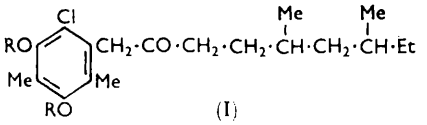
762. *The Chemistry of Fungi. Part XLV.*[1] *The Synthesis of Sclerotinol*

By J. N. Chatterjea and W. B. Whalley

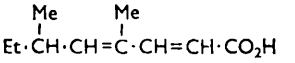
Sclerotinol, a major degradation product of sclerotiorin, has been synthesised from 2-chloro-3,5-dimethoxy-4,6-dimethylphenylacetonitrile and (+)-3,5-dimethylheptylmagnesium bromide.

Exhaustive hydrogenation of the fungal metabolite sclerotiorin yields *inter alia* a dihydric phenol, sclerotinol, $C_{19}H_{29}ClO_3$, which contains all the carbon atoms of the parent nucleus, and has been formulated as 2-chloro-3,5-dihydroxy-4,6-dimethylbenzyl-3,5-dimethylheptyl ketone (I; R = H). We now report confirmation of this structure through the synthesis of sclerotinol.

Hydrogenation of (+)-4,6-dimethylocta-2,4-dienoic acid (II),[2-4] in which the asymmetric centre has the (*S*)-configuration[4,6] gives the corresponding (+)-4,6(*S*)-dimethyloctanoic acid (III; R = H).[2-4] Gas chromatography clearly showed that the methyl ester (III; R = Me), and hence the parent acid, consisted predominantly (>95%) of one stereoisomer. Degradation of silver (+)-4,6(*S*)-dimethyloctanoate by the Hunsdiecker method[5] gave (+)-3,5(*S*)-dimethylheptyl bromide (IV), apparently stereochemically homogeneous.



(I)



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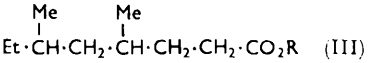

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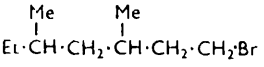

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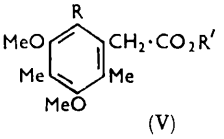
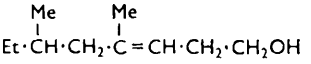


(V)



(VI)

Chlorination of ethyl 3,5-dimethoxy-2,4-dimethylphenylacetate (V; R = H, R′ = Et), the n.m.r. spectrum of which exhibited a singlet at τ 3·47 (one aromatic proton), readily gave

[1] Part XLIV, D. W. Mathieson and W. B. Whalley, *J.*, 1964, 4640.
[2] R. A. Eade, H. Page, A. Robertson, K. Turner, and W. B. Whalley, *J.*, 1957, 4913.
[3] H. Watanabe, *J. Pharm. Soc. Japan*, 1952, **72**, 807.
[4] J. H. Birkinshaw, *Biochem. J.*, 1952, **52**, 283.
[5] J. E. Gowan and T. S. Wheeler, "Name Index of Organic Reactions," Longmans, London, 1960, p. 36.
[6] L. Crombie, M. Manzoor-i-Khuda, and R. J. D. Smith, *J.*, 1957, 479.

the ester (V; R = Cl, R′ = Et). Hydrolysis of this ester produced 2-chloro-3,5-dimethoxy-4,6-dimethylphenylacetic acid in which the absence of the aromatic proton signal, together with the persistence of the two $=\overset{|}{C}-Me$ signals at τ 7·82 and 7·86, clearly established the constitution as (V; R = Cl, R′ = H) (cf. ref. 7). 2-Chloro-3,5-dimethoxy-4,6-dimethylphenylacetonitrile was readily obtained from (V; R = Cl, R′ = H) by standard methods. Reaction of this nitrile with the Grignard reagent from the bromide (IV) gave the ketone (I; R = Me) which was demethylated to (I; R = H), identical with sclerotinol from sclerotiorin. Since (+)-4,6(*S*)-dimethyloctanoic acid (III; R = H) has been synthesised,[6] our work constitutes a total synthesis of sclerotinol. Syntheses of the analogous 2-chloro-3,5-dimethoxy-4,6-dimethyl- and 3,5-dimethoxy-4-methyl-phenylacetone are recorded.

Hydrogenation of (II) and of (+)-4,6(*S*)-dimethyloct-3-en-1-ol (VI), which constitutes the penultimate stage in the synthesis of (III; R = H), were assumed to be relatively non-stereospecific.[6] It was further implied [6] that (+)-4,6-dimethyloctanoic acid from both synthetic and natural sources consisted of a mixture of 4(*R*),6(*S*)-dimethyl- and 4(*S*),6(*S*)-dimethyl-octanoic acid in a similar (though not necessarily 1 : 1) ratio. It appears from our investigation that these two hydrogenations proceed with a relatively high degree of stereospecificity to give stereochemically equivalent products.

Experimental

Infrared spectra were determined with an Infracord spectrophotometer. Analyses are by Mr. G. Crouch and his associates. Nuclear magnetic resonance spectra were determined in deuterochloroform solution, using tetramethylsilane as internal standard, on a Varian A-60 spectrometer, by Miss J. Lovenack.

2-*Chloro*-3,5-*dimethoxy*-4,6-*dimethylphenylacetonitrile*.—3,5-Dimethoxy-2,4-dimethylphenylacetic acid was converted, according to the published procedure,[7] using ethanol in place of methanol, into the *ethyl ester*, b. p. 150°/0·2 mm., which slowly solidified to prisms, m. p. 37° (Found: C, 65·7; H, 7·6. $C_{14}H_{20}O_4$ requires C, 66·1; H, 7·9%).

A solution of this ester (1·3 g.) in carbon tetrachloride (60 ml.) was treated with sulphuryl chloride (0·75 g.) in carbon tetrachloride (5 ml.) at 0°, together with a few crystals of benzoyl peroxide. After 48 hr. the solvent was removed and the crude product warmed (steam-bath) for ½ hr. with sodium hydroxide (0·5 g.) in aqueous methanol (20 ml.). After isolation, 2-chloro-3,5-dimethoxy-4,6-dimethylphenylacetic acid (0·9 g.) separated from benzene in needles, m. p. 148°, identical with a specimen previously prepared [7] by an alternative method.

A solution of this acid (1 g.) in benzene (10 ml.) containing phosphorous pentachloride (1 g.) was refluxed for 1 hr. After removal of the solvent a solution of the residue in acetone (20 ml.) was stirred with ammonium acetate (4 g.) for ¾ hr. Isolated in the usual manner, 2-*chloro*-3,5-*dimethoxy*-4,6-*dimethylphenylacetamide* separated from water in needles (0·9 g.), m. p. 212° (Found: C, 55·7; H, 6·1; Cl, 13·6; N, 5·6. $C_{12}H_{16}ClNO_3$ requires C, 56·0; H, 6·2; Cl, 13·7; N, 5·4%).

A suspension of this amide (1·3 g.) in pyridine (4 ml.) containing toluene-*p*-sulphonyl-chloride (1·2 g.) was kept at 40—50° for 2 hr. The mixture was diluted with water and the product isolated with ether, to yield 2-*chloro*-3,5-*dimethoxy*-4,6-*dimethylphenylacetonitrile*, b. p. 170°/0·3 mm., which formed needles (1 g.), m. p. 82° [from light petroleum (b. p. 60—80°)] (Found: C, 59·7; H, 5·7; N, 5·8. $C_{12}H_{14}ClNO_2$ requires C, 60·1; H, 5·8; N, 5·8%).

(+)-1-*Bromo*-3,5(S)-*dimethylheptane*.—(+)-4,6(*S*)-Dimethyloctanoic acid was converted quantitatively (diazomethane) into the (+)-*methyl ester*, b. p. 100°/18 mm., $[\alpha]_D^{24}$ +17·9° (*c* 5·4 in chloroform) (Found: C, 71·2; H, 12·1. $C_{11}H_{22}O_2$ requires C, 70·9; H, 11·8%). Gas chromatography revealed that it was predominantly (>95%) one stereoisomer.

(+)-4,6(*S*)-Dimethyloctanoic acid (7·7 g.) was converted into the ammonium salt with excess ammonium hydroxide solution. The warm salt solution was treated with excess aqueous silver nitrate, and the precipitate collected, washed with water and acetone, and dried to constant weight at 40° for 10 hr. (11·9 g.). A solution of bromine (1·3 g.) in carbon tetrachloride (10 ml.) was added to a refluxing suspension of this silver salt (2·8 g.) in carbon tetrachloride (50 ml.) until no more bromine was consumed (rigorous exclusion of moisture). The mixture

[7] J. S. E. Holker, W. J. Ross, J. Staunton, and W. B. Whalley, *J.*, 1962, 4150.

was refluxed for ½ hr., cooled, filtered, and the salts washed with hot carbon tetrachloride. The combined carbon tetrachloride solutions were washed with N-sodium hydroxide, dried, and distilled, to yield (+)-1-*bromo*-3,5(S)-*dimethylheptane* (1·4 g.), b. p. 83°/17 mm., $[\alpha]_D^{24}$ +18° (*c* 10·0 in chloroform), as a fragrant mobile oil (Found: Br, 38·7. $C_9H_{19}Br$ requires Br, 38·6%), shown by gas chromatography to be stereochemically homogeneous. Unchanged acid (0·32 g.) was recovered from the alkaline washings.

Sclerotinol.—The Grignard reagent was prepared, under nitrogen, from the previous bromo-compound (1·1 g.) in refluxing ether (20 ml.) containing magnesium (0·12 g.) together with a crystal of iodine, during 3 hr. After the addition of a solution of 2-chloro-3,5-dimethoxy-4,6-dimethylphenylacetonitrile (1 g.) in ether (20 ml.), the mixture was refluxed for a further 14 hr., when the complex was decomposed by the addition of aqueous ammonium chloride. The ethereal solution was washed with 2N-hydrochloric acid (3 × 10 ml.) and the acidic extract heated on a steam-bath for 1 hr. The oil which separated was distilled to give di-*O*-methylsclerotinol (65 mg.), b. p. 190°/0·13 mm. (Found: C, 68·9; H, 8·5. Calc. for $C_{21}H_{33}ClO_3$: C, 69·4; H, 9·0%). The infrared spectrum (in $CHCl_3$) was identical with that of the natural material. Demethylation of this product (50 mg.) in boiling acetic acid (2 ml.) containing hydrobromic acid (48%; 1 ml.) occurred during 2 hr., to yield synthetic sclerotinol in needles (15 mg.), m. p. 85—86° [from light petroleum (b. p. 60—80°)] (Found: C, 66·4; H, 8·3. Calc. for $C_{19}H_{29}ClO_3$: C, 66·9; H, 8·6%), identical with the natural product in m. p., mixed m. p., and infrared spectrum. The di-*O*-acetates of synthetic and natural sclerotinol were identical (m. p., mixed m. p., and infrared spectra).

The semicrystalline residue from the distillation of synthetic di-*O*-methylsclerotinol was purified from alcohol, to yield what is probably *di-(2-chloro-3,5-dimethoxy-4,6-dimethylphenyl) ketone* (10 mg.), in needles, m. p. 168° (Found: C, 61·1; H, 6·3; N, 0. $C_{23}H_{28}Cl_2O_5$ requires C, 60·7; H, 6·1%).

2-*Chloro*-3,5-*dimethoxy*-4,6-*dimethylphenylacetone.*—Prepared in a manner similar to that used for di-*O*-methylsclerotinol by the interaction of 2-chloro-3,5-dimethoxy-4,6-dimethylphenylacetonitrile and excess methylmagnesium iodide, this *product* formed an oil (20%), b. p. 150—155°/0·1 mm. (Found: C, 61·3; H, 7·0; Cl, 14·4. $C_{13}H_{17}ClO_3$ requires C, 60·8; H, 6·5; Cl, 13·8%). The 2,4-*dinitrophenylhydrazone* separated from alcohol in yellow prisms, m. p. 142° (Found: C, 51·2; H, 5·0; N, 13·1. $C_{19}H_{21}ClN_4O_6$ requires C, 52·2; H, 4·9; N, 12·8%).

3,5-*Dimethoxy*-4-*methylphenylacetone.*—(*a*) Prepared by the interaction of 3,5-dimethoxy-4-methylphenylacetamide (0·65 g.) and toluene-*p*-sulphonyl chloride (0·6 g.) in pyridine (4 ml.) during 6 hr., 3,5-*dimethoxy*-4-*methylphenylacetonitrile* formed needles (0·5 g.), m. p. 63° [from light petroleum (b. p. 40—60°)] (Found: C, 69·2; H, 6·9; N, 7·3. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·8; N, 7·3%).

A solution of this nitrile (0·6 g.) in ether (20 ml.) containing excess methylmagnesium iodide was refluxed for 6 hr. After isolation, 3,5-*dimethoxy*-4-*methylphenylacetone* formed an oil (0·3 g.), m. p. 145°/0·6 mm., $\nu_{max.}$ 1721 cm.$^{-1}$ (>C=O) (Found: C, 68·9; H, 8·1. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). The *semicarbazone* formed plates, m. p. 210° (from alcohol) (Found: C, 59·6; H, 7·3; N, 15·7. $C_{13}H_{19}N_3O_3$ requires C, 58·9; H, 7·2; N, 15·8%). The 2,4-*dinitrophenylhydrazone* separated from acetic acid in yellow prisms, m. p. 197° (Found: C, 55·1; H, 5·5; N, 13·4. $C_{18}H_{20}N_4O_6$ requires C, 55·7; H, 5·2; H, 14·4%).

(*b*) Prepared by the interaction of phosphorous pentachloride and the corresponding acid, 3,5-*dimethoxy*-4-*methylphenylacetyl chloride* formed needles, m. p. 61° [from light petroleum (b. p. 60—80°)] (Found: C, 56·9; H, 5·5. $C_{11}H_{13}ClO_3$ requires C, 57·8; H, 5·7%). A solution of this acid chloride (0·5 g.) in benzene (6 ml.) was added to dimethylcadmium [prepared by the treatment of methylmagnesium iodide (0·5 g.) in ether (30 ml.) with cadmium chloride (0·5 g.)] in benzene (35 ml.). The mixture was refluxed for 20 min., and treated in the usual way, to yield 3,5-dimethoxy-4-methylphenylacetone, b. p. 145°/0·6 mm. (0·35 g.), identical with the product obtained by method (*a*) (Found: C, 68·9; H, 8·1%).

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THE SCHOOL OF PHARMACY, UNIVERSITY OF LONDON,
29—39 BRUNSWICK SQUARE, LONDON W.C.1.

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