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RADICINOL, A NEW METABOLITE OF COCHLIOBOLUS LUNATA, AND ABSOLUTE STEREOCHEMISTRY OF RADICININ

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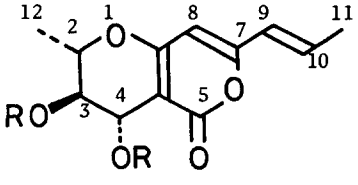
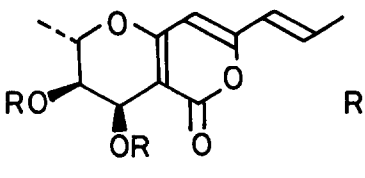
In the course of our investigation on aversion factors,[1] which were defined as antibiotics among different strains of a fungal species,[2] a new metabolite was isolated from one (IFO 6288) of ten IFO strains of Cochliobolus lunata, accompanied with radicinin, a known metabolite already isolated from the same fungus[3] and Stemphylium radicinum.[4] We wish now to describe the isolation and structural determination of the new metabolite named radicinol and also the elucidation of the absolute stereochemistry of radicinin. Radicinin was also isolated from other two strains (IFO 6299 and 6382) of C. lunata.

C. lunata IFO 6288 was cultured with a jar fermentor in malt-dextrose medium at 30°C for 6 days. A mixture of radicinol and radicinin, obtained through column chromatography (silicic acid, 60% ethyl acetate in n-hexane) of the ethyl acetate extracts of the culture filtrate, was separated through Sephadex LH-20 (acetone) into radicinol (colorless viscous oil, yield 2.4 mg/L) and radicinin (pale yellow needles, mp 235-238°C). The latter compound was identified as radicinin, based on the identity of its spectral (ir, nmr and optical rotation) properties with those reported on radicinin.[4] Radicinol (1), $C_{12}H_{14}O_5$ (m/e 238.082; calcd. 238.084); $[\alpha]_D^{31}$ -175° (c 1.02, $CHCl_3$), had two more hydrogens than radicinin (2), and showed the following physical properties which satisfied the structure (1). UV: λ_{max}^{EtOH} 226 nm(ε 39300), 262 (3100), 271 (3200), 318 (10800); ir: $\nu_{max}^{CHCl_3}$ 3425 cm^{-1} (OH), 1680 (α-pyrone); pmr: δ($CDCl_3$) 6.72 (dq, J=7 and 16 Hz, 10-H), 6.02 (dq, J=2 and 16 Hz, 9-H), 5.85 (s, 8-H), 4.75 (bs, two OH), 4.70 (d, J=6.5 Hz, 4-H), 4.23 (dq, J=8 and 6.5 Hz, 2-H), 3.76 (dd, J=6.5 and 8 Hz, 3-H), 1.92 (dd, J=2 and 7 Hz, 11-H), 1.52 (d, J=6.5 Hz, 2-CH_3); cmr: δ($CDCl_3$) 165.4 (s, 5-C), 164.5 (s, 8a-C), 158.9 (s, 7-C), 135.7 (d, 10-C), 122.7 (d, 9-C), 100.6 (s, 4a-C), 99.1 (d, 8-C), 76.8, 72.5, 68.0 (each d, for 2-, 3- and 4-C), 18.4, 17.0 (each q, for 11- and 12-C). The pmr spectrum of 1, when compared with that of 2,indicated that the α-pyrone ring and the propylene side chain were similarly present in 1. Only difference in pmr spectra of the both compounds was that two more proton signals assigned as >CH(OH)(chemical shifts, vide supra) were present on the dihydropyrane ring of 1. This suggests that 1 may be a compound derived from radicinin (2), whose ketone at C-4 was reduced to a secondary hydroxyl group. The suggestion was confirmed from the cmr spectrum of 1, which lacked the signal of carbonyl carbon



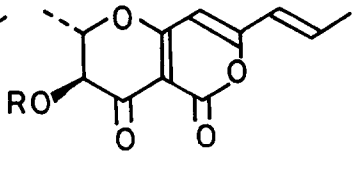
1: R=H

4: R=p-Cl-Bz



3: R=H

5: R=p-Cl-Bz



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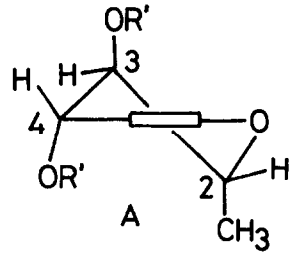
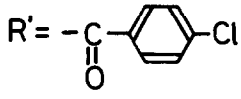
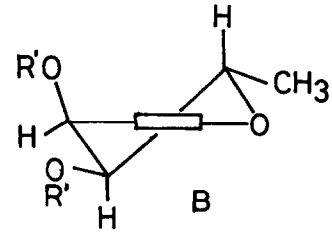
observed at δ 188 in 2, and showed the new methin carbon at δ 68.0. An easy formation of the diacetate (M^+ m/e 322) upon acetylation (Ac_2O and pyridine) indicated the presence of two acetylable hydroxyls in 1. An unambiguous evidence on the structure of 1 was obtained by successful derivation of 1 from 2. 2 was reduced with $NaBH_4$ in MeOH, affording two products, one of which, the less polar, was found to be identical with radicinol in spectral (ir, pmr, mass and optical rotation) properties. Another more polar product was 4-epi-radicinol (3), which showed the physical properties similar to those of 1, as follows; amorphous; $[\alpha]_D^{28}$ -92°(c 0.48, $CHCl_3$); ir: $\nu_{max}^{CHCl_3}$ 3425 cm^{-1} (OH), 1685 (α-pyrone); pmr: δ($CDCl_3$) 6.75 (dq, J=7 and 16 Hz, 10-H), 5.99 (dq, J=1.5 and 16 Hz, 9-H), 5.80 (s, 8-H), 4.78 (d, J=4 Hz, 4-H), 4.30 (dq, J=6.5 and 8.5 Hz, 2-H), 3.60 (dd, J= 4 and 8.5 Hz, 3-H), 1.90 (dd, J=1.5 and 7 Hz, 11-H), 1.45 (d, J=6.5 Hz, 2-CH_3). Based on chemical correlation of 1 with 2 as described above, all of three compounds, 1, 2 and 3, should have the same absolute stereochemistry at C-2 and -3 positions. The relative stereochemistry at these chiral centers was shown to be trans from the large coupling constant (J=10 Hz) between C-2 and -3 protons of 2. 3 formed easily an acetonide, m/e 278 (M^+); δ 1.52 (6H, s, >$C(CH_3)_2$), upon treatment with 2,2-dimethoxypropane and p-TsOH, whereas the acetonide formation did not occur on 1. These data indicated that the vicinal glycol at C-3 and -4 positions of 3 should be in cis, and that of 1, in trans relation. The absolute stereochemistry was determined by exciton chirality[5] of 3,4-bis-p-Cl-benzoate derivatives (4 and 5) of 1 and 3. First, the conformation of the dihydropyrane ring of these derivatives was determined by their pmr spectra. That two p-Cl-benzoyloxy groups of 4 were directed in trans diaxial orientation, as shown in the conformer A, was indicated from a small coupling constant (3.0 Hz) both for $J_{2,3}$ and $J_{3,4}$ values. On the other hand, 5 showed 10.6 and 3.5 Hz as the corresponding J values, indicating that the two groups must be oriented as shown in the conformer B. Therefore, a splitting CD Cotton effect is expected in the case of 5. Actually, 5 showed the negative sign of the first CD Cotton effect at 249 nm (Δε -31.7) and the second one at 233 nm (Δε +18.1), accompanied with another weak Cotton effect at 313 nm (Δε +9.27) which might originate from the α-pyrone chromophore. On the other hand, 4 showed the two Cotton effects at 247 nm (Δε +51) with shoulder (232 nm) and at 315 nm (Δε -8.42). These data agreed well with the conformers A and B speculated from the pmr spectra, elucidating that the vicinal glycol at C-3 and -4 positions of 5 should have the chirality of counterclockwise twist. Thus, the absolute stereochemistry of 1 was established as 2S,3R,4S, and that of 2, 2S,3S.







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