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THE SYNTHESES OF SCLERIN AND SCLEROLIDE, METABOLITES OF SCLEROTINIA LIBERTIANA

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Sclerin and sclerolide are the metabolites of Sclerotinia libertiana and the former compound is of considerable interest because of its growth promoting action for various plants (1). We have recently proposed the structures XVI and XXIII, respectively for sclerin and sclerolide (2) and now wish to report their syntheses, which confirm the previous structure assignments.

The first goal of sclerin synthesis was the dl-nor-acid (IX), obtainable from sclerin by decarboxylation with 40% potassium hydroxide solution at 180° (2) and IX could, in turn, be converted to sclerin (XVI) by introducing a carboxyl function on the aromatic ring.

Friedel-Crafts acetylation of hemimellitene (3) at room temperature yielded the mixture (5:4) of the isomeric acetophenones (I) and (II), separable by fractional distillation on a column. Nitration of 2,3,4-trimethylacetophenone (I) by the conventional method gave 2,3,4-trimethyl-5-nitroacetophenone (III), m.p. 64-66° in 68% yield with small amounts of 2,3,4-trimethyl-5,6-dinitroacetophenone, m.p. 138-140° and 2,3,4-trimethyl-5-nitrobenzoic acid, m.p. 176-177°. The nitroacetophenone (III) was converted to

5-hydroxy-2,3,4-trimethylacetophenone (V), m.p. 168° in 53% yield via reduction with stannous chloride and following diazotization of the resulted aminoacetophenone (IV), m.p. 124-127°. Methylation of V with dimethylsulfate and potassium carbonate in acetone followed by reduction with lithium aluminum hydride afforded 1-(1-hydroxyethyl)-5-methoxy-2,3,4-trimethylbenzene (VI), m.p. 68-69° which was identical with the specimen (2) derived from sclerin. The chloride prepared from (VI) through the treatment with thionyl chloride was reacted with sodium cyanide in dimethylsulfoxide at 120°. Hydrolysis of the resultant nitril (VII) was effected by its heating with the mixture of aq. 20% potassium hydroxide solution and ethylene glycol to give the nor-acid methyl ether (VIII), m.p. 131°. Corresponding amide, m.p. 126-128° was obtained by the hydrolysis in milder condition. Demethylation of VIII with hydroiodic acid afforded the nor-acid (IX), m.p. 128-130°. Identity of VIII and IX with the corresponding compounds (2) derived from natural sclerin was secured from the comparison of their infrared spectra.

Nitration of VIII in acetic anhydride solution at -30° produced the nitro-acid (X), m.p. 208-209°, which was reduced catalytically in a warm acetic acid solution at the presence of palladized carbon. The product was the five-membered lactam (XI), m.p. 211-213°, ν_{max}^{Nujol} 3180, 1700, 1636 cm^{-1}, even after the carboxyl group was protected as methyl ester. This prevented the further transformation by way of Sandmeyer reaction. Eventually the introduction of one extra carbon atom on the nuclear position was achieved by the chloromethylation of XII, which furnished, with concomitant lactonization, the six-membered lactone (XIV), m.p. 115-116°, ν_{max}^{Nujol} 1735 cm^{-1}, n.m.r.τ($CDCl_3$) 4.39, 4.72 (AB quartet, J=14 cps., $ArCH_2OCO$-), 6.07 (q., J=8 cps., $CH_3\underline{C}H$-), 7.78, 7.83 (each s., $3ArCH_3$), 8.54 (d., J=8 cps., $\underline{CH_3}CH$-) in 76% yield. (XIV) was oxidized with Jones' reagent for 24 hours to yield the dicarboxylic acid (XIII), (30% yield), which, on treatment with hot acetic anhydride, was converted to sclerin methyl ether (XV), m.p. 104-105°, identical with the one (2) derived previously from sclerin. Finally demethylation of (XV) with borontribromide (4) afforded racemic sclerin, of which infrared spectrum in chloroform solution was indistinguishable with that of natural specimen.

The starting point for our synthesis of sclerolide was 5-hydroxy-2,3,4-trimethylacetophenone (V). Nitration of V in the mixture of acetic acid and carbon tetrachloride gave in 80% yield 3-hydroxy-4,5,6-trimethyl-2-nitroacetophenone (XVII), m.p. 99-100°. Methylation of XVII was performed by treating its

sodium salt with dimethylsulfate in refluxing benzene to afford 3-methoxy-4,5,6-trimethyl-2-nitroacetophenone (XVIII), m.p. 70-72°. XVIII was subsequently transformed to 2-amino-3-methoxy-4,5,6-trimethylacetophenone (XIX) through the treatment with stannous chloride, while insufficient reduction led to the formation of 7-methoxy-3,4,5,6-tetramethylanthranil (XX), m.p. 80°, ν_{max}^{Nujol} 1635, 1570, 1535 cm^{-1}, λ_{max}^{EtOH} 330 mμ (ε 27600). Sandmeyer reaction of XIX furnished 2-cyano-3-methoxy-4,5,6-trimethylacetophenone (XXI), ν_{max}^{Nujol} 2230, 1695 cm^{-1}, which was converted, on alkaline hydrolysis, to sclerolide methyl ether (XXII), m.p. 145.5-146.5° (2). XXII was identified by mixed melting point determination and the comparison of the infrared spectra. On demethylation with hydrobromic acid XXII was transformed to sclerolide, identical with the compound obtained from the fungus.

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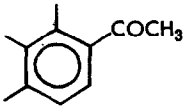

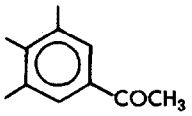

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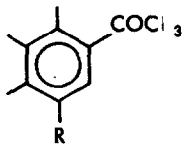
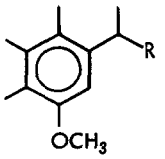
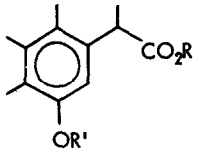


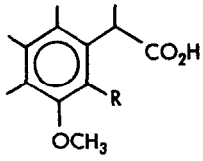
III R=NO_2
IV R=NH_2
V R=OH



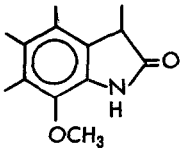
VI R=OH
VII R=CN



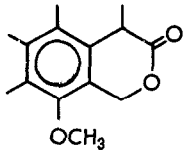
VIII R=OH, R'=CH_3
IX R=R'=H
XII R=R'=CH_3



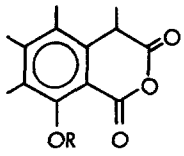
X R=NO_2
XIII R=CO_2H



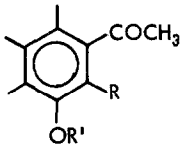
XI



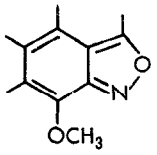
XIV



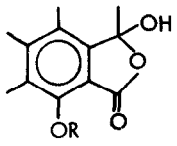
XV R=CH_3
XVI R=H



XVII R=NO_2, R'=H
XVIII R=NO_2, R'=CH_3
XIX R=NH_2, R'=CH_3
XXI R=CN, R'=CH_3



XX



XXII R=CH_3
XXIII R=H