

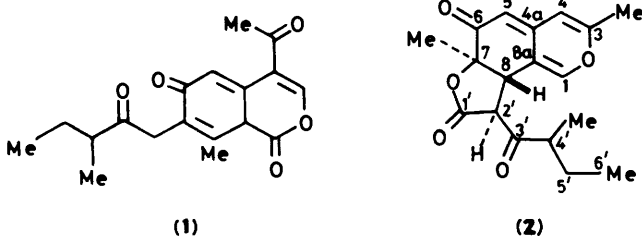
A Reinvestigation of the Structure of Monochaetin, a Metabolite of *Monochaetia compta*

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The long-range carbon-proton connectivity pattern for monochaetin, as determined by the heteronuclear selective population inversion (SPI) n.m.r. technique, is incompatible with the previously reported structure (1) and instead establishes the azaphilone structure (2) for the metabolite.

In an earlier communication the isolation and structure elucidation of monochaetin, a metabolite elaborated by the fungus *Monochaetia compta*, was reported.¹ The biosynthetic origins of the metabolite are not obvious from a cursory inspection of the reported structure (1) and this prompted us to investigate the biosynthesis. The preliminary stage of any biosynthetic study generally is the unambiguous assignment of the resonances in the natural-abundance ¹³C n.m.r. spectrum and from the outset it was evident that the reported structure (1) for monochaetin was in error. We now present n.m.r. evidence which leads to the structure (2).



Monochaetin (2), C₁₈H₂₀O₅, showed $[\alpha]_D^{20} + 715^\circ$ (c 0.53 in CHCl₃). First-order analysis of the resonances in the ¹H n.m.r. spectrum yielded the values of the proton chemical shifts and proton-proton coupling constants (see Table). From the value of the coupling constants as corroborated by ¹H{¹H} decoupling experiments the proton-proton connectivity pattern could be constituted. The ¹³C n.m.r. data as collated in the Table were obtained from proton-decoupled and single-frequency nuclear Overhauser effect (n.O.e.) spectra, and indicated the presence of only one methylene carbon atom (δ_C 26.27 p.p.m.), three *sp*³ methine carbon atoms (δ_C 52.13, 46.70, and 43.66 p.p.m.), and one *sp*³ quaternary carbon atom (δ_C 82.55 p.p.m.). These chemical-shift values and multiplicities are clearly incompatible with the structure (1) previously assigned to monochaetin.¹

The next step in the structure elucidation was to correlate the signals of all the proton-bearing carbon atoms *via* their one-bond (¹³C,¹H) coupling constants with specific proton resonances in a two-dimensional (¹³C,¹H) shift-correlation experiment.^{2,3} The results allowed us to assign the ¹³C resonances of the carbon atoms of the methyl groups as well as C-4' and C-5'. Extensive heteronuclear ¹³C{¹H} selective population inversion (SPI) experiments,⁴ using a π -pulse with γH_2 5 Hz, defined the two- and three-bond (¹³C,¹H) connectivity pattern as shown in the Figure, and established unambiguously the structure (2) for monochaetin. The assignment of the resonances at δ_C 145.52 and 116.22 p.p.m. to C-4a and C-8a, respectively, is based on chemical-shift considerations and the reported values for the corresponding

Table. ¹³C (125.76 MHz) and ¹H (500.13 MHz) N.m.r. data for monochaetin (2)

Carbon atom	δ_C /p.p.m. ^a	¹ J(CH)/Hz	δ_H ^b	J(HH)/Hz
1	143.30(D)	194.6	6.791(dd)	1.9, 1.3
3	158.52(S)			
4	107.04(D)	166.6	6.017(q)	<0.4
4a	145.52(S)			
5	105.73(D)	165.3	5.294(d)	1.3
6	191.77(S)			
7	82.55(S)			
8	43.66(D)	128.4	3.761(dd)	12.8, 1.9
8a	116.22(S)			
1'	169.10(S)			
2'	52.13(D)	129.9	4.050(d)	12.8
3'	205.94(S)			
4'	46.70(D)	130	3.189(qdd)	6.7, 7.4, 5.4
5'	26.27(T)	127.9	1.805(qdd)	7.4, 13.0, 7.4
			1.480(qdd)	7.4, 13.0, 7.4
6'	11.45(Q)	126.2	0.968(t)	7.4
3-Me	19.49(Q)	130.3	2.130(d)	<0.4
7-Me	18.92(Q)	129.8	1.322(s)	
4'-Me	14.39(Q)	128.1	1.107(d)	6.7

^a Chemical shifts relative to CDCl₃ at δ_C 77.00 p.p.m. Capital letters refer to the pattern resulting from directly bonded (C,H) couplings. S = singlet, D = doublet, T = triplet, and Q = quartet. ^b Chemical shifts relative to CDCl₃ at δ_H 7.240. S = singlet, d = doublet, t = triplet, and q = quartet.

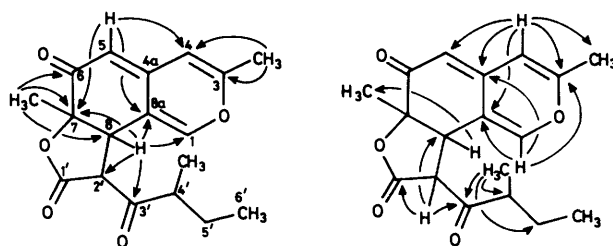
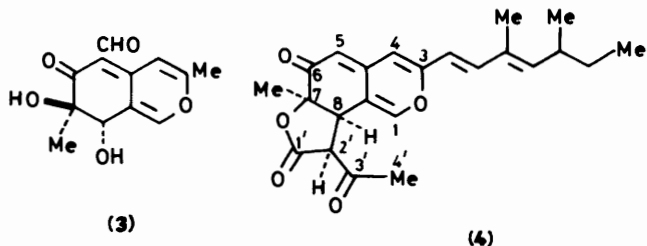


Figure. The two- and three-bond (¹³C,¹H) connectivity pattern observed for monochaetin (2)

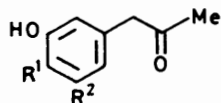
carbon atoms of other azaphilones, *e.g.* austdiol (3)⁵ and ochrephilone (4).⁶

The relative configuration at C-7, C-8, and C-2' of monochaetin (2) was deduced from the results of proton-proton nuclear Overhauser effect (n.O.e.) experiments.⁷ The *cis* configuration of the C-7 methyl group and 2'-H follows from the n.O.e. observed for 2'-H upon irradiation of the protons of the C-7 methyl group. The *trans* configuration of 8-H and 2'-H is based on the fact that no n.O.e. is observed for 8-H in this experiment. The relative configuration as shown in structure (2)



is in agreement with the allylic coupling of 1.9 Hz observed for the C-8 and C-1 protons. In contrast no allylic coupling was observed for the C-1 and C-8 protons in the ^1H n.m.r. spectrum of ochrephilone (4). The C-1 proton (δ_{H} 7.382) of (4) appears as a doublet (J 1.3 Hz) as a result of coupling with 5-H. Furthermore, the doublet signals at δ_{H} 3.806 and 3.762 p.p.m. constitute an AB spin system (J 12.2 Hz) and are assigned to 2'-H and 8-H. These data suggest that the C-8 chiral centres in monochaetin (2) and ochrephilone (4) are epimeric and therefore that the C-7 methyl group in compound (4) is *cis* to both the C-8 and C-2' protons. This deduction was confirmed by the n.o.e.s observed for both 8-H and 2'-H upon irradiation of the C-7 methyl protons (δ_{H} 1.563 p.p.m.) in ochrephilone.

The chemical reactions previously reported¹ for monochaetin can be rationalized in terms of the new structure (2). Monochaetin, unlike other azaphilones, failed to react characteristically with conc. ammonia to yield a vinylogous γ -pyridone, and instead the γ -lactone ring was converted into a primary amide.¹ The reaction of monochaetin with 1 equiv. *N*-bromosuccinimide (NBS) results in the formation of the 5-bromo derivative.¹ The use of 2 equiv. of NBS, however, yields the 5,2'-dibromo derivative, which reacts with potassium carbonate with the elimination of hydrogen bromide to generate the $\Delta^{8,2'}$ double bond.¹ Prolonged treatment of monochaetin with 5% aqueous sodium hydroxide results in the formation of a phenol, with two *meta* orientated aromatic protons (J 1.6 Hz), which must be assigned structure (5), and not (6).¹ The initial product formed under the experimental conditions must contain both a methyl ketone and an aldehyde group to account for the formation of iodoform upon addition of an alkaline solution of iodine and potassium iodide, and a positive Tollens reaction, respectively.¹



(5) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{CH}_2\text{COCH}(\text{Me})\text{CH}_2\text{Me}$

(6) $\text{R}^1 = \text{CH}_2\text{COCH}(\text{Me})\text{CH}_2\text{Me}$, $\text{R}^2 = \text{Me}$

Structural analysis of monochaetin suggests that the metabolite is formed by condensation of two preformed β -ketoacyl chains. A similar biosynthetic route is involved in the biosynthesis of ochrephilone (4).⁶

Experimental

The optical rotation was measured at 24 °C on a Perkin-Elmer 241 polarimeter for a solution in chloroform. N.m.r. spectra of [^2H]chloroform solutions were recorded on a Bruker WM-500 spectrometer operating at 500.13 MHz for ^1H , and 125.76 MHz for ^{13}C nuclei.

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