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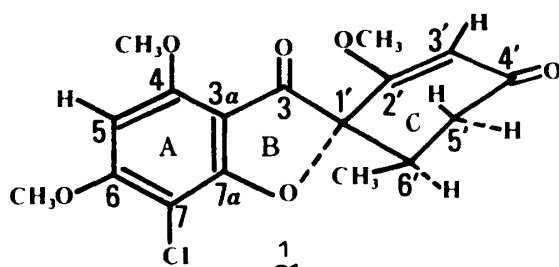
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# Griseofulvin Biosynthesis: New Evidence of Two Acetate-Dispositions in the Ring A from $^{13}\text{C}$ Nuclear Magnetic Resonance Studies\*

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Griseofulvin (**1**), the antibiotic produced by *Penicillium* species, is known to be derived from acetate. In this communication, we report the biosynthetic studies of griseofulvin by  $^{13}\text{C}$  nmr using  $[1-^{13}\text{C}]$ -,  $[2-^{13}\text{C}]$ -, and  $[1,2-^{13}\text{C}]$ -acetate as tracers. In order to elucidate the acetate-disposition especially on the ring A of griseofulvin, first  $^{13}\text{C}$  nmr of naturally occurring griseofulvin and two of its derivatives, 5-bromogriseofulvin and dechlorogriseofulvin, were recorded in penta-deuteriopyridine solution with Varian XL-100-12 WG NMR spectrometer equipped with a Varian 620/L computer, operating at 25.2 MHz at 30°C, and  $^{13}\text{C}$  chemical shifts were assigned from off-resonance-decoupled, proton-noise-decoupled (p.n.d.) and selective single-frequency-hetero-nuclear-decoupled spectra. The chemical shifts of griseofulvin are shown in Table I, with enhancements observed in  $[1-^{13}\text{C}]$ - and  $[2-^{13}\text{C}]$ -acetate-enriched samples and coupling constants of  $[1,2-^{13}\text{C}_2]$ -acetate-enriched **1**. Then, *Penicillium urticae* was fermented for 7 days and the mycelium thus obtained was



used for the biosynthetic experiments in the medium containing sodium  $[1-^{13}\text{C}]$ -,  $[2-^{13}\text{C}]$ - and  $[1,2-^{13}\text{C}_2]$ -acetate as tracers. The p.n.d.  $^{13}\text{C}$  nmr spectra of the  $[1-^{13}\text{C}]$ - and  $[2-^{13}\text{C}]$ -acetate enriched samples showed the enhancements at the anticipated positions in the skeleton (Table I). Furthermore, the enhancements were observed in the three methoxyl groups in the spectrum of griseofulvin enriched by feeding  $[2-^{13}\text{C}]$ -acetate. The p.n.d.  $^{13}\text{C}$  nmr spectrum of the  $[1,2-^{13}\text{C}_2]$ -acetate-derived sample showed ten pairs of  $^{13}\text{C}$ - $^{13}\text{C}$  couplings indicating that  $\text{C}(6'-\text{CH}_3)-\text{C}(6')$ ,  $\text{C}(5')-\text{C}(4')$ ,  $\text{C}(3')-\text{C}(2')$  and  $\text{C}(1')-\text{C}(3)$  in the rings C and B, and  $\text{C}(3a)-\text{C}(4)$ ,  $\text{C}(5)-\text{C}(6)$ ,  $\text{C}(7)-\text{C}(7a)$ ,  $\text{C}(3a)-\text{C}(7a)$ ,  $\text{C}(7)-\text{C}(6)$  and  $\text{C}(5)-\text{C}(4)$  in the ring A originate from intact acetate units. Thus the grisan ring system of griseofulvin will be

\* Tetrahedron Letters, 1976, 3971.

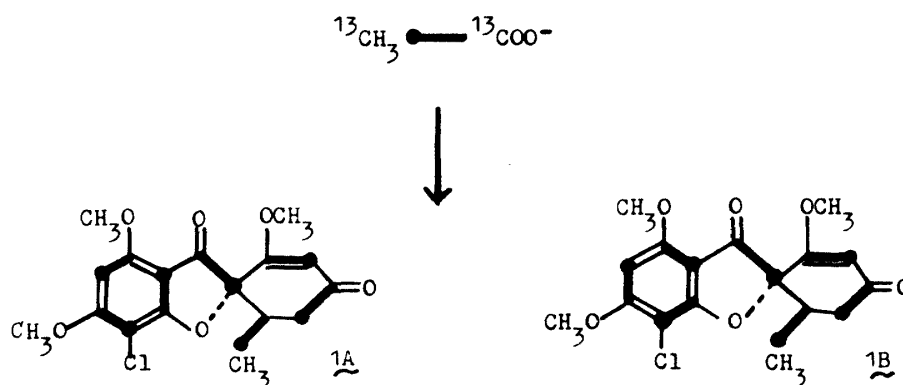
formed by condensation of a heptaketide chain. This observation suggests that, through a polyketomethylene intermediate, griseophenone C is formed and its phloroglucinol moiety makes a rotation to an equilibrium, and a chlorination to give griseophenone B, followed by several steps of reactions will afford griseofulvin. This evidence clearly indicates that griseofulvin is composed of 1A and 1B shown in Scheme.

Table I  $^{13}\text{C}$ -Chemical shifts ( $\delta$ ) of griseofulvin (1); signal patterns of off-resonance-decoupled spectrum of 1; coupling constants (Hz) of  $[1,2-^{13}\text{C}]$ -acetate-enriched 1; and signal enhancements observed in a)  $[2-^{13}\text{C}]$ -acetate-enriched 1 and b)  $[1-^{13}\text{C}]$ -acetate-enriched 1.

Carbon	$\delta_{\text{ppm}}$	$J_{\text{C-C}}$ (Hz)	Enrichment * *	
			a)	b)
6'-CH <sub>3</sub>	14.3 Q*	36	+	
6'	36.8 D	36		+
5'	40.5 T	40	+	
6-OCH <sub>3</sub>	56.4 Q	—	+	
2'-OCH <sub>3</sub>	56.6 Q	—	+	
4-OCH <sub>3</sub>	57.1 Q	—	+	
5	90.7 D	71 73	+	
1'	91.0 S	40	+	
7	96.9 S	81 81	+	
3'	105.4 D	74	+	
3a	105.5 S	75 75	+	
4	158.2 S	76 72		+
6	164.9 S	70 80		+
7a	169.6 S	80 74		+
2'	170.6 S	74		+
3	191.9 S	41		+
4'	195.5 S	41		+

\* Q, quartet; T, triplet; D, doublet; S, singlet.

\* \* +, signal enhancement



Scheme