Tetrahedron Vol. 48, No. 30, pp. 6317-6324, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00
Pergamon Press Ltd

CYTOCHALASINS U AND V, TWO NEW CYTOCHALASANS, FROM PHOMA EXIGUA VAR. HETEROMORPHA

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(*Received in UK 27 May* 1992)

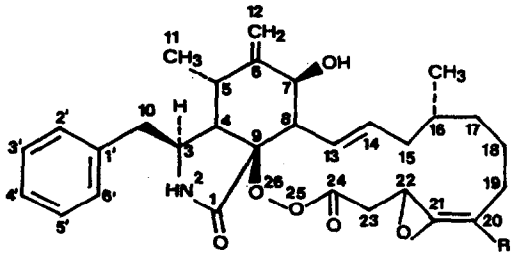
Abstract: Two additional cytochalasins were isolated from liquid culture filtrates of Phoma exigua var. heteromorpha together with some already known cytochalasins. The two new metabolites, named cytochalasin U and V, represent the first natural occurrence of a 25,26-dioxa[16] and 25-oxa[15]cytochalasan, respectively, both bearing a formyl group on the macrocyclic ring. Cytochalasins U and V showed respectively significant and weak activity in the brine shrimp assay.

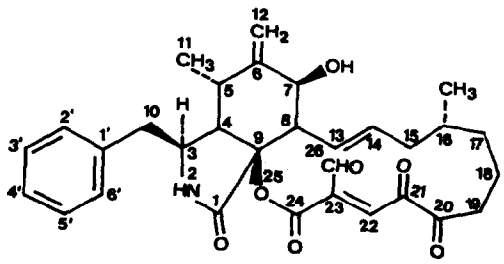
During the study, which is still in progress, and which aims to purify the hydrophilic and polymeric phytotoxin produced by Phoma exigua var. heteromorpha, the fungal causal agent of a foliar disease of Oleander (Nerium oleander L.), some cytochalasins have been isolated[1,2].

This paper describes both the isolation and characterization of two new metabolites, having structure unusual in the cytochalasan family[3].

The crude oily residue obtained from the organic extracts of the culture filtrates was purified through a combination of column and TLC chromatography, as in detail described in the Experimental, to yield the two metabolites 1 and 2 as homogeneous solids, named cytochalasins U and V, respectively.

The IR spectrum of both cytochalasins U and V showed the presence of hydroxy, benzene, olefinic and carbonyl groups[4,5], while their EI mass spectrum showed that the peaks generated by the typical loss of the benzyl residue from the molecular ion were the most prominent ones[1-3]. The accurate inspection of their 1D ^{1}H and ^{13}C NMR spectra (Table 1) showed





1 R = ^{27}CHO

3 R = ^{27}CH$_2$OH

2

that both **1** and **2** contained the same 3-benzylperhydroisoindolyl residue and the same fragment between C-13 and C-19 of the macrocyclic ring present in cytochalasins A and B[1,3]. Conversely, **1** and **2** were different from each other and from the latter cytochalasins with regard to both the size and functionalization of the macrocyclic ring. In fact, the results of the analysis of the 2D ^{1}H,^{1}H (COSY) and 2D ^{13}C,^{1}H NMR spectra[6] (Table 1) also agree with the above considerations. The same spectra showed the very original structure of the closure fragment of the macrocyclic between C-19 and C-9.

Both new cytochalasins showed the presence of an exocyclic α,ß-unsaturated aldeyde group appearing in the ^{1}H NMR spectrum of **1** and **2** as a singlet at the typical chemical shift value[7,8] of δ 9.90 and 10.06 and in the ^{13}C NMR spectrum as a doublet at δ 183.9 and 182.5, respectively[6,8]. This latter was attached to a carbon of the C-5 membered moiety, situated between C-19 and C-9, but the nature of the other functional groups contained in this fragment of the macrocycle were different.

The cytochalasin U had the molecular formula of $C_{31}H_{37}NO_7$, and its UV spectrum exhibited an absorption maximum at 323 nm, attributed to the α,ß-unsaturated aldehyde chromophore, whose conjugation was probably further extended[5,9]. Further inspection of the ^{1}H NMR spectrum (Table 1) showed the presence of an ABX system, of which the X part (H-22) appeared at δ 4.20 and the corresponding AB part at δ 3.62 (H-23) and 3.38 (H-23'), chemical shift values consistent with a CH_2 α-located between an epoxy ring and a lactonic carbonyl group[7]. The latter proton (H-23'), by the effects observed in the long-range 2D ^{13}C,^{1}H correlation experiment[6], recorded on **1**, (Table 1) was coupled with the lactonic carbonyl group (C-24) resonating at δ 171.2 in the ^{13}C NMR spectrum (Table 1)[6]. In the same experiment the other singlet present at δ 170.8 in the ^{13}C NMR spectrum correlated with H-8, thus confirming its assignment to the amide CO group (C-1)[6-8]. Another support to the resulting OOC-CH_2-CH-O fragment was the presence of the signals at δ 45.1 and 46.5 in the ^{13}C NMR spectrum assigned to C-22 and C-23, respectively, while the remaining two singlets

Table 1. ^{1}H and ^{13}C NMR data of Cytocalasins U (1) and V (2). The chemical shifts are in δ-values (ppm) from TMS.

	1				2			
C*	δ	m+	^{1}Hδ*	m§	2D ^{1}H, ^{13}C LRC#	δ	m+	^{1}Hδ*	m§	2D ^{1}H, ^{13}C LRC#
1	170.8	s[a]			2.98	169.9	s			3.02
2			5.52	br s				5.66	br s	
3	53.8	d	3.28	m	3.00	54.0	d	3.33	ddd	3.19
4	49.4	d	2.64	dd		49.7	d	2.92	dd	
5	32.2	t[a]	3.10	m		32.1	d[a]	3.19	m	
6[b]	148.5	s[a]				149.9	s			
7	67.5	d	3.78	br d	2.98, 5.46, 5.19	67.8	d	3.93	br d	5.26 3.02
8	43.9	d	2.98	m		52.9	d	3.02	dd	
9	84.0	s			2.98	83.9	s			3.02
10	43.4	t	3.00	m		43.6	t	3.19	m	
10'			2.85	dd				2.96	dd	
11	15.3	q	1.17	d (3H)		14.8	q	1.16	d (3H)	
12	113.8	t	5.46	br s		114.7	t	5.50	br s	
12'			5.19	br s				5.26	br s	
13	125.9	d	5.85	ddd		126.4	d	5.89	ddd	
14	137.8	d	5.47	ddd		138.7	d	5.81	ddd	2.22
15	39.6	t	2.18	br d		40.8	t	2.22	br d	
15'			1.85	ddd				2.02	ddd	
16	30.6	d	1.60	m		31.4	d	1.69	m	
17	27.7	t	1.45	ddd		31.9	t	1.67	m	
17'			1.17	m				1.10	m	
18	21.9	t	1.60	m (2H)		25.4	t	1.93	m	
18'								1.65	m	
19	31.7	t	3.00	m		25.6	t	3.19	m	
19'			2.25	m				2.82	ddd	
20	137.7	s[a]				142.8	s[a]			7.95
21	153.6	s[a]				148.3	s			
22	45.1	d	4.20	dd		140.2	d[c]	7.95	s	
23	46.5	t	3.62	dd		139.4	s[d]			7.95
			3.38	dd						
24	171.2	s[a]			3.38	160.7	s[d]			7.95
26						182.5	d	10.06	s	
27	183.4	d[a]	9.90	s						
1'	137.0	s[a]				137.8	s			3.19, 2.96
2'-6'	129.1	d				129.2	d			
3'-5'	129.0	d	7.10-7.35			129.0	d	7.20-7.40		
4'	127.1	d				127.1	d			
Me-16	19.7	q	0.92	d (3H)		21.3	q	1.01	d (3H)	

§J(Hz) 1, 2: 3,10=9.9; 5,11=6.6; 7,8=11.6; 8,13=9.2; 10,10'=13.2; 13,14=15.2; 13,15=2.1; 14,15=3.2; 14,15'=10.6; 15,15'=14.5; 15',16=10.6; Me,16=6.6; 1: 3,4=3,10'=4,5=22,23=4.6; 12,12'=2.3; 17,17'=10.2; 22,23'=11.6; 23,23'=19.8; 2: 3,4=3,10'=4,5=3.7; 19,19'=11.2

*2D ^{1}H, ^{1}H (COSY) and ^{13}C, ^{1}H, experiments delineated the correlation of all protons and the corresponding carbons in 1 and 2.

+Multiplicities were determined by DEPT spectra; #Long-range correlation spectra.

a,c,dThese carbons appeared as multiplets, broad doublet and doublets, respectively, in the gated decoupled ^{13}C NMR spectra recorded on 1 and 2.

bAssigned in agreement with the data recorded for the same carbon in other cytochalasins[3-5].

observed in the ^{13}C NMR spectrum at δ 153.6 and 137.7 must be attributed to the two quaternary carbons C-21 and C-20, respectively[6-8]. As the molecular formula of $C_{31}H_{37}NO_7$ provides a total of 14 unsaturations, eight of those were localized in the 3-benzylperhydroisoindolyl residue and two in the macrocyclic ring, the remaining four unsaturations, as well as the resulting five oxygen atoms were located in the C(19)-C(9) fragment. Considering the functional groups above mentioned, the macrocyclic ring was closed by a peroxyester bond on C-9, which, as expected, appeared as a singlet at δ 84.0 in the ^{13}C NMR spectrum[6,7] and correlated with H-8 in the long-range 2D $^{13}C,^{1}H$ NMR experiment.

From these results structure 21,22-epoxy-20-formyl-7-hydroxy-16-methyl-10-phenyl-25,26-dioxa[16]cytochalasa-6(12),13, 20-triene-24-one (**1**) was assigned to cytochalasin U.

Structure **1** was supported by a gated decoupled ^{13}C NMR spectrum[6,7] recorded on cytochalasin U and from its HR EIMS spectrum. The latter showed fragmentation pathways, all starting from the molecular ion, and consistent with structure **1**[5].

In fact, the molecular ion at m/z 535.2444 ($C_{31}H_{37}NO_7$), by successive losses of CO_2, which is a typical fragmentation mechanism of peroxyesters[10], C_7H_7 and OH residues, produced the ion at m/z 491.2540 ($C_{30}H_{37}NO_5$) and 383.2091 ($C_{23}H_{29}NO_4$), respectively. Moreover, although the CO_2 loss is also diagnostic for the presence of a carbonate group[10], this hypothesis was incosistent with the ^{13}C and IR data of O=C-24 while they were in full agreement with the peroxyester nature of the closure point of the macrocyclic ring[4,6-8].

The spectroscopic behaviour of cytochalasin U (**1**) agreed with that of synthetic peroxyesters[11,12]; in addition, cyclic peroxides were found in bioactive marine metabolites[13].

The results of a series of ^{1}H NOE difference spectra (NOEDS)[7] (Table 2) confirmed the structure **1** assigned to cytochalasin U and the spatial proximity of the aldehyde proton at H-19.

Table 2. ^{1}H NOE effects measured on compounds **1** and **2**

1			**2**		
Exp.	Irradiated	Observed	Exp.	Irradiated	Observed
a	9.90 (H-27)	3.00 (H-19)	a	10.06 (H-26)	3.19 (H-19)
b	3.00 (H-19)	9.90 (H-27)	b	7.95 (H-22)	5.81 (H-14)
			c	5.81 (H-14)	7.95 (H-22)
			d	2.82 (H-19')	7.95 (H-22)
			e	1.69 (H-16)	7.95 (H-22)

This stereochemical feature was confirmed by preparing the 27-dihydroderivative of cytochalasin U (**3**) by reduction of **1** with $NaBH_4$. In fact, the ^{1}H

NMR of **3** differed from that of **1** only in the expected absence of the aldehyde proton, shown by the presence of two doublets centred at δ 4.38 and 4.30 due to the unusual AB system of the $HOCH_2$-27 group broaded by a probable long-range coupling[7,14] with H_2C-19 and for the surprisingly upfield (Δδ 1.03) of the multiplet of the HC-19; the other geminal methylene proton (HC-19') remained unchanged. This result represents further evidence for the localization of the formyl group on C-20 in **1**. In fact, the $HOCH_2$-27 of **3** lost its rotation freedom as consequence of the assumed presence of the intramolecular hydrogen bond with the epoxy ring, thus its appearance as an AB system was justified[5,7]. As expected the UV and the IR spectra of **3** lacked the absorption attributed in **1** to the conjugated aldehyde group. Finally, its EI mass spectrum showed the molecular ion at m/z 537 and typical fragmentation peaks at m/z 519, 501 and 483 produced by successive losses of three H_2O molecules. The ions at m/z 519 and 501 yielded the ions at m/z 475 and 457 by loss of CO_2, typical for peroxyesters as above mentioned[10].

Cytochalasin V (**2**) had the molecular formula $C_{31}H_{35}NO_7$, contained also the conjugated aldehyde group mentioned above, which in this metabolite was also linked to a quaternary olefinic carbon appearing in the ^{13}C NMR spectrum of **2** (Table 1) at the very typical chemical shift value of δ 139.4 (C-23)[6,7]. This olefinic carbon (C-23) belongs to a trisubstituted double bond present in fragment between C-19 and C-9, since it correlated with the olefinic proton H-22 in the long-range 2D $^{13}C,^{1}H$ experiment[6] recorded for **2** (Table 1). Obvious effects were also noted in this spectrum between the same olefinic proton (H-22) and the lactonic (C-24) and ketonic (C-20) carbonyl groups resonating at δ 160.7 and 142.8, respectively, in the ^{13}C NMR spectrum of **2** (Table 2). The lactonic nature of the closure of the macrocyclic ring was also supported by the oxygenated nature of C-9 appearing as a singlet at δ 83.9 in the same spectrum and by its correlation, in the long-range 2D $^{13}C,^{1}H$ spectrum, with H-8. From the above results, the double bond was linked to the lactonic group, while the ketonic group at C-20 was α-positioned with respect to the H_2C-19 of the same ring as confirmed also by the evidence from a gated decoupled ^{13}C NMR experiment, carried out on **2** (Table 1). Considering the molecular formula ($C_{31}H_{35}NO_7$) and the total of 15 unsaturations, of which eight were located in the 3-benzylperhydroisoindolyl residue, six in the macrocyclic ring, while the remaining unsaturation and carbon and oxygen atoms accounted for another ketonic group (C-21), which, in fact, resonated as a singlet at δ 148.3 in the ^{13}C NMR spectrum (Table 1).

The very strong absorption maximum at 296 nm observed in the UV spectrum of **2** was consistent with the presence of an α,ß-unsaturated ester, whose conjugation was extended by an aldehyde group and an α-diketon system, the latter probably with a trans-conformation[5,9] as resulted also from the intense band present at 1711 cm^{-1} in the IR spectrum[4]. From these

results the extra carbonyl group O=C-21 mentioned above was trans-linked to the other ketonic group at C-20 and α-positioned with respect to HC-22.

The results of the HR EIMS of **2** showed interesting fragmentation mechanisms all starting from the molecular ion at m/z 533.2490 ($C_{31}H_{35}NO_7$) through the loss of the typical C_7H_7 residue[1-3], H_2O molecules, OH and CO residues and consistent with the stucture assigned to cytochalasin V[7].

From these results the structure 23-formyl-7-hydroxy-16-methyl-10-phenyl-25-oxa[15]cytochalasa-6(12),13,22-triene-20,21,24-trione (**2**) was assigned to cytochalasin V.

The structure assigned to cytochalasin V was also confirmed by the evidence obtained from a series of ^1H NOE difference spectra[7] carried out on **2** (Table 2). These results revealed the spatial proximity between the two olefinic protons H-22 and H-14, as well that of the same H-22 with both H-16 and H-19', while the aldehyde proton (H-26) resulted near located to the HC-19.

In the fungicide activity, tested on Geotrichum candidum[15], both metabolites were inactive; in the mycotoxicity assay on brine shrimp (Artemia salina)[15], cytochalasin V (**2**) showed a significant activity while cytochalasin U (**1**) was weakly active.

EXPERIMENTAL

General. Optical rotations: $CHCl_3$; IR and UV: neat and MeCN, respectively; ^1H and ^{13}C NMR: $CDCl_3$, 400 and/or 270 MHz and 100/or 67.92 MHz, respectively, using the same solvent as internal standard. Carbon multiplicities were determined by DEPT (Distortionless Enhancement by Polarization Transfer) spectra[6]. DEPT, NOEDS, COSY 45 (correlated spectroscopy), 2D heteronuclear and long-range heteronuclear chemical shift correlation experiments were performed using Bruker standard microprograms; EI and HR EIMS: 70 eV. Analytical and preparative TLC: silica gel (Merck, Kieselgel 60 F_{254}, 0.25 and 0.50 mm) or on reverse phase (Whatman, KC18 F_{254}, 0.20 mm) plates; Column chromatography: silica gel (Merck, Kieselgel,60, 0.063-0.2 mm); solvent systems: (A) $CHCl_3$-*iso*-PrOH (32.3:1); (B) MeCN-H_2O (1.5:1).

Production, extraction and purification of cytochalasins. Phoma exigua var. heteromorpha (Schulzer et Sacc.) Noordeloss et Boerema [=Ascochyta heteromorpha (Schulzer et Sacc.) Curzi], freshly isolated from infected oleander leaves, was grown in culture under the conditions described previously[1]. The lyophilized material (25.7, 24.8 and 19.3 g) obtained from the culture filtrate (8.0, 8.0 and 7.5 l, respectively) of three successive productions, was resuspended in distilled H_2O and extracted with CH_2Cl_2 as described in detail in a previous paper[1]. The combined oily

residues (1.18 g) were chromatographed on a silica gel column eluted with solvent A, yielding 9 groups of homogeneous fractions. The second and third groups (100.7 and 96.4 mg, respectively) were further purified on preparative TLC using the same conditions. Five zones, revealed by exposure to UV light, were scraped off and eluted with the same solvent. Evaporation of the solvent from the two fractions containing a metabolite located slightly above cytochalasin A (R_f 0.45 by TLC on silica gel, eluent A) as the main component, yielded residues A (16.3 mg) and B (22.4 mg). Finally, the purification of residues A and B by two successive preparative reverse phase TLC steps (eluent B) yielded compounds **1** and **2** (R_f 0.36 and 0.20, respectively), called cytochalasin U and V (5.6 and 12.7 mg, 0.24 and 0.54 mg/l, respectively) as two homogeneous solids withstanding crystallization.

Cytochalasin U (**1**): $[\alpha]25_D$ -71.7 (c 0.75); UV λ_{max} nm log (ε): 323 (3.41); IR ν_{max} cm^{-1}: 3436, 3260, 1718, 1670, 1608, 1557, 1491, 1246, 1213; ^1H and ^{13}C NMR spectra: Tables 1; HR EIMS, m/z (rel. int.): 535.2444 ($C_{31}H_{37}NO_7$, calcd. 535.2101, 53) $[M]^+$, 491.2540 ($C_{30}H_{37}NO_5$, 5) $[M-CO_2]^+$, 444.1938 ($C_{24}H_{30}NO_7$, 36) $[M-C_7H_7H]^+$, 442.1710 ($C_{24}H_{28}NO_7$, 100) $[M-C_7H_7-2H]^+$, 427.1712 ($C_{23}H_{25}NO_7$, 2) $[M-C_7H_7-2H-Me]^+$, 426.1887 ($C_{24}H_{28}NO_6$, 3) $[M-C_7H_7-H_2O]^+$, 424.1805 ($C_{24}H_{26}NO_6$, 16) $[M-C_7H_7-2H-H_2O]^+$, 408.1934 ($C_{24}H_{26}NO_5$, 29) $[M-C_7H_7-2xH_2O]^+$, 406.1547 ($C_{24}H_{24}NO_5$, 8) $[M-C_7H_7-2H-2xH_2O]^+$, 383.2091 ($C_{23}H_{29}NO_4$, 2) $[M-CO_2-C_7H_7-OH-CO]^+$.

Cytochalasin V (**2**): $[\alpha]25_D$: +26.9 (c 0.66); UV λ_{max} nm log(ε): 296 (4.11), 207 (sh); IR ν_{max} cm^{-1}: 3370, 3238, 1711, 1674, 1608, 1538, 1498, 1264; ^1H and ^{13}C NMR spectra: Tables 1; HR EIMS, m/z (rel. int.): 533.2490 ($C_{31}H_{35}NO_7$, calcd. 533.2765, 9) $[M]^+$, 515.2394 ($C_{35}H_{33}NO_6$, 14) $[M-H_2O]^+$, 442.1698 ($C_{24}H_{28}NO_7$, 100) $[M-C_7H_7]^+$, 424.1653 ($C_{24}H_{26}NO_6$, 27) $[M-C_7H_7-H_2O]^+$, 406.1625 ($C_{24}H_{24}NO_5$, 3) $[M-C_7H_7-2xH_2O]^+$, 379.1640 ($C_{23}H_{25}NO_4$, 1) $[M-C_7H_7-H_2O-OH]+$.

27-dihydrocytochalasin U (**3**). Cytochalasin U (**1**, 2 mg) in MeOH (2 ml) was treated with $NaBH_4$ (20 mg) with stirring at room temperature for 30 min. The oily residue (1.5 mg), obtained after the usual work-up of the reaction, was purified by preparative TLC (silica gel, eluent A) to give **3** as a homogeneous compound (0.9 mg) : UV λ_{max} < 220 nm; IR ν_{max} cm^{-1} 3406, 3311, 1714, 1608, 1538, 1498, 1250, 1227 ; ^1H NMR, δ: differed from that of **1** for the following signal systems: 4.38 (1H, br d, $J_{27,27'}$=12.5 Hz, H-27), 4.30 (1H, br d, $J_{27,27'}$=12.5 Hz, H-27'), 3.35 (1H, m, H-23) 3.17 (1H, m, H-23'), 3.09 (1H, dd, $J_{7,8}$=11.6 and $J_{8,13}$=9.3 Hz, H-8), 2.96

(1H, dd, $J_{3,10}$=9.3 and $J_{10,10'}$=13.5 Hz, H-10), 1.97 (1H, m, H-19). EIMS, m/z (rel. int.): 537 $[M]^+$ (12), 519 $[M-H_2O]^+$ (5), 501 $[M-2xH_2O]^+$ (6), 483 $[M-3xH_2O]^+$ (2), 475 $[M-H_2O-CO_2]^+$ (6), 457 $[M-2xH_2O-CO_2]^+$ (2), 446 $[M-C_7H_7]^+$ (6), 418 $[M-C_7H_7-CO]^+$ (30), 410 $[M-2xH_2O-C_7H_7]^+$ (21), 392 $[M-3xH_2O-C_7H_7]^+$ (100), 384 $[M-H_2O-CO_2-C_7H_7]^+$ (42).

ACNOWLEDGEMENTS

This investigation was supported in part by grants from the Italian Ministry for University and Scientific and Technological Research and in part by the National Research Council special ad hoc program 'Chimica Fine II', subproject 3.

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