The Chemistry of Fungi. Part LXI.[1] The Synthesis of (±)-Sclerotiorin, of (±)-4,6-Dimethylocta-*trans*-2,*trans*-4-dienoic Acid, and of an Analogue of Rotiorin

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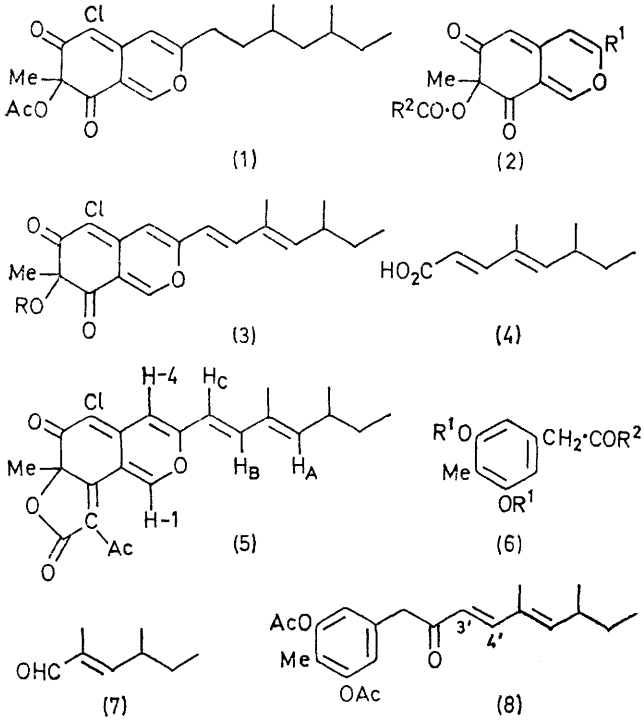
Syntheses of (±)-sclerotiorin, the principal pigment of several fungi including *Penicillium multicolor* and *P. sclerotiorum*, of (±)-4,6-dimethylocta-*trans*-2,*trans*-4-dienoic acid [a major degradation product of (+)- and of (−)-sclerotiorin] and of (+)-5-chloroisorotiorin, an angular analogue of rotiorin, are described.

OUR synthesis [1] of (±)-tetrahydrosclerotiorin (1) established a potential route, *mutatis mutandis*, to substances of the type (2), and hence to the sclerotiorin group of fungal metabolites in general. We have developed this method to provide a synthesis of sclerotiorin (3; R = Ac), the principal pigment [2] of, *inter alia*, *Penicillium multicolor* Grigorieva-Manoilova and Poradielova and *P. sclerotiorum* van Beyma. The present paper also describes the synthesis of (±)-4,6-dimethylocta-*trans*-2,*trans*-4-dienoic acid (4), a major degradation product of both (+)-[2] and (−)-sclerotiorin,[3] together with the synthesis of (+)-5-chloroisorotiorin (5), an angular analogue of rotiorin.[4]

The starting point for our synthesis of sclerotiorin was 3,5-dihydroxy-4-methylbenzoic acid, which after formation of the di-*O*-benzyl-ether was transformed by application of the Arndt–Eistert reaction into 3,5-dibenzyloxy-4-methylphenylacetic acid (6; $R^1 = PhCH_2$, $R^2 = OH$). This acid was converted successively into

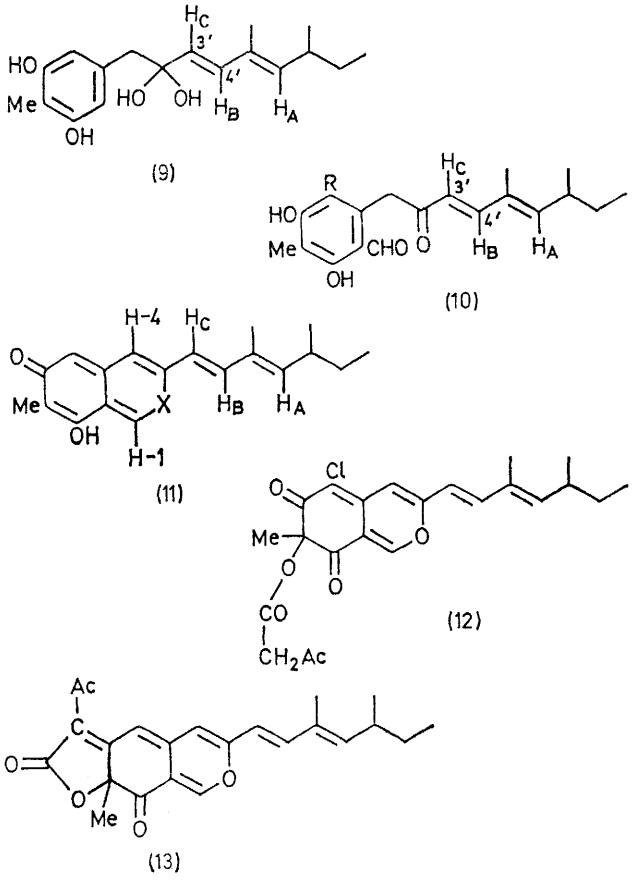
[1] Part LX, G. R. Birchall, M. N. Galbraith, R. W. Gray, R. R. King, and W. B. Whalley, preceding paper.
[2] R. A. Eade, H. Page, A. Robertson, K. Turner, and W. B. Whalley, *J. Chem. Soc.*, 1957, 4913.
[3] E. M. Gregory and W. B. Turner, *Chem. and Ind.*, 1963, 1625.
[4] Preliminary communication, R. Chong, R. R. King, and W. B. Whalley, *Chem. Comm.*, 1969, 1512.

the acid chloride (6; $R^1 = PhCH_2$, $R^2 = Cl$), the diazo-ketone (6; $R^1 = PhCH_2$, $R^2 = CHN_2$), and finally 1-bromo-3-(3,5-dibenzyloxy-4-methylphenyl)acetone (6; $R^1 = PhCH_2$, $R^2 = CH_2Br$), the n.m.r. spectrum of which had signals at τ 7·78 (3H, s, Ar*Me*), 6·22 and 6·16 (each 2H, s, $ArCH_2{\cdot}CO{\cdot}CH_2Br$), and 4·90 (4H, s, $PhCH_2{\cdot}O$). Debenzylation of the ketone (6; $R^1 = PhCH_2$, $R^2 = CH_2Br$) with boron tribromide at −70° gave 1-bromo-3-(3,5-dihydroxy-4-methylphenyl)acetone



(6; $R^1 = H$, $R^2 = CH_2Br$), which was acetylated under acidic conditions to yield 1-bromo-3-(3,5-diacetoxy-4-methylphenyl)acetone (6; $R^1 = Ac$, $R^2 = CH_2Br$) having n.m.r. signals at τ 8·00 (3H, s, Ar*Me*), 7·69 (6H, s, OAc), 6·09 (4H, s, $ArCH_2{\cdot}CO{\cdot}CH_2Br$), and 3·12 (2H, s, aromatic protons).

The phosphorane (6; $R^1 = PhCH_2$, $R^2 = Ph_3P{=}CH$) from this bromo-ketone was obtained by reaction at room temperature with triphenylphosphine, with propene oxide as scavenger. The resulting bromopropanol was removed by several distillations with 1,2-dichlorobenzene. Condensation of this phosphorane with (±)-2,4-dimethyl-*trans*-hex-2-enal (7) (for synthesis see later) gave 1-(3,5-diacetoxy-4-methylphenyl)-5,7-dimethylnona-*trans*-3,*trans*-5-dien-2-one (8), M^+ 372, τ (CCl_4) 8·27 (3H, d, J 1·1 Hz, $CH_3{\cdot}CH{=}CH$), 8·08 (3H, s, Ar*Me*), 7·78 (6H, s, OAc), 6·32 (2H, s, $ArCH_2{\cdot}CO$), 4·31 (1H, dm, J 10 Hz, $CO{\cdot}CH{=}CH{\cdot}CMe{=}CH$), 3·98 and 2·82 (each 1H, d, J 15·8 Hz), and 3·20 (2H, s, aromatic protons). The reaction conditions for the sequence (6; $R^1 = PhCH_2$, $R^2 = CH_2Br$) ⟶ (8) are critical. Deacetylation of compound (8) gave (±)-1-(3,5-dihydroxy-4-methylphenyl)-5,7-dimethylnona-*trans*-3,*trans*-5-dien-2-one as a stable hydrate (9), the i.r. spectrum of which was devoid of carbonyl absorption. Under carefully controlled conditions, condensation of the phenol (9) with triethyl orthoformate under the influence of toluene-*p*-sulphonic acid yielded (±)-1-(2-formyl-3,5-dihydroxy-4-methylphenyl)-5,7-dimethylnona-*trans*-3,*trans*-5-dien-2-one (10; R = H), τ 8·19 (3H, d, J 2 Hz, $CH_3{\cdot}CH{=}$), 7·92 (3H, s, Ar*Me*), 7·8—7·4 (1H, envelope, $-CHMeEt$), 5·92 (2H, s, $ArCH_2{\cdot}CO$), 4·17 (1H, d, J 10 Hz, H_A), 3·80 [1H, d, J 16 Hz, H_B (or H_C)], 2·63 [1H, d, J 16 Hz, H_C (or H_B)], and 0·09 (1H, s, CHO, exchangeable).



Chlorination of compound (10; R = H) with sulphuryl chloride (propylene oxide as scavenger) gave (±)-1-(2-chloro-6-formyl-3,5-dihydroxy-4-methylphenyl)-5,7-dimethylnona-*trans*-3,*trans*-5-dien-2-one (10; R = Cl), which was converted by dissolution in ethanol containing phosphorus pentoxide into (±)-aposclerotiorin (11; X = O). The n.m.r. spectrum of compound (10; R = Cl) showed signals, at τ 8·18 (3H, d, $CH_3{\cdot}C{=}CH$), 7·81 (3H, s, Ar*Me*), 5·62 (2H, s, $ArCH_2{\cdot}CO$), 4·15 (1H, d, J 10 Hz, H_A), 3·77 [1H, d, J 16 Hz, H_B (or H_C)], 2·60 [1H, d, J 16 Hz, H_C (or H_B)], and −0·08 (1H, s, CHO). When (+)-sclerotiorin (3; R = Ac) was treated with zinc and acetic acid it gave (+)-aposclerotiorin (11; X = O) [*cf.* the similar formation [5]

[5] H. C. Fielding, N. B. Graham, A. Robertson, R. B. Travers, and W. B. Whalley, *J. Chem. Soc.*, 1957, 4931.

of (+)-aposclerotioramine (11; X = NH)], τ 8·28 (3H, s, CH_3·C=C), 7·92 (3H, s, ArMe), 5·47 (1H, s, H-4), 4·60 (1H, d, *J* 10 Hz, H_A), 3·94 (1H, s, H-1), 4·02 [1H, d, *J* 16 Hz, H_B (or H_C)], and 3·43 [1H, d, H_C (or H_B), *J* 16 Hz].

In contrast to tetrahydroaposclerotiorin, which was obtainable only in solution[1] and could be isolated[1] only in the hydrated open-chain form, type (10), aposclerotiorin (11; X = O) was sufficiently stable to allow isolation and recrystallisation (with care). Treatment of (+)- [or of (±)-]aposclerotiorin (11; X = O) with warm dilute sodium hydroxide solution furnished the (+)- [or the (±)-]aldehyde (10; R = Cl), from which (+)- or (±)-]aposclerotiorin was regenerated by dissolution in ethanol containing phosphorus pentoxide. Synthetic (±)-aposclerotiorin (11; X = O) and the synthetic (±)-aldehyde (10; R = Cl) were (respectively) indistinguishable (t.l.c., i.r., u.v., n.m.r., and mass spectra) from the derivatives obtained from (+)-sclerotiorin. Treatment with lead tetra-acetate in acetic acid of (+)-aposclerotiorin (11; X = O), used as a relay, gave a product having the general properties of sclerotiorin (3; R = Ac). Although acetoxylation at C-7 would be non-stereospecific, the product was indistinguishable (t.l.c., i.r., n.m.r., and mass spectra) from (+)-sclerotiorin. Since synthetic sclerotiorin (3; R = Ac) must contain both possible C-7 isomers, and since synthetic (±)-aposclerotiorin contains the enantiomer with the *S*-configuration, characteristic[6] of the side-chains of both (+)- and (−)-sclerotiorin, our work constitutes a formal, total synthesis of (+)- and of (−)-sclerotiorin, and the first synthesis of a member of this group of fungal metabolites.

Although sclerotiorin is degraded rapidly by aqueous alcoholic sodium hydroxide solution (presumably initiated by nucleophilic attack of hydroxide ion at C-1 of the pyrone system), deacetylation of (+)-sclerotiorin occurs readily with cold sodium ethoxide solution to yield (+)-deacetylsclerotiorin (3; R = H) (*cf.* ref. 7). Although the hydroxy-group in structure (3; R = H) is tertiary, its location between the two α-carbonyl substituents enhances its reactivity and re-acetylation readily regenerates (+)-sclerotiorin.

The (±)-2,4-dimethylhex-*trans*-2-enal (7) was prepared essentially by the method of Hagemeyr and Hudson,[8] by base-catalysed condensation of α-methylbutyraldehyde and propionaldehyde followed by an initial purification of the product by fractional distillation.[8] However, the n.m.r. spectrum (CCl_4) showed intensity ratios of the upfield protons to the C*H*O proton (τ 0·63) and the −C*H*=CH·CH_3 proton (τ 3·82, dq, *J* 10 Hz) of 14 : 1 : 1, thereby indicating the presence of an impurity, possibly 2-methylpent-2-enal (from self-condensation of the propionaldehyde). The (±)-2,4-dimethylhex-*trans*-2-enal (7) was therefore further purified by way of the 2,4-dinitrophenylhydrazone, which had the same behaviour on t.l.c. and the same spectral characteristics as the (+)-2,4-dinitrophenylhydrazone obtained as a degradation product from (+)-sclerotiorin[2] and rotiorin.[9] This (±)-2,4-dinitrophenylhydrazone had n.m.r. signals at τ −0·88 (1H, C*H*=N) and 4·25 (1H, dq, *J* 10 Hz, C*H*=CH·CH_3) and the requisite ratio (1 : 1 : 13) of these protons to the upfield protons. Regenerated from this (±)-2,4-dinitrophenylhydrazone, (±)-2,4-dimethylhex-*trans*-2-enal still contained a small amount (of the same?) impurity, as indicated by the n.m.r. signal ratio. The aldehyde was used, however, directly for condensation with the phosphorane (6; R^1 = Ac, R^2 = Ph_3P=CH). The impurity was eliminated at the stage of the phenol (9), by several recrystallisations.

The chemical shift (CCl_4) of the aldehydic proton in 2-methyl αβ-unsaturated aldehydes is diagnostic[10-12] of the configuration (*cis*-isomer τ *ca.* 0·0, *trans*-isomer τ 0·75—0·70). On this basis our (±)-2,4-dimethylhex-2-enol (7) may be assigned the *trans*-structure as anticipated on general grounds. Since the n.m.r. data clearly establish the *trans*-nature of the 3′,4′-double bonds in the dienes (8), (9), and (10) and of the corresponding bond in aposclerotiorin (11; X = O) it may be assumed that all these dienes have the *trans,trans*-configuration.

Condensation of (±)-2,4-dimethylhex-*trans*-2-enal with ethoxycarbonylmethylenetriphenylphosphorane (prepared from triphenylphosphine and ethyl bromoacetate) readily gave (±)-4,6-dimethylocta-*trans*-2,*trans*-4-dienoic acid[2] (4), indistinguishable (spectra and t.l.c.) from the dextrorotatory isomer.[2]

Condensation of (+)-deacetylsclerotiorin (3; R = H) dissolved in pyridine–benzene with a solution of diketen in benzene previously saturated with hydrogen chloride readily gave (+)-5-chloroisorotiorin (5), τ 1·22 (1H, s, H-1), 2·84 [1H, d, *J* 16 Hz, H_C (or H_B)], 3·36 (1H, s, H-4), 3·90 [1H, d, *J* 16 Hz, H_B (or H_C)], 4·25 (1H, d, *J* 10 Hz, H_A), 7·39 (3H, s, Ar*Me*), and 8·13 (3H, s, C·CH_3). The generation of the rotiorin analogue (5) may be rationalised as follows. Diketen and hydrogen chloride probably produce acetoacetyl chloride *in situ* (*cf.* the similar reaction with hydrogen fluoride[13]): this acid chloride with (+)-desacetylsclerotiorin forms the transient acetoacetyl ester (12), which rapidly undergoes a base-catalysed internal aldol condensation (in the presence of excess of pyridine as solvent) to yield (5). The angular structure of (5) is in agreement with (*a*) the n.m.r. spectrum, (*b*) the u.v. spectrum, which indicates a less highly conjugated system than in the linear analogue, rotiorin (13), and (*c*) the anticipated greater susceptibility of the C-8 (rather than the C-6) carbonyl group, to nucleophilic attack, since the

[6] G. A. Ellestad and W. B. Whalley, *J. Chem. Soc.*, 1965, 7260.
[7] G. Zemplen and A. Kuntz, *Ber.*, 1923, **56***B*, 1705.
[8] H. J. Hagemeyer and G. V. Hudson, U.S.P. 2,852,563 (*Chem. Abs.*, 1959, **53**, 4136).
[9] G. B. Jackman, A. Robertson, R. B. Travers, and W. B. Whalley, *J. Chem. Soc.*, 1958, 1825.
[10] E. Bertele and P. Schudel, *Helv. Chim. Acta*, 1967, **50**, 2445.
[11] A. F. Thomas, *Chem. Comm.*, 1968, 1657.
[12] K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, 1968, **33**, 3382.
[13] G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, 1961, **26**, 225.

C-8 carbonyl group suffers considerable distortion[14] out of the general plane of the (+)-desacetylsclerotiorin molecule.

This method for the construction of the rotiorin system constitutes a formal analogy to the possible[15] biosynthetic pathway.

EXPERIMENTAL

Light petroleum refers to the fraction of b.p. 40—60°. N.m.r. spectra were determined for solutions in deuteriochloroform (tetramethylsilane as internal standard) with a Varian A60A spectrometer.

1-Bromo-3-(3,5-diacetoxy-4-methylphenyl)acetone (6; R^1 = Ac, R^2 = CH_2Br).— A solution of methyl 3,5-dihydroxy-4-methylbenzoate (35 g.) in acetone (100 ml.) containing benzyl bromide (50 ml.) and potassium carbonate (80 g.) was refluxed for 6 hr.; the resultant *methyl 3,5-dibenzyloxy-4-methylbenzoate* was purified from methanol to yield glistening plates, m.p. 105° (Found: C, 76·3; H, 6·2. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%). Hydrolysis of this ester during 1 hr. with boiling 10% sodium hydroxide [water–ethanol (1 : 5)] followed by purification from chloroform gave *3,5-dibenzyloxy-4-methylbenzoic acid* (48 g.) in needles, m.p. 220° (Found: C, 75·8; H, 5·7. $C_{22}H_{20}O_4$ requires C, 75·8; H, 5·8%).

The mother liquors remaining from the purification of this benzoic acid were evaporated to dryness *in vacuo*. The residue was extracted with chloroform to yield *2-benzyl-3,5-dibenzyloxy-4-methylbenzoic acid* (1·1 g.), m.p. 180—181° (from acetone) (Found: C, 79·4; H, 6·0. $C_{29}H_{26}O_4$ requires C, 79·4; H, 6·0%).

A solution of 3,5-dibenzyloxy-4-methylbenzoyl chloride [prepared from 3,5-dibenzyloxy-4-methylbenzoic acid (10·4 g.) and thionyl chloride (10 ml.) in benzene (10 ml.)] in ether–benzene (2 : 1) (300 ml.) was added slowly, at 0°, to an ethereal solution (150 ml.) of diazomethane generated from *N*-nitroso-*N*-methylurea (12 g.). After 20 hr. at 0° the crystalline deposit of diazoketone was collected: dilution of the filtrate with light petroleum furnished a second crop. Purification of the combined product from benzene–light petroleum gave *1-diazo-3-(3,5-dibenzyloxy-4-methylphenyl)acetone* (6; R^1 = $PhCH_2$, R^2 = CHN_2) (9·0 g.) in yellow prisms, m.p. 134° (decomp.) (Found: C, 74·0; H, 5·4; N, 8·1. $C_{23}H_{20}N_2O_3$ requires C, 74·2; H, 5·4; N, 7·5%).

Four drops of a solution of silver benzoate (0·75 g.) in triethylamine (20 ml.) were added to a stirred suspension of this diazo-ketone (9·0 g.) in methanol (250 ml.). After 30 min., the stirred suspension was refluxed for 2·5 hr. with dropwise addition of the remainder of the silver benzoate solution during that time. Refluxing was then continued for 1 hr.; inorganic solids were collected and the filtrate was concentrated *in vacuo* until crystallisation of the methyl ester commenced. This ester was purified from ether–methanol to yield *methyl 3,5-dibenzyloxy-4-methylphenylacetate* (7 g.) in prisms, m.p. 87° (Found: C, 76·5; H, 6·6. $C_{24}H_{24}O_4$ requires C, 76·6; H, 6·4%).

Hydrolysis of this ester with boiling 2·5% sodium hydroxide in water–ethanol (2 : 5; 70 ml.) during 1·5 hr. gave *3,5-dibenzyloxy-4-methylphenylacetic acid* (5·7 g.) in prisms, m.p. 172° (Found: C, 76·1; H, 6·4. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%).

A mixture of this acid (6·75 g.) and oxalyl bromide (6·3 g.) in benzene (50 ml.) was refluxed for 30 min, then evaporated to dryness *in vacuo*. The crystalline residue was dissolved in toluene (35 ml.) and the solution was evaporated to remove excess of oxalyl bromide. The residue in toluene (75 ml.) was added dropwise during 30 min. to an ethereal solution (138 ml.) of diazomethane (1·73 g.) at −20°. After 16 hr. at 0° the mixture was concentrated (to 100 ml.) *in vacuo* (below 35°). A solution of hydrogen bromide [generated from bromine (20 ml.) and tetralin] in ether (25 ml.) was added dropwise to the solution of the diazo-ketone at −30°. After a further 10 mins. at −30° the mixture was poured on ice. Isolation in the normal manner gave *1-bromo-3-(3,5-dibenzyloxy-4-methylphenyl)acetone* (6; R^1 = $PhCH_2$, R^2 = CH_2Br) (5·7 g.) in flat prisms, m.p. 84° (decomp.) (from ether–light petroleum) (Found: C, 65·3; H, 5·2; Br, 18·1. $C_{24}H_{23}BrO_3$ requires C, 65·5; H, 5·2; Br, 18·2%).

Boron tribromide (2·2 ml.) was added rapidly to a stirred solution of the foregoing ketone (2·0 g.) in methylene bromide (50 ml.) at −70°. After 15 min. at −70° water (25 ml.) was added slowly, and the stirred mixture was allowed to attain room temperature. Isolation in the usual way, followed by chromatography on silica from benzene (to remove benzyl bromide) and then crystallisation from ether–light petroleum gave *1-bromo-3-(3,5-dihydroxy-4-methylphenyl)acetone* (6; R^1 = H, R^2 = CH_2Br) (1·0 g.) in prisms, m.p. 107° (decomp.) (Found: C, 47·0; H, 4·5; Br, 29·3. $C_{10}H_{11}BrO_3$ requires C, 46·3; H, 4·3; Br, 30·8%).

A solution of this phenol (0·5 g.) in acetic anhydride (3·0 ml.) containing concentrated sulphuric acid (2 drops) was kept at room temperature during 1 hr., and then cooled to 0°; ice was then added. After isolation by extraction with ether, *1-bromo-3-(3,5-diacetoxy-4-methylphenyl)acetone* (6; R^1 = Ac, R^2 = CH_2Br) (0·35 g.) formed prisms, m.p. 83° (from methylene chloride–carbon tetrachloride) (Found: C, 48·2; H, 4·5; Br, 24·0. $C_{14}H_{15}BrO_5$ requires C, 49·0; H, 4·4; Br, 23·3%).

(±)-2,4-*Dimethyl*-trans-*hex*-2-*enal* (7).—Prepared by the condensation[8] of 2-methylbutyraldehyde (74 g.) and propionaldehyde (25 g.), (±)-2,4-dimethyl-*trans*-hex-2-enal (23·0 g.) had b.p. 56°/9 mm. The (±)-2,4-*dinitrophenylhydrazone* separated from ethyl acetate in orange needles, m.p. 162—164° (Found: C, 54·9; H, 5·6; N, 18·5. $C_{14}H_{18}N_4O_4$ requires C, 54·9; H, 5·9; N, 18·3%), mixed m.p. with the natural (+)-2,4-dinitrophenylhydrazone (m.p. 158°) 161—163°.

(±)-2,4-Dimethyl-*trans*-hex-2-enal was regenerated from the 2,4-dinitrophenylhydrazone (9·9 g.) by heating at 100° for 6 hr. with a mixture of acetic acid (50 ml.), 10% sulphuric acid (5 ml.), and acetylacetone (6·4 g.). The (±)-2,4-dimethyl-*trans*-hex-2-enal (2·78 g.) had b.p. 63—65°/17 mm.

(±)-4,6-*Dimethylocta*-trans-2,trans-4-*dienoic Acid* (4).— A mixture of (±)-2,4-dimethyl-*trans*-hex-2-enal (7) (3·5 g.), ethyl bromoacetate (2·2 ml.), triphenylphosphine (5·2 g.), and propylene oxide (2·0 ml.) in chloroform (25 ml.) was refluxed for 24 hr.; the solvent was then removed *in vacuo* and the residue was triturated with ether–light petroleum. Triphenylphosphine oxide, m.p. 100°, crystallised. This was collected and the filtrate was evaporated. The

[14] F. M. Dean, J. Staunton, and W. B. Whalley, *J. Chem. Soc.*, 1959, 3004.

[15] J. S. E. Holker, J. Staunton, and W. B. Whalley, *J. Chem. Soc.*, 1963, 3641.

oily ethyl ester remaining was hydrolysed during 1 hr. with a boiling mixture of 2N-sodium hydroxide (20 ml.) and ethanol (25 ml.). Isolation in the normal manner, followed by purification from light petroleum and aqueous methanol, gave the *acid* (4) (1·7 g.) in needles, m.p. 83—84° (Found: C, 71·4; H, 9·7. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%).

1-(3,5-*Dihydroxy*-4-*methylphenyl*)-5,7-*dimethylnona*-trans-3,trans-5-*dien*-2-*one*.—A mixture of 1-bromo-3-(3,5-diacetoxy-4-methylphenyl)acetone (6; R^1 = Ac, R^2 = CH_2-Br) (0·48 g.), triphenylphosphine (0·38 g.), propene oxide (2 ml.), and methylene chloride (10 ml.) was kept for 16 hr.; the solvent was then removed *in vacuo* (below 50°). The residue was dissolved in 1,2-dichlorobenzene (50 ml.) and the solution was distilled slowly (bath temp. 30—40°/2 mm.) to dryness, to remove bromopropanol. (±)-2,4-Dimethyl-*trans*-hex-2-enal (7) (0·2 g.) was added to a solution of the residue in 1,2-dichlorobenzene (2 ml.), and the stirred mixture was heated at 130° for 16 hr. under nitrogen. T.l.c. on silica gave 1-(3,5-diacetoxy-4-methylphenyl)-5,7-dimethylnona-*trans*-3,*trans*-5-dien-2-one (0·32 g.) as a pale yellow oil. A solution of this di-*O*-acetate (0·2 g.) in methanol (35 ml.) and 5% sodium hydroxide solution (1·8 ml.) was kept for 10 min. (under nitrogen), water (5 ml.) was added, and the product was isolated. Purification from light petroleum and then from aqueous methanol gave the diphenol as a stable *hydrate* (9) in prisms (84 mg.), m.p. 78—80° (Found: C, 70·9; H, 8·5%; M^+, 288. $C_{18}H_{24}O_3,H_2O$ requires C, 70·6; H, 8·6%. $C_{18}H_{24}O_3$ requires *M*, 288).

1-(2-*Chloro*-6-*formyl*-3,5-*dihydroxy*-4-*methylphenyl*)-5,7-*dimethylnona*-trans-3,trans-5-*dien*-2-*one* (10; R = Cl).—(*a*) A solution of toluene-*p*-sulphonic acid (5 mg.) in benzene–ether (3 : 1) (10 ml.) was added to a solution of 1-(3,5-dihydroxy-4-methylphenyl)-5,7-dimethylnona-*trans*-3,*trans*-5-dien-2-one (80 mg.) in triethyl orthoformate (0·4 ml.) and the mixture was kept under nitrogen. After 5 min. light petroleum (10 ml.) was added and 35 min. later the mixture was extracted with ice-cold N-sodium hydroxide (10 ml.) and then with ice-cold 1% sodium hydroxide (2 × 10 ml.). The combined extracts were acidified (0°) with cold 1% sulphuric acid and the acidified mixture was extracted with ether. Purification of the product from aqueous methanol gave 1-(2-*formyl*-3,5-*dihydroxy*-4-*methylphenyl*)-5,7-*dimethylnona*-trans-3,trans-5-*dien*-2-*one* (10; R = H) (84 mg.), in needles, m.p. 123—124·5° (Found: C, 71·7; H, 7·8%; M^+, 316. $C_{12}H_{24}O_4$ requires C, 72·1; H, 7·7%; *M*, 316).

To a solution of the formyl-ketone (10; R = H) (40 mg.) in ether–propene oxide (10 : 1; 2·2 ml.), a solution of sulphuryl chloride in methylene chloride (2·3% w/v; 0·77 ml.) was added with cooling. Thirty min. later the solvent was removed *in vacuo* and the product was purified by t.l.c., followed by crystallisation from ether–light petroleum and then aqueous ethanol to give the *chloro-derivative* (10; R = Cl) (30 mg.) in needles, m.p. 120—121° (Found: C, 65·5; H, 6·5. $C_{19}H_{23}ClO_4$ requires C, 65·1; H, 6·6%).

(*b*) A solution of sclerotiorin (3; R = Ac) (2 g.) in acetic acid (25 ml.) containing zinc dust (1 g.) was agitated for 3 hr.; the mixture was then diluted with water and the total precipitate was collected. This was dissolved in N-sodium hydroxide (100 ml.) and the resultant solution was warmed on a steam-bath for 15 min. Extraction of the neutralised solution with light petroleum (b.p. 60—80°) and purification of the residue from aqueous ethanol gave (7S)-(+)-1-(2-*chloro*-6-*formyl*-3,5-*dihydroxy*-4-*methylphenyl*)-5,7-*dimethylnona*-trans-3,-trans-5-*dien*-2-*one* (0·19 g.), in needles, m.p. 123—125° (Found: C, 65·4; H, 6·6; Cl, 9·9. $C_{19}H_{23}ClO_4$ requires C, 65·1; H, 6·6; Cl, 10·1%).

Aposclerotiorin (11; X = O).—(a) *From sclerotiorin* (3; R = Ac). A solution of sclerotiorin (2 g.) in acetic acid (25 ml.) containing zinc dust (1 g.) was agitated for 3 hr.; the solution was then diluted with water (100 ml.) and the precipitate was collected and extracted (at room temperature) with light petroleum (3 × 100 ml.). The extract was evaporated *in vacuo* at 15° to yield a pale yellow oil, which crystallised upon addition of light petroleum, to yield (+)-*aposclerotiorin* (11; X = O) (0·23 g.) in yellow prisms, m.p. 169—172° (Found: C, 67·9; H, 6·3; Cl, 10·6. $C_{19}H_{21}ClO_3$ requires C, 68·6; H, 6·4; Cl, 10·7%). Treatment of (+)-aposclerotiorin with cold 2N-sodium hydroxide rapidly gave a quantitative yield of (7*S*)-1-(2-chloro-6-formyl-3,5-dihydroxy-4-methylphenyl)-5,7-dimethylnona-*trans*-3,-*trans*-5-dien-2-one, identical with the previously prepared specimen.

(b) *By synthesis*. A solution of the synthetic dienone (10; R = Cl) (60 mg.) in ethanol (10 ml.) containing phosphorus pentoxide (30 mg.) was warmed on a steam-bath for 5 min, rapidly cooled, and extracted with ether. The extract was evaporated *in vacuo* at 15° to give [as in (a)] aposclerotiorin (34 mg.), indistinguishable from that prepared by method (a).

Synthetic (±)-*Sclerotioramine*.—A mixture of the synthetic chloro-dienone (10; R = Cl) (60 mg.) in ammonium acetate (15 mg.) was heated at 70—80° for 15 min. The resultant gel was extracted with ether to give (±)-aposclerotioramine (11; X = NH) (42 mg.) in yellow prisms, m.p. 236—238° (from aqueous ethanol), having the requisite spectral and R_F characteristics.

A solution of this aposclerotioramine (0·4 g.) in acetic acid (15 ml.) was treated with lead tetra-acetate (0·45 g.). Six hr. later excess of oxidising agent was destroyed by addition of ethylene glycol (1 ml.), and the product was isolated and purified by t.l.c. on silica [chloroform–methanol (20 : 1)] to give (±)-*sclerotioramine* which formed red plates (38 mg.), m.p. 155° (decomp.) (Found: C, 65·1; H, 6·1; N, 2·9. $C_{21}H_{24}ClNO_4$ requires C, 64·7; H, 6·2; N, 3·6%).

(±)-*Sclerotiorin* (3; R = Ac).—Aposclerotiorin (11; X = O) (0·26 g.) was added to a solution of lead tetra-acetate (0·31 g.) in acetic acid (10 ml.). After 30 min. excess of oxidising agent was destroyed with ethylene glycol (1 ml.), and the mixture was taken up in ether. The product was isolated by t.l.c., on silica [benzene–ether (10 : 1)] followed by purification from aqueous ethanol to yield (±)-*sclerotiorin* in yellow needles (36 mg.), m.p. 158—164° (Found: C, 64·7; H, 6·3; Cl, 9·7. $C_{21}H_{23}ClO_5$ requires C, 64·5; H, 5·9; Cl, 9·1%).

(+)-*Deacetylsclerotiorin* (3; R = H).—(+)-Sclerotiorin (3; R = Ac) (0·5 g.) was added to a saturated solution of sodium ethoxide (10 ml.). Twenty min. later the mixture was diluted with water and acidified with N-hydrochloric acid; the product was isolated with ether. Purification from light petroleum gave (+)-*deacetylsclerotiorin* (0·26 g.) in yellow needles, m.p. 133—135° (decomp.), $[\alpha]_D^{20}$ +480° (*c* 0·01 in EtOH) (Found: C, 65·5; H, 6·2; Cl, 10·3. $C_{19}H_{21}ClO_4$ requires C, 65·4; H, 6·1; Cl, 10·2%). Acetylation of this compound by the acetic anhydride–pyridine method quantitatively regenerated (+)-sclerotiorin.

Interaction of (+)-deacetylsclerotiorin (80 mg.) with

benzoyl chloride (0·1 g.) in boiling benzene (10 ml.) containing pyridine (1 ml.) during 2·5 hr. gave (+)-*deacetylsclerotiorin benzoate* (3; R = Bz), which separated from aqueous ethanol in yellow plates (56 mg.), m.p. 78—80° (Found: C, 68·5; H, 6·3. $C_{26}H_{25}ClO_5$ requires C, 68·9; H, 5·6%).

(+)-5-*Chloroisorotiorin* (5).—A solution of (+)-deacetylsclerotiorin (3; R = H) (0·2 g.) in benzene (10 ml.) and pyridine (2 ml.) was added to a solution of diketen (0·2 ml.) in benzene (5 ml.) which had previously been saturated with hydrogen chloride. The mixture was heated on a steam-bath for 45 min. and then diluted with excess of aqueous sodium hydrogen carbonate. Purification of the product from light petroleum gave (+)-5-*chloroisorotiorin* (0·14 g.) in orange plates, m.p. 79—81° (decomp.) $\lambda_{max.}$ (EtOH) 250, 289, 368, and 442 nm. (log ε 4·25, 4·08, 4·65, and 4·20), $[\alpha]_D^{20}$ +405° (*c* 0·02 in $CHCl_3$) (Found: C, 66·7; H, 5·7. $C_{23}H_{23}ClO_5$ requires C, 66·6; H, 5·6%).

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