chloro-dienone (XVI) is formed, but other non-oxidisable mineral acids do not greatly affect the reaction. The best solvents were methanol, ethanol, and other alcohols, especially the non-oxidisable t-butyl alcohol.

The technical cerium dioxide used in this work was at least 20 years old. When the work was repeated with a specimen of recent manufacture no oxidation took place. There was also no oxidation with freshly prepared pure cerium dioxide. At first this difference was attributed to a variation in rare earth content but, in fact, the original specimen of cerium dioxide became inactive if dissolved and reprecipitated. It was then established that the activity of the cerium dioxide was dependent on its thermal history. Precipitation of either pure or technical cerium dioxide at pH 12 followed by pyrolysis at 900 °C gave material that was reproducibly as active as the original specimen.

The oxidations observed are, we consider, best regarded as occurring on the surface of the cerium

dioxide with singlet oxygen, also generated on the surface. It is only by invoking surface reactions that one can understand that the amide (V) is smoothly oxidised whereas the corresponding ester (XIV) is untouched. The cerium dioxide–hydrogen peroxide system deserves further investigation.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were measured for Nujol mulls or thin films unless otherwise stated. N.m.r. spectra were recorded with a Varian A60 instrument for solutions in [^{2}H]chloroform with tetramethylsilane as internal standard unless otherwise stated. All solvents were purified prior to use by standard techniques. Light petroleum refers to the fraction of b.p. 40—60°.

2,6-Dihydroxy-3,4-dimethylbenzamide (V).—Methyl 3-formyl-2,6-dihydroxy-4-methylbenzoate was hydrogenolysed over 10% palladium–carbon in glacial acetic acid to give the dihydroxy-dimethylbenzoate (XIV) (94%), m.p. 108° (lit.,[17] 108°). Treatment of this ester (XIV) with ammonia (d 0.880) gave the benzamide [17] (V) (90%), m.p. 232—234°, $\nu_{max.}$ 1 625, 1 660, 3 250, and 3 400 cm^{-1}.

2-Hydroxy-4,5-dimethyl-3,6-dioxocyclohexa-1,4-dienecarb-oxamide (VI).—The benzamide (V) (50 mg) in t-butyl alcohol (10 ml) was treated with ammonium molybdate (20 mg) and hydrogen peroxide (30%; 5 ml). After 30 min the orange solution was diluted with water (50 ml) and extracted with chloroform (3 × 30 ml). Evaporation of the dried extracts and crystallisation of the residue from benzene gave the quinone (VI) (50 mg, 92%), m.p. 145—147°, $\nu_{max.}$ 3 400, 3 300, and 1 650 cm^{-1}, τ 7.9 (6 H, s), 4.1—3.5 (2 H, s), and 1.5—1.0br (1 H, s, exchanged by D$_2$O) (Found: C, 55.5; H, 4.9; N, 7.1. $C_9H_9NO_4$ requires C, 55.4; H, 4.7; N, 7.2%). The above experiment was carried out with sodium molybdate in place of ammonium molybdate, to give the quinone (VI) (45 mg, 80%), m.p. 163—166°. Solution spectra (i.r. and n.m.r.) were identical with those of the above preparation.

4-Hydroperoxy-4-methyl-2,6-di-t-butylcyclohexa-2,5-dienone (IV; $R^1 = R^3 = Bu^t$, $R^2 = Me$).—The phenol (III; $R^1 = R^3 = Bu^t$, $R^2 = Me$) (220 mg) in ethanol (20 ml) was treated with technical cerium(IV) oxide (400 mg) and hydrogen peroxide (30%; 10 ml). The mixture was heated under reflux for 2 h, cooled, and filtered. The filtrate was diluted with water (200 ml) and extracted with ether (3 × 30 ml). Evaporation of the dried extracts (MgSO$_4$) gave the hydroperoxy-dienone (IV; $R^1 = R^3 = Bu^t$, $R^2 = Me$) (180 mg, 70%), m.p. 115—116° (lit.,[7] 115°) (from light petroleum), $\nu_{max.}$ 3 300, 1 660, 1 640, and 870 cm^{-1} (OOH), τ 8.8 (18 H, s), 8.7 (3 H, s), and 5.4—5.0br (1 H, s, exchanged by D$_2$O).

4-Hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone (IV; $R^1 = R^2 = R^3 = Me$).—Mesitol (III; $R^1 = R^2 = R^3 = Me$) (140 mg) in ethanol (10 ml) was treated with technical cerium(IV) oxide (400 mg) and hydrogen peroxide (30%; 20 ml) and the mixture was stirred at reflux. After 2 h the mixture was filtered and the filtrate diluted with water (100 ml) and extracted with ether (3 × 30 ml). Evaporation of the dried extract gave the hydroperoxy-dienone [5] (IV; $R^1 = R^2 = R^3 = Me$) (120 mg), m.p. 98—99.5° (from

[15] P. Bladon, J. Chem. Soc., 1955, 2176.
[16] K. Pfoertner and D. Bose, Helv. Chim. Acta, 1970, 1553.
[17] A. Robertson and W. B. Whalley, J. Chem. Soc., 1949, 3038.

light petroleum), $\nu_{max.}$ 3 370, 1 685, 1 630, 925, and 850 cm^{-1}, τ 8.1 (6 H, s), 8.6 (3 H, s), 3.3 (2 H, s), and 1.6—1.3br (1 H, s, exchanged by D_2O) (Found: C, 64.1; H, 7.0. Calc. for $C_9H_{12}O_3$: C, 64.3; H, 7.2%).

4-*Hydroperoxy-4-methylcyclohexa-2,5-dienone* (IV; R^1 = R^3 = H, R^2 = Me).—*p*-Cresol (III; R^1 = R^3 = H, R^2 = Me) (100 mg) in ethanol (10 ml) was treated with technical cerium(IV) oxide (400 mg) and hydrogen peroxide (30%; 20 ml) under the conditions described above. Work-up gave the hydroperoxy-dienone (IV; R^1 = R^3 = H, R^2 = Me) (100 mg) as a pale yellow oil, $\nu_{max.}$ 3 400, 1 680, 845, and 280 cm^{-1}, τ 8.95 (3 H, s), 4.1 and 3.4 (2 × 2 H, d, J 10 Hz), and 2.8—2.0br (1 H, exchanged by D_2O), *m/e* 124 (*M* − 16).

3-*Hydroperoxy-2-hydroxy-3,4-dimethyl-6-oxocyclohexa-1,4-dienecarboxamide* (VII).—The benzamide (V) (50 mg) in t-butyl alcohol (4 ml) was treated with technical cerium(IV) oxide (110 mg) and hydrogen peroxide (30%; 4 × 2 ml) added over 6 h at 65 °C. After 6 h the mixture was cooled and filtered and the filtrate diluted with water (60 ml). Extraction with chloroform (3 × 20 ml) and evaporation of the dried extract at room temperature gave the crude *hydroperoxy-dienone* (VII) (47 mg, 80%), m.p. 137—139° (from benzene–light petroleum), $\nu_{max.}$ 3 400, 3 250, 1 720, 1 685, and 1 580 cm^{-1}, $\lambda_{max.}$ 228, 257, and 307 nm (ε 16 220, 6 070, and 4 470), 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) (Found: C, 50.5; H, 5.3; N, 6.3. $C_9H_{11}NO_5$ requires C, 50.7; H, 5.2; N, 6.6%), *m/e* 213 (*M*$^+$) and 197 (*M*$^+$ − 16).

4-*Hydroxy-4-methyl-2,6-di-t-butylcyclohexa-2,5-dienone* (VIII).—Prepared by reduction of the hydroperoxide (IV; R^1 = R^3 = Bu^t, R^2 = Me) with potassium hydroxide–potassium iodide,[9] this had m.p. 112—113° (lit.,[9] 112—113°), $\nu_{max.}$ 3 300, 1 660, and 1 640 cm^{-1}.

2,3-*Dihydroxy-3,4-dimethyl-6-oxocyclohexa-1,4-dienecarboxamide* (IX).—The hydroperoxide (VII) (100 mg) in methanol (5 ml) was treated with sodium iodide (300 mg) and potassium hydroxide (400 mg). After 2 h, sodium thiosulphate (500 mg) in water (60 ml) was added and the resulting solution neutralised with hydrochloric acid (6N). Extraction with chloroform (3 × 30 ml) and evaporation of the dried (Na$_2$SO$_4$) extracts gave the *hydroxy-dienone* (IX) (37 mg, 40%), m.p. 146—147° (from benzene–light petroleum), $\nu_{max.}$ 3 500, 3 380, 3 200, 1 685, and 1 585 cm^{-1}, 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) (Found: C, 54.9; H, 5.4; N, 7.3. $C_9H_{11}NO_4$ requires C, 54.8; H, 5.6; N, 7.1%).

The hydroperoxide (VII) (70 mg) in dry tetrahydrofuran (5 ml) was treated with dimethyl sulphide (1 ml). The mixture was kept at room temperature for 3 h, and then evaporated to dryness to give the hydroxy-dienone (IX) (65 mg, 95%), identical with an authentic sample (i.r. spectrum, m.p., and mixed m.p.).

2,3-*Epoxy-2,3-dihydro-1,4-naphthoquinone* (X).—1-Naphthol (100 mg) in t-butyl alcohol (10 ml) was treated with technical cerium(IV) oxide (300 mg) and the mixture heated at reflux for 2 h, during which time hydrogen peroxide (30%; 5 × 5 ml) was added. The mixture was cooled and filtered, and the filtrate diluted with water (100 ml). Extraction with chloroform and evaporation of the dried (Na$_2$SO$_4$) extracts gave the epoxide (X) (100 mg, 83%), m.p. 134—135° (lit.,[10] 133—135°).

5-*Hydroxy-1,4-naphthoquinone* (XI).—Naphthalene-1,5-diol (180 mg) in t-butyl alcohol (10 ml) was treated with technical cerium(IV) oxide (450 mg). To this mixture at

room temperature hydrogen peroxide (30%; 2 × 0.4 ml) was added. After 24 h the mixture was diluted with water (50 ml) and filtered through Celite. Extraction with chloroform and evaporation of the dried extracts gave an oil which was chromatographed on silica gel [elution with ethyl acetate–light petroleum (1 : 9)] to give the quinone (XI)[18] (30 mg, 18%), m.p. 135—145°, $\nu_{max.}$ 1 655, 1 635, 860, and 840 cm^{-1}.

4-*Hydroxy-2,4-dimethylcyclohexa-2,5-dienone* (XIII).—2,4-Xylenol (III; R^1 = R^2 = Me, R^2 = H) (200 mg) in t-butyl alcohol (10 ml) was treated with technical cerium(IV) oxide–hydrogen peroxide in the usual way. Work-up gave a pale yellow oil which was treated with dimethyl sulphide (1 ml) in dry tetrahydrofuran (5 ml) for 3 h. Evaporation, followed by chromatography over silica gel [elution with ethyl acetate–light petroleum (2 : 3)] gave the hydroxy-dienone (XIII) (100 mg, 46%), m.p. 73° (from light petroleum) (lit.,[11] 73—74°).

Methyl 2,3-Dihydroxy-3,4-dimethyl-6-oxocyclohexa-1,4-dienecarboxylate (XV).—The ester (XIV) (300 mg) in t-butyl alcohol (10 ml) was treated with cobalt(II) acetate (180 mg) and hydrogen peroxide (30%; 5 × 0.5 ml), over 19 h at room temperature. Dilution of the mixture with water (100 ml), extraction with chloroform (3 × 30 ml), and evaporation of the dried (Na$_2$SO$_4$) extracts gave the *hydroxy-dienone* (XV)[12] (100 mg, 29%), m.p. 111—113° (from chloroform–light petroleum), $\nu_{max.}$ 3 420, 1 680, and 1 580 cm^{-1}, τ 8.6 (3 H, s), 7.9 (3 H, d, J 1.5 Hz), 6.1 (3 H, s), 4.0 (1 H, d, J 1.5 Hz), and −4.2br (1 H, s, exchanged by D_2O).

Similarly, the amide (V) (300 mg) was treated with cobalt(II) acetate–hydrogen peroxide in the presence of the sodium salt of ethylenediaminetetra-acetic acid. After work-up the hydroxy-dienone (IX) was isolated in *ca.* 10% yield.

Oxidation of Mesitol (III; R^1 = R^2 = R^3 = Me) *with Uranyl Chloride–Hydrogen Peroxide.*—The phenol (III; R^1 = R^2 = R^3 = Me) (120 mg) in t-butyl alcohol (10 ml) was treated with uranyl chloride (12 g) and hydrogen peroxide (30%; 10 ml). After 3 days at room temperature the mixture was filtered and the filtrate diluted with water (50 ml) and extracted with chloroform (3 × 30 ml). The extracts were evaporated and the residue chromatographed on silica gel [elution with ethyl acetate–light petroleum (1 : 4)] to give the hydroperoxy-dienone (IV; R^1 = R^2 = R^3 = Me) (60 mg, 40%), m.p. 98—99°, mixed m.p. 87—99°.

Similarly, the phenol (III; R^1 = R^3 = Bu^t, R^2 = Me) gave the hydroperoxy-dienone (IV; R^1 = R^3 = Bu^t, R^2 = Me) (50%), m.p. 115°, mixed m.p. 114—115°.

The benzamide (V) (100 mg) under similar conditions with uranyl chloride–hydrogen peroxide gave a yellow oil, $\nu_{max.}$ 3 370, 1 660, and 1 570 cm^{-1}, *m/e* 249 ($C_9H_9Cl_2NO_3$).

The benzamide (V) (200 mg) in t-butyl alcohol (10 ml) was treated with hydrochloric acid (6N; 5 ml) and hydrogen peroxide (30%; 5 ml). After 13 h at room temperature, work-up gave 3,3-*dichloro-2-hydroxy-4,5-dimethyl-6-oxocyclohexa-1,4-dienecarboxamide* (XVI) (120 mg, 40%), m.p. 119—121° (from aqueous methanol), $\nu_{max.}$ 3 370, 1 660, and 1 570 cm^{-1}, τ 7.8 (s), *m/e* 249 (Found: C, 43.3; H, 4.8; Cl, 28.2; N, 5.5. $C_9H_9Cl_2NO_3$ requires C, 43.2; H, 3.6; Cl, 28.4; N, 5.6%).

5α,8α-*Epidioxy-5,8-dihydroergosteryl Acetate* (XVIII).—Ergosteryl acetate (XVII) (70 mg) in ethanol–chloroform (1 : 1; 10 ml) was treated with cerium(IV) oxide (210 mg)

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[18] R. Willstatter and A. S. Wheeler, *Chem. Ber.*, 1914, **47**, 2796.

and hydrogen peroxide (30%; 15 ml). After 7 days at 60 °C the mixture was filtered and the filtrate diluted with water (50 ml) and extracted with chloroform (3 × 30 ml). The dried (Na$_2$SO$_4$) extract was evaporated and the residue chromatographed (p.l.c.) on silica gel (elution with ethyl acetate–light petroleum) to give ergosteryl acetate (XVII) (8 mg) and the 5α,8α-peroxide (XVIII) (25 mg, 38%), m.p. 194—197° (from light petroleum) (lit.,[14] 196—202°).

5β,8β-*Epidioxy*-5,8-*dihydrolumisteryl Acetate* (XX).— Lumisteryl acetate (XIX) (150 mg) in t-butyl alcohol (4 ml) was treated with technical cerium(IV) oxide (450 mg) and hydrogen peroxide (30%; 2 × 4 ml). After 48 h the mixture was filtered and the filtrate diluted with water (50 ml) and extracted with chloroform (3 × 30 ml). Evaporation of the dried (Na$_2$SO$_4$) extracts afforded the endo-peroxide (XX) (75 mg, 45%), m.p. 158—160° (lit.,[15] 157—160°).

Rate Comparison: Oxygenation of Ergosteryl and Lumisteryl Acetates (XVII) *and* (XIX).—The dienes (XVII) and (XIX) (100 mg of each) in t-butyl alcohol (20 ml) were treated with technical cerium(IV) oxide (600 mg) and

hydrogen peroxide (30%; 10 ml) at 68 °C under nitrogen. After 1.8 h the reaction was worked up in the usual way to give the peroxides (XVIII) (34 mg) and (XX) (15 mg) (separated by p.l.c.).

Singlet Oxygenation of the Benzamide (V).—The benzamide (V) (300 mg) in ethanol (50 ml) containing eosin (4 ml) was irradiated with a tungsten lamp while oxygen was bubbled through the solution. After 7 days the mixture was evaporated and the residue dissolved in tetrahydrofuran (5 ml) and treated with dimethyl sulphide (0.5 ml). Evaporation gave the hydroxy-dienone (IX) (200 mg), identical with an authentic sample. The crude product contained some quinone (VI) (t.l.c.).

Activation of Cerium(IV) *Oxide.*—Cerium(IV) oxide (5 g) was dissolved in hot sulphuric acid (6N; 100 ml) and the cooled solution treated with sodium hydroxide solution (4N) to pH 12. The precipitated oxide was filtered off, washed with water (200 ml), and dried *in vacuo*. The sample was heated at *ca.* 900 °C for 24 h.