The Synthesis of Sclerotiorin and of an Analogue of Rotiorin

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Summary The total synthesis of the fungal metabolite sclerotiorin, and of an analogue of the cognate metabolite, rotiorin, are described.

IN continuation of our investigations in the sclerotiorin group of fungal metabolites, we report the total synthesis of sclerotiorin[1] (**1**; R = Ac) and of isochlororotiorin (**2**), an analogue of rotiorin.[2]

Thus, 3,5-dibenzyloxy-4-methylphenylacetic acid (**3**; $R^1 = PhCH_2$, $R^2 = OH$), [available from 3,5-dihydroxy-4-methylbenzoic acid] was converted successively into the acid chloride (**3**; $R^1 = PhCH_2$, $R^2 = Cl$), the diazo-ketone (**3**; $R^1 = PhCH_2$, $R^2 = CHN_2$), and the ω-bromophenylacetone (**3**; $R^1 = PhCH_2$, $R^2 = CH_2Br$). Treatment of (**3**; $R^1 = PhCH_2$, $R^2 = CH_2Br$) with boron tribromide at $-70°$ in methylene chloride gave 1-(3,5-dihydroxy-4-methylphenyl)-3-bromoacetone (**3**; $R^1 = H$, $R^2 = CH_2Br$). The di-*O*-acetate (**3**; $R^1 = Ac$, $R^2 = CH_2Br$), triphenylphosphine, propylene oxide, and methylene chloride were kept at room temperature for 16 hr. when the solvent was removed *in vacuo* at $< 50°$. A solution of the residue in 1,2-dichlorobenzene was evaporated *in vacuo* at $< 40°$ to remove 2-bromopropan-1-ol.† A solution of the resultant phosphorane in 1,2-dichlorobenzene containing (±)-2,4-dimethylhex-*trans*-2-enal (**4**), was heated at 130° under nitrogen for 16 hr. to yield (±)-1-(3,5-diacetoxy-4-methylphenyl)-5,7-dimethylnona-*trans*-*trans*-3,5-dien-2-one (**5**). This was converted (5% sodium hydroxide solution under nitrogen) into the corresponding phenol, m.p. 78—80°, which exists as the stable hydrate (**6**). Formylation of (**6**) with triethyl orthoformate (benzene–ether–toluene-*p*-sulphonic acid) in nitrogen during 5 min., followed by dilution with light-petroleum and isolation at 0° in nitrogen, 35 min. later† gave (±)-1-(2-formyl-3,5-dihydroxy-4-methylphenyl)-5,7-dimethylnona-*trans*-*trans*-3,5-dien-2-one (**7**; R = H), m.p. 123°, which was chlorinated to (±)-(**7**; R = Cl) during 30 min. at room temperature using

† Conditions critical.

sulphuryl chloride in methylene chloride containing propylene oxide.

Cyclisation of (**7**; R = Cl) with phosphorus pentoxide in ethanol furnished the very unstable pyronoquinone (**8**), [(±)-aposclerotiorin], indistinguishable (t.l.c., i.r., u.v., and mass spectra) from (+)-aposclerotiorin, m.p. 173°, obtained by the action of zinc–acetic acid on (+)-sclerotiorin. Natural aposclerotiorin on treatment with potassium acetate furnished (+)-(**7**; R = Cl), spectroscopically and chromatographically identical with the synthetic material.

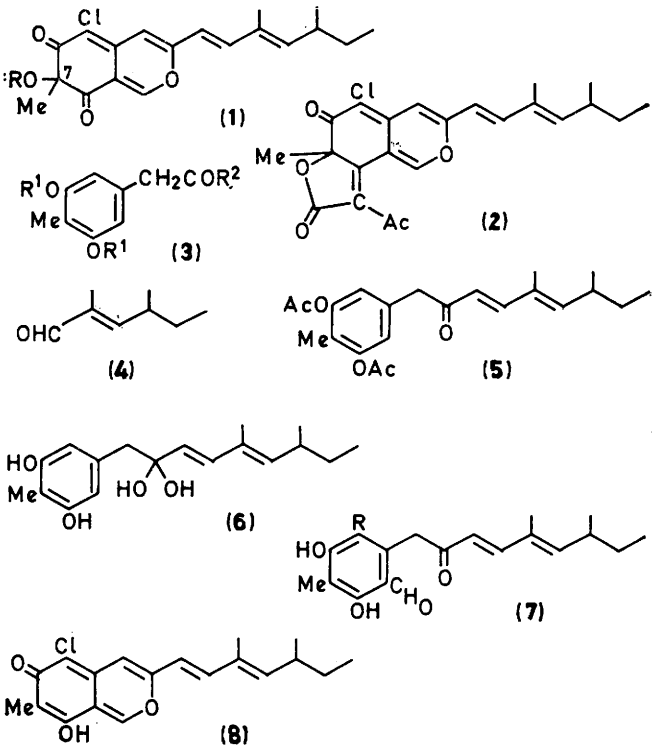
Treatment of (+)-(**8**) (used as a relay) with lead tetra-acetate in acetic acid gave a substance having the general properties of sclerotiorin (**1**; R = Ac). Thus, although acetoxylation at C-7 would be non-specific, the product had the correct n.m.r. spectrum and was indistinguishable on the basis of t.l.c., i.r., u.v., and mass spectra from authentic (+)-sclerotiorin.[1] Since synthetic (**1**; R = Ac) will contain species of both configurations at C-7 our work constitutes a total synthesis of (+)-sclerotiorin[1] and of (−)-sclerotiorin[3] and the first total synthesis within this novel group of fungal metabolites.

Treatment of (+)-(**7**; R = Cl) with ammonium acetate gave aposclerotioramine.[1] (+)-2,4-Dimethylhex-*trans*-2-enal (**4**) was prepared by the base-catalysed condensation of (±)-2-methylbutyraldehyde with propionaldehyde followed by purification by distillation and by forming the 2,4-dinitrophenylhydrazone which was spectroscopically indistiguishable from the derivative from (+)-sclerotiorin.[4]

Reaction of the hexenal (**4**), with ethyl bromoacetate and triphenylphosphine in chloroform containing propylene oxide at the boiling point during 24 hr., followed by hydrolysis of the ester gave (±)-4,6-dimethylocta-2,4-*trans*-*trans*-dienoic acid, indistinguishable on the basis of t.l.c., i.r., u.v., and n.m.r. spectra from authentic (+)-acid.[4]

Hydrolysis of (+)-sclerotiorin (**1**; R = Ac) with sodium ethoxide at 0° gave (+)-deacetylsclerotiorin (**1**; R = H) which regenerated (+)-sclerotiorin upon acetylation.

Reaction of (+)-deacetylsclerotiorin (**1**; R = H) with diketen–hydrogen chloride in hot pyridine–benzene gave isochlororotiorin (**2**), in high yield. This constitutes the first synthesis of a system analogous to that present in rotiorin,[2] rubropunctatin,[5] and monascorubrin.[6]‡



(*Received, November 13th*, 1969; *Com.* 1731.)

‡ All new compounds had the requisite analytical and spectral characteristics.

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