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THE BIOSYNTHESIS OF QUADRONE AND TERRECYCLIC ACID

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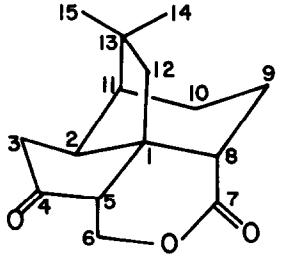
Abstract: Feedings of [1-^{13}C]- and [1,2-$^{13}C_2$]acetate to *Aspergillus terreus* gave quadrone and terrecyclic acid which were analyzed by ^{13}C NMR. The pattern of ^{13}C-enrichments and couplings is consistent with the formation of **1** and **2** by cyclization of farnesyl pyrophosphate.

The synthetic virtuosity of nature is nowhere more apparent than in the rich variety of sesquiterpenes containing polyquinane ring systems,[2,3] each formally derivable by cyclization of humulene.[4] Not surprisingly, the discovery in 1978 of yet another representative of this class, the tetracyclic lactone quadrone (**1**),[5] a metabolite of *Aspergillus terreus*, excited considerable interest among synthetic chemists, resulting to date in several reported total syntheses.[6] Very recently, the structure of a closely related metabolite of *A. terreus*, terrecyclic acid (**2**), was also reported.[7] Interestingly, the latter substance was already known, having served as the penultimate intermediate in Danishefsky's quadrone synthesis.[6a] Our own continuing interest in the biosynthesis of dimethylcyclopentane sesquiterpenes[8] has led us to examine the biosynthesis of **1** and **2** and our results, which demonstrate the mevalonoid origin of these novel fungal metabolites, are reported below.



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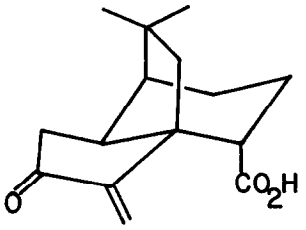


2

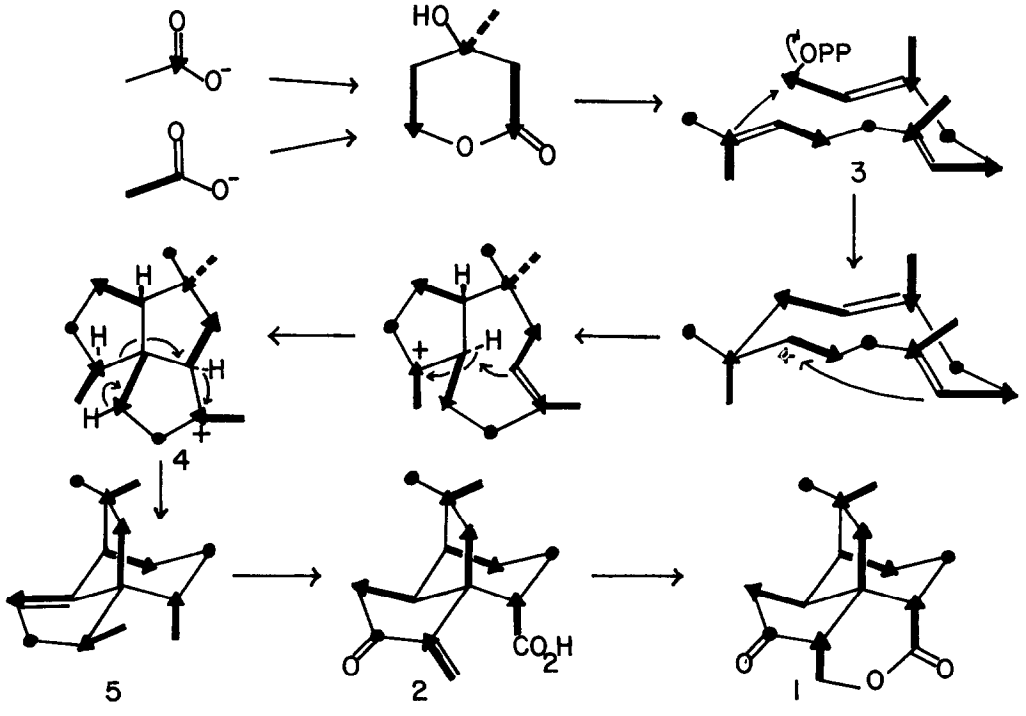
Cultures of *A. terreus* NRRL 11,156 were grown for 74 h at 25 ^{0}C, as previously described,[5] before being fed, in separate experiments, solutions of sodium [1-^{13}C]acetate[9] and [1,2-$^{13}C_2$]acetate[10] according to standard methods. After incubation for a total of 172 h, the fermentation broths were recovered and extracted with $CHCl_3$. Chromatography of the concentrated extracts gave labeled samples of both quadrone (**1**) (7-16 mg/L) and terrecyclic acid (**2**) (22-36 mg/L) which were analyzed by 62.9 MHz ^{13}C NMR. As summarized in Table I, the samples of **1** and **2** derived from [1-^{13}C]acetate each displayed 6 enhanced resonances in their respective ^{13}C NMR spectra (avg. enrichment, 3 %), while the corresponding spectra for quadrone and terrecyclic acid derived from [1,2-$^{13}C_2$]acetate each showed 3 enhanced singlets and 6 pairs of enhanced and coupled doublets. The latter sets of signals corresponded to intact acetate units, while the singlets arose from labeled carbon atoms which had lost their labeled neighbor. It is worth noting that the majority of the ^{13}C NMR signal assignments could be unambiguously made on the ^{13}C-enriched metabolites themselves, taking advantage of the observed J_{CC} coupling constants, off-resonance multiplicities, and simple chemical shift rules. This analysis was aided by the presence of four end groups in each metabolite, corresponding to C-6, 7, 14, and 15, three of which were uniquely coupled to their neighboring carbon atoms in **1** and **2**, respectively. For example, of the two quaternary carbon atoms in quadrone, only the upfield resonance at 40.5 ppm is enhanced by [1-^{13}C]acetate. This signal is clearly due to C-13, since C-14, which is not enriched by [1-^{13}C]acetate, is coupled to its neighbor in the sample of **1** derived from [1,2-$^{13}C_2$]acetate. Several of the ^{13}C NMR assignments were further corroborated by 2D ^{1}H COSY and single frequency off-resonance decoupled ^{13}C NMR analysis of samples of unlabeled **1**.

The observed labeling patterns are typical of isoprenoid metabolites[11] and are easily rationalized by the cyclization mechanism illustrated in Scheme I.[12] Thus cyclization of farnesyl pyrophosphate (**3**), derived from acetate via three molecules of mevalonate, will generate a humulyl cation folded in the CC conformation illustrated.[13,14] Intramolecular attack on the 6,7-double bond followed by a hydride shift and a further transannular cyclization at C-2 will generate the fused tricyclic cation (**4**). A second hydride shift, Wagner-Meerwein rearrangement, and deprotonation is expected to yield the parent sesquiterpene hydrocarbon **5**. It should be noted that this postulated intermediate is predicted to be epimeric to quadrone at C-5. Oxidation and reduction by a sequence analogous to that recently established for the conversion of sabinene to 3-thujone[15] will generate the C-4 ketone and further oxidation at C-5 and 6 will lead to terrecyclic acid. Cyclization of **2** results in net inversion at C-5 and yields quadrone. Further tests of the mechanistic and stereochemical implications of Scheme I are in progress.[16]

Table I. ^{13}C NMR Spectra of **1** and **2** and Incorporation of Labeled Acetates.[a]

	Quadrone			Terrecyclic Acid		
C	δ_C(m)	[1-^{13}C]-acetate	[1,2-$^{13}C_2$]-acetate J_{CC}, Hz	δ_C(m)	[1-^{13}C]-acetate	[1,2-$^{13}C_2$]-acetate J_{CC}, Hz
2	52.6(d)		35.8	46.5(d)		35.1
3	43.2(t)	*	35.6	41.5(t)	*	35.0
4	216.2(s)		*	207.1(s)		*
5	52.3(d)	*	35.5	150.7(s)	*	72.4
6	65.3(t)		35.5	115.8(t)		72.5
7	173.8(s)		50.8	179.7(s)		56.4
8	46.1(d)	*	51.0	48.0(d)	*	55.5
9	19.4(t)		*	22.6(t)		*
10	28.9(t)	*	32.3	29.0(t)	*	32.4
11	49.0(d)		32.1	49.1(d)		32.5
1	50.0(s)		34.2	55.0(s)		32.5
12	52.8(t)	*	34.4	54.3(t)	*	32.4
13	40.5(s)	*	36.8	40.5(s)	*	36.7
14[b]	26.9(q)		36.7	27.4(q)		36.4
15[b]	34.9(q)		*	34.8(q)		*

a) Bruker WM-250, 62.83 MHz; $CDCl_3$ **1**: spectral width 16129 Hz, 32K data points, 22.5° pulse, acquisition time 1.02 s; **2**: spectral width 15151 Hz, 32K data points, 12.9° pulse, acquisition time 1.08 s; b) The assignments for the individual methyl groups in **1** and **2** may be interchanged.



Scheme I

References and Notes

1. National Institutes of Health Research CareerDevelopment Award, 1978-1983.

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9. A total of 0.99 g of sodium [1-^{13}C]acetate (90 atom % ^{13}C) was administered in three equal portions at 74, 98, and 122 h, respectively, to 10 100-mL cultures.

10. A mixture of 0.30 g of sodium [1,2-$^{13}C_2$]acetate (99 atom % ^{13}C) and 0.90 g of unlabeled sodium acetate was administered in three equal portions at 74, 98, and 122 h, respectively to 11 100-mL cultures.

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12. For an alternative cyclization mechanism via a caryophyllene intermediate, see ref. 3, p. 105. The similarity of the quadrone biosynthetic pathway to that leading to senoxydene has also been pointed out.[3]

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14. Since the absolute configuration of quadrone is not yet known, only the relative configuration of the humulyl conformer can be specified at this time. It should be noted, however, that the CC-conformer has been implicated in the biosynthesis of the coriolin sesquiterpenes.[4,8c]

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16. This work was supported by the N.I.H., GM 22172. A sample of quadrone was the gift of Dr. Matthew Suffness of the National Cancer Institute. The Bruker WM-250 NMR spectrometer used in this work was purchased with funds provided by the NSF and the Montedison Group of Milan.

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