

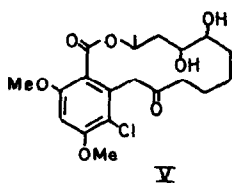
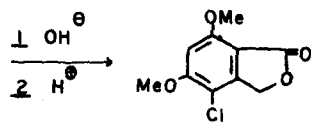
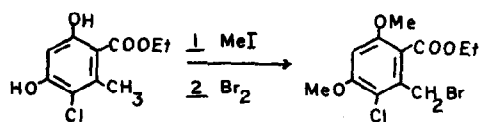
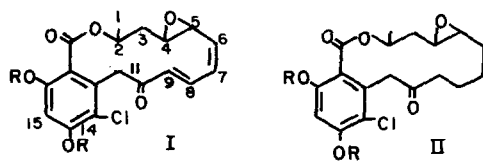
THE CONSTITUTION OF RADICICOL

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Ether extracts of the culture filtrate of a strain of Nectria radicicola Gerlach et Nilsson (syn. Cylindrocarpon radicicola Wr.) (1) yield radicicol, a colourless crystalline phenol, m.p. 195°; $[\alpha]_D +216^\circ$ (c, 1.0 in CHCl_3); ν_{\max} 3300, 1655-1555 cm^{-1} (Nujol); λ_{\max} 265 μm , ϵ 17700 (neutral or acidic ethanol); λ_{\max} 254, 274, 319 μm , ϵ 22600, 22600, 15000 (alkaline ethanol). Analyses and molecular weights, which were determined mass spectrometrically, of radicicol and several derivatives establish the formula $\text{C}_{18}\text{H}_{17}\text{O}_6\text{Cl}$. By chemical degradation and by spectroscopic methods the structure I (R=H) is deduced for radicicol.

Methylation of radicicol with methyl iodide-potassium carbonate gave the dimethyl ether I (R=Me), m.p. 186-187°; $[\alpha]_D -58^\circ$ (c, 1.0 in CHCl_3); ν_{\max} 1723 (aromatic ester), 1652 cm^{-1} (conjugated ketone), no hydroxyl absorption (Nujol); λ_{\max} 279 μm , ϵ 19200 (ethanol). Catalytic hydrogenation of radicicol yielded a tetrahydro-derivative II (R=H), m.p. 170-172°; $[\alpha]_D -29^\circ$ (c, 1.0 in CHCl_3); ν_{\max} 3150 (phenolic hydroxyl), 1705 (saturated ketone), 1660 cm^{-1} (H-bonded aromatic ester); λ_{\max} 215, 265, 310 μm , ϵ 25000, 7880, 4760 (neutral or acidic ethanol); λ_{\max} 251, 320 μm , ϵ 12450, 20000 (alkaline ethanol). When this neutral ultraviolet spectral curve was subtracted from that of radicicol, the resultant curve had λ_{\max} 280 μm , ϵ 12000,



which is characteristic of the dienone system, $-C=C-C=C-O$.

Hydrogenation of I (R=Me) or methylation of II (R=H) afforded dimethyltetrahydradicicol II (R=Me), m.p. 134-136°; $[\alpha]_D -83^\circ$ (c, 1.0 in $CHCl_3$); ν_{max} 1718 (ester), shoulder at $1705cm^{-1}$ (saturated ketone) (Nujol); λ_{max} 245 (inflexion), 292 $m\mu$, ϵ 5300, 3980 (ethanol). Subtraction of this curve from that of I (R=CH₃) gave a curve with λ_{max} 278 $m\mu$, ϵ 16800.

Acetylation of radicicol gave the diacetyl derivative I (R=Ac), m.p. 189-190°; ν_{max} 1785, 1773 (two phenolic acetates), 1732 (ester) $1662cm^{-1}$ (conjugated ketone) (Nujol); λ_{max} 279 $m\mu$, ϵ 15800; NMR¹, two singlets, intensity 3H each at 2.26, 2.35 ppm.

The above reactions and the spectral properties of the products show the presence in radicicol of two phenolic hydroxyl groups, a hydrogen-bonded carbonyl group (most likely ester) conjugated with an aromatic ring and an isolated dienone system.

Mild alkaline treatment of I (R=Me) gave 4-chloro-5,7-dimethoxyphthalide (III) whose identity was proven by synthesis from the known ester (IV) (2) as shown.

The nature of five of the oxygen atoms of radicicol was thus accounted for; information that the sixth was linked in an epoxide was first obtained from the NMR spectra. Chemically, the presence of an epoxide was demonstrated by treatment of II (R=Me) with formic acid at room temperature to yield a glycol monoformate which was then hydrolysed to give the trans-diol (V), m.p. 250°; ν_{max} 3300 (two hydroxyl groups), $1710cm^{-1}$ (saturated ketone and aromatic ester) (Nujol); λ_{max} 249 (inflexion), 290 $m\mu$, ϵ 7130, 3640 (ethanol). The diol could also be prepared directly from II (R=Me) by treatment with boron trifluoride in butanol. Periodate cleavage of the diol yielded crotonaldehyde by a β -elimination. This result proved the relationship of the epoxide and the ester functions and the presence of a methyl group at C₂.

Finally, direct oxidation of II (R=Me) with chromic acid in acetic acid yielded adipic acid. Together with the other degradation products, this accounted for all of the carbon atoms of radicicol and established the structure of the latter as I (R=H).

The signals in the NMR spectra of radicicol and its derivatives were exceptionally well resolved for such complex molecules. The spectrum of I (R=CH₃) was interpreted as follows.

Singlet at 6.52 ppm (intensity 1 H): aromatic proton at C₁₅. This signal was also present in the spectrum of II (R=Me) (at 6.49 ppm) and of III (at 6.45 ppm).

Doublet at 6.08 ppm (intensity 1 H): H₉, J_{9,8} 16 c/s (trans); doublet of doublets at 7.48 ppm (intensity 1 H): H₈, J_{8,9} 16 c/s (trans), J_{8,7} 9 c/s (vicinal, approximately planar configuration); doublet of doublets at 6.15 ppm (intensity 1 H); H₇, J_{7,8} 9 c/s, J_{7,6} 10.5 c/s (cis); doublet of doublets at 5.66 ppm (intensity 1 H): H₆, J_{6,7} 10.5 c/s, J_{6,5} 4.5 c/s. An additional long-range coupling (3) between H₇ and H₅ (J approximately 1 c/s) was also observable. The spectrum of II (R=Me) showed no resonances in the region between 6.5 and 5.3 ppm. *

AB quartet near 4.1 ppm and partially superimposed on methoxyl signals (vide infra) (intensity 2H): methylene protons at C₁₁. In radicicol I (R=H) the corresponding signals are H_A 3.97 ppm, H_B 4.81 ppm, J_{AB} 16 c/s (geminal coupling). In diacetyl radicicol I (R=Ac) H_A 3.91 ppm, H_B 4.13 ppm, J_{AB} 16.5 c/s. In tetrahydro-dimethylradicicol II (R=Me) H_A 3.92 ppm, H_B 4.10 ppm, J_{AB} 18 c/s.

Two singlets at 3.8 and 3.9 ppm (total intensity 6H): methoxyl groups. These signals are absent in the spectra of I (R=H) and I (R=Ac) but occur (at almost identical frequency) in the spectrum of II (R=Me).

Doublet at 1.52 ppm (intensity 3 H): C₁ methyl, J_{1,2} 6.5 c/s. This signal is also present in the spectra of I (R=H), I (R=Ac) and II (R=Me) at almost identical frequencies.

* NMR spectra were recorded on a Varian A-60 spectrometer for solutions in deuteriochloroform. Chemical shifts are in ppm from tetramethylsilane as internal reference. Coupling constants are derived from first order considerations only.

Symmetrical multiplet at 5.35 ppm (intensity 1 H): H_2 , split into a quartet (J 6.5 c/s) by C_1 methyl and into doublets (J approximately 3.5 and 4 c/s respectively) by the methylene protons at C_3 (vicinal, gauche coupling). This signal is also seen, with the same multiplicity, in the spectra of II (R=Me) at 5.18 ppm, of I (R=H) at 5.57 ppm and of I (R=Ac) at 5.40 ppm.

Multiplet of half-height width of 8 c/s at 3.45 ppm (intensity 1 H): H_5 . Doublet of approximate triplets at 3.06 ppm (intensity 1 H): H_4 , J_{doublet} 9 c/s, due to interaction with one of the methylene protons at C_3 (vicinal, trans coupling), J_{triplet} 3 c/s due to approximately equal interactions with the other methylene proton at C_3 (vicinal, gauche coupling) and with H_5 (trans coupling in an epoxide ring) (4,5). Signals assigned to H_4 and H_5 also occur at almost identical frequencies and the same multiplicities in the spectra of I (R=H) and I (R=Ac). In the spectrum of II (R=Me) no resonances can be seen between the group near 4 ppm (8 protons, methoxyls and methylene at C_{11}) and 3.0 ppm indicating that H_5 is allylic and hence is shifted upfield on hydrogenation of I (R=Me).

Doublet of approximate triplets at 2.4 ppm (intensity 1 H): one of the methylene protons at C_3 , J_{doublet} 15 c/s (geminal coupling to the other methylene proton), J_{triplet} 3.5 c/s due to approximately equal coupling to H_4 and H_2 (vicinal, gauche coupling)

Multiplet near 1.7 ppm (intensity approximately 0.5 H): the other methylene proton at C_3 . Four lines are resolved (spacings of 8.5 and 4 c/s), the remainder is overlapped by the signal due to methyl at C_1 . The discernable splittings are assigned to a vicinal gauche interaction with H_2 (J 4 c/s) and a vicinal trans interaction with H_4 (J 8.5 c/s). The geminal coupling (presumably 15 c/s) to the second methylene proton at C_3 (signal at 2.4 ppm, see above) is most likely responsible for the part of the multiplet under the methyl resonance.

Spin decoupling experiments, performed by L.F. Johnson of Varian Associates, Palo Alto, have confirmed the coupling of H_2 with methylene proton at C_3 which gives rise to the resonance at

2.4 ppm, of H₅ with H₆ and of H₄ with the methylene proton at C₃ resonating at 1.7 ppm.

Biogenetically, radicicol appears to be derived in an unexceptionable manner from acetate units.

After this work had been completed it was learnt (during a social visit by one of us to the University of British Columbia) that structure I (R=H) had also been assigned by A.I. Scott and N.S. Bhacca (following paper) to the substance "monorden". This was first isolated from the culture filtrates of Monosporium bonorden by Delmotte and Delmotte-Plaquee (6), who assigned to it the formula C₁₇H₁₆O₇, with m.p. 193.5°, [α]_D²⁰ +203 (in CHCl₃). Comparison of "radicicol" with "monorden" established their identity.

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