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PASPALINE AND PASPALICINE, TWO INDOLE-MEVALONATE METABOLITES FROM CLAVICEPS PASPALI

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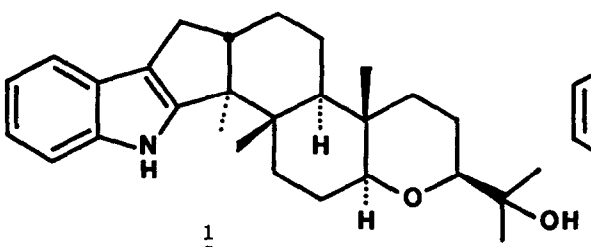
Summary: The crystal and molecular structures of paspaline and paspalicine, indole-mevalonate metabolites from Claviceps paspali are presented.

The unusual fungal metabolites paspaline (1) and paspalicine (2) were isolated from Claviceps paspali by Prof. D. Arigoni and his co-workers.[1,2,3] Recently we showed that paxilline (3), the tremorgenic metabolite from Penicillium paxilli Bainier,[4] had the closely related structure 3.[5] The biosynthesis of the novel hexacyclic array of compounds 1-3 has been investigated independently by M. Tanabe[6] and D. Arigoni.[7] Paxilline (3) possesses striking biological activity in that it causes sustained tremors in test animals (ED_{50} of 25 mg/kg, mice, oral).[4,5] Our continued interest in naturally occurring tremorgens led us to investigate the detailed stereostructures of 1 and 2. Relative and absolute configurations of five of the seven chiral centers in paspaline (1) had been proposed[2] but



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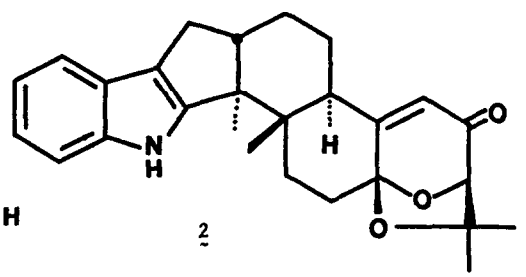

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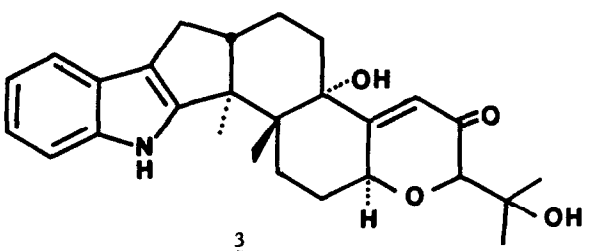

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no stereochemical assignments had been made for paspalicine (2).[3] In this note we wish to report x-ray diffraction studies that establish the complete stereostructure of paspaline (1) and paspalicine (2).

A summary of pertinent crystallographic data is given in the Table. Paspalicine (2) has at least two crystalline modifications. The first crystals were obtained from MeOH and belonged to space group $P2_1$ with two molecules in the asymmetric unit. A $P2_12_12_1$ modification with only one molecule in the asymmetric unit was found on recrystallization from acetone. This crystal structure and that for paspaline were solved relatively easily using a multisolution, weighted tangent formula approach.[8] For additional crystallographic details consult reference 9.

Table of Pertinent Crystallographic Data

	Paspaline (1)	Paspalicine (2)	Paspalicine (2)
a	49.388(5)	9.706(1)	13.439(2)
b	6.527(1)	10.670(1)	11.740(1)
c	7.891(1)	21.775(2)	15.295
β			97.38(1)
space group	$P2_12_12$	$P2_12_12_1$	$P2_1$
asymmetric unit	$C_{28}H_{39}NO_2 \cdot (CH_3OH)_{1/2}$	$C_{27}H_{31}NO_3$	$2(C_{27}H_{31}NO_3)$?
obsd. refl.	1535 (74%)	1583 (89%)	2312 (65%)
final residual	0.038	0.033	————

A drawing of the final x-ray model of paspaline (1) less hydrogens is given in Figure 1. The x-ray analysis confirmed the relative stereochemistry previously given at C(4), C(7), C(9), C(12) and C(13).[2] The methyl group at C(3) is trans to both the methyl at C(4) and the hydrogen at C(16). This information completes the absolute stereostructure of paspaline (1). The methanol of crystallization is found at the special two-fold position 0, 1/2, Z and 1/2, 0, -Z and forms hydrogen bonds with O(30) of 2.73Å.

A drawing of the final x-ray model of paspalicine is given in Figure 2. The major difference is that a five membered ketal has been formed by linking O(30) to C(7). The relative configurations of all equivalent asymmetric centers are identical for paspaline (1), paspalicine (2) and paxilline (3) except for the inverted configuration of C(7) of paspalicine caused by ketal formation. Both paspaline and paspalicine differ from the tremorgen paxilline in that they lack the tertiary hydroxyl at C(13).

Since the absolute configuration of paspaline (1) is known[2] and the compound has been shown[10] to be a biosynthetic precursor of paspalicine, paspalicine is therefore correctly formulated with the absolute stereochemistry shown in 2. The CD spectrum of paspalicine (2) shows a positive

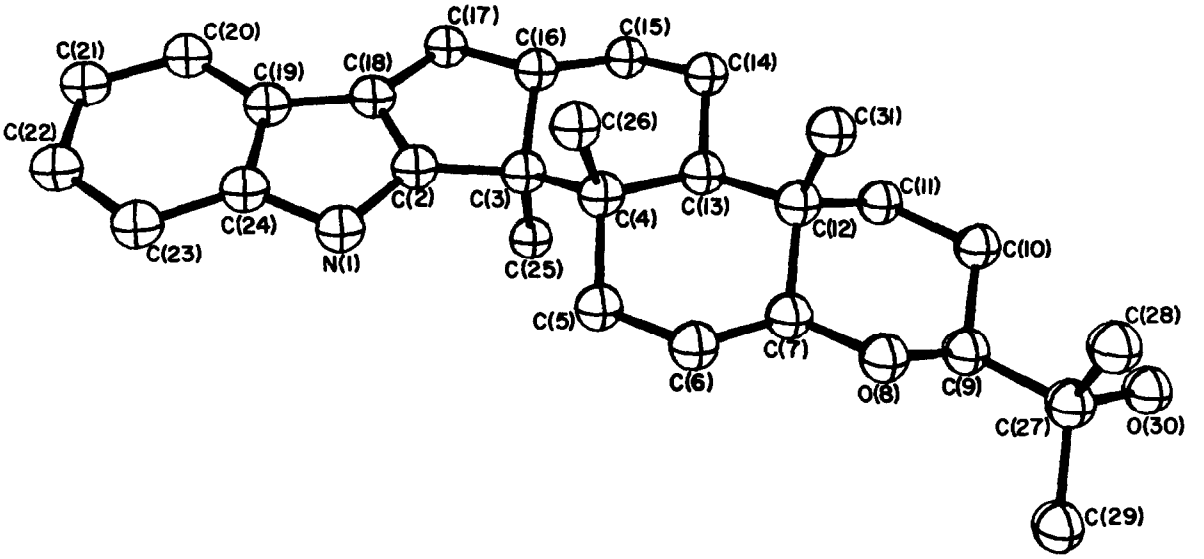

Figure 1. A computer generated perspective drawing from the crystal structure of paspaline (1) with hydrogens and the molecule of methanol omitted for clarity.

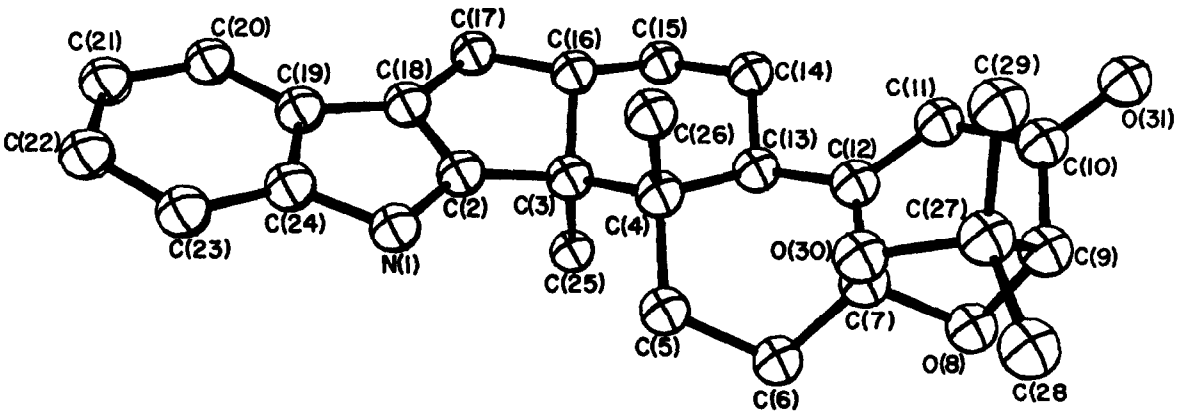

Figure 2. A computer generated perspective drawing from the crystal structure of paspalicine (2) with hydrogens omitted for clarity.

cotton effect for the band at 348 nm with $[\theta] = +3.9 \times 10^4$. Because the equivalent band in the CD spectrum of paxilline is also positive,[5] paxilline (3) is presumed to have the same absolute configuration as paspalicine (2).

Paspaline (1) was tested as has been previously described[4,11] but found to possess neither toxic nor tremorgenic activity. Limited amounts of paspalicine (2) precluded similar tests.

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11. We thank Dr. Richard J. Cole for performing these studies.

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