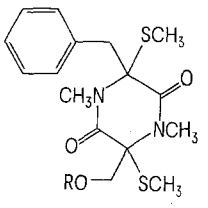
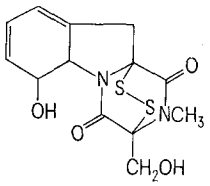
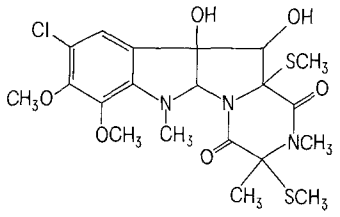


1a R = H
1b R = Ac



2



3

wesenheit einer Benzylgruppe (*m/e* = 91) und von zwei CH_3S-Gruppen (*m/e* = 307 und 260).

Die nachgewiesenen Strukturelemente, in denen sämtliche Atome des Metaboliten erfasst worden sind, bedingen das Vorliegen einer bicyclischen Struktur; daraus ergeben sich zwangsläufig für Gliovictin und dessen *O*-Acetyl-Derivat die Formeln **1a** bzw. **1b**, worin lediglich die relative und absolute Konfiguration unbestimmt bleiben. Gliovictin gehört demnach zur Reihe jener schwefelhaltigen mikrobiellen Metaboliten wie Gliotoxin, **2**, und Sporidesmin D, **3**, deren Entstehung durch nachträgliche Funktionalisierung eines Diketopiperazinvorläufers gedeutet werden kann[2].

In einer kürzlich erschienenen Arbeit[3] ist die von uns dem Gliovictin zugeteilte Struktur für einen Metaboliten vorgeschlagen worden, welcher neben zwei strukturell verwandten Stoffen von einem nicht näher identifizierten Pilz gebildet worden ist. Die dort angegebenen physikalischen Daten reichen für eine eindeutige Identifizierung der zwei Substanzen nicht aus.

Summary. Gliovictin, a new metabolite of *Helminthosporium victoriae*, is shown on the basis of instrumental analysis to possess structure **1a**.

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CH–8006 Zürich (Switzerland), 21. November 1973.

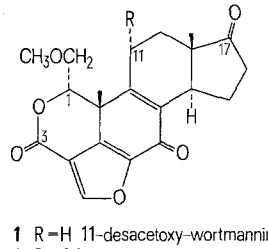
[2] Für Übersichtsartikel vgl. W. B. Turner, in *Fungal Metabolites* (Academic Press, London 1971), p. 327. – A. Taylor, in *Microbial Toxins* (Eds. S. Kadis, A. Ciegler und S. J. Ajl; Academic Press, New York 1971), vol. 8, p. 337.

[3] R. L. de Vault und W. Rosenbrook, jr., J. Antibiotics *26*, 532 (1973).

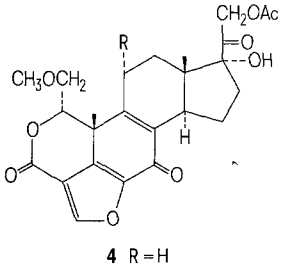
[4] Wir danken Sandoz AG (Basel) für finanzielle Unterstützung, Prof. R. P. Scheffer für den Stamm von *H. victoriae*, Dr. Z. Kis für den Hinweis auf Referenz[3] und Frau S. Dorn für Mithilfe bei der mikrobiologischen Arbeit.

Antiinflammatory Activity of the New Mould Metabolite 11-Desacetoxy-Wortmannin and of Some of its Derivatives

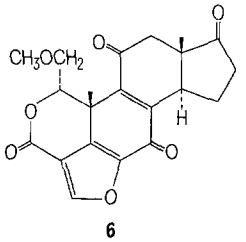
11-Desacetoxy-wortmannin (**1**; $C_{21}H_{22}O_6$; m.p. 178–180°) is a new metabolite, which we have isolated from the culture filtrate of *Penicillium funiculosum Thom*[1]. Structure **1** is based on spectroscopic evidence and chemical correlation[1] with wortmannin (**2**)[2–4]. **1** shows only weak antifungal activity but is a highly active antiinflammatory agent. This interesting property, taken together with the steroid-like structure, induced us to prepare derivatives of **1** and **2**. In analogy to the known antiinflammatory steroids, our main goals were the introduction of a corticoid side chain at position 17 and the transformation of the acetoxy group at C-11 into an alcohol or a ketone[5].



1 R = H 11-desacetoxy-wortmannin
2 R = OAc wortmannin
3 R = OH



4 R = H
5 R = OAc



6

In Table I, the antiinflammatory potency of 11-desacetoxy-wortmannin (**1**) is compared with dexamethasone, indomethacin and phenylbutazone. 11-Desacetoxy-wortmannin (**1**) has a strong antiinflammatory effect on acute edema, as well as on phlogistic tissue proliferation. Its activity in inhibiting the carrageenin paw edema is about 1/4 of that of dexamethason, but it equals the activity of indomethacin and is about 6 times more potent than phenylbutazone. Analog studies with bilaterally adrenalectomized rats gave similar results. Thus stimulation of the adrenal glands is of minor importance for the action of **1**. In the granuloma pouch test it is less active than dexamethasone, but as good or better than the non-steroidal agents. In developing adjuvant arthritis in rats, **1** has no effect on the primary swelling in the injected paw, but it reduces the symptoms of a generalized arthritis.

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[5] W. Haefliger and D. Hauser, the chemical part of this work will be the subject of a separate publication.

Table I. ED_{50} in mg/kg per os[a]

	Carrageenin paw edema[b]	Granuloma pouch test[c]		Freund adjuvant arthritis[d]			Improved grip function	Toxicity DL_{50} (mg/kg p.o.)
				Primary swelling	Generalized arthritis			
		Exudate	Tissue	day of appl. 0–14	day of application 0–14	12–16	on day 16	
11-Desacetoxy-wortmannin (**1**)	> 3 resp. 2[e]	2	3	> 1	0.7	2	2 × 0.3 mg/kg/day 63%	28
Dexamethasone	0.5	0.03	0.1	0.05	< 0.05	0.3	0.3 mg/kg/day 85%	>3
Indomethacin	2	2	—[f]	0.5	—[f]	—[f]	1 mg/kg/day 12%	10
Phenylbutazone	13	65	—[f]	50	32	—[f]	100 mg/kg/day 46%	215

[a] The animals used were male resp. female rats of the Jffa Credo strain or Wistar strain depending on the test. The test substances were given in an appropriate solvent or suspended in 0.5% tragant. [b] The experimental paw edema was produced by a 1% Carrageenin suspension according to the method described by WINTER[6]. [c] The granuloma pouch was performed according to SELYE's[7] technique, modified by TSURUFUJI[8]. [d] The Freund adjuvant arthritis, carried out according to a modified method described by NEWBOULD[9], was chosen as an experimental model of a generalized arthritis. [e] 4 times daily before carrageenin injection. [f] No or only weak activity at reasonable doses.

Table II.

Compound	Carrageen paw edema		Granuloma pouch test			Toxicity DL_{50}
	mg/kg p.o.	3 h	mg/kg p.o.[a]	Exudate	Tissue	
1	3	−41%	1	−15%	−13%	28 mg/kg p.o.
			2	−55%	−43%	
2	0.1	−33%	0.1	− 6%	− 7%	>3 <10 mg/kg p.o.
	1	−33%	0.3	−67%	−51%	
3	0.3	0%	0.3	−19%	+10%	7 × 1.3 mg/kg:
	1	−25%	0.9	− 9%	−14%	weight loss
	3	−75%	1.3	−50%	−42%	−160% compared to control
	ED_{50} = 1.7 mg/kg		ED_{50} (exudate): 1.3 mg/kg			
4	30	−24%	31	+13%	+23%	
5	10	0%	3	+12%	− 3%	
6	10	−53%	0.9	+29%	+ 4%	7 × 6 mg/kg: weight loss
	30	−61%	6	−57%	−73%	−300% compared to control

2: 0.1 mg/kg/day: no activity on Freund adjuvant arthritis; **3**: 1 mg/kg/day: weak activity on Freund adjuvant arthritis.
[a] Doses calculated from food intake

In established adjuvans arthritis **1** shows a dose-dependent inhibition of primary and secondary arthritis, resulting in an improvement of the grip function[10].

In contrast do dexamethasone **1** inhibits the paw edema markedly only after some days of pretreatment, has little effect on the primary swelling of the adjuvant arthritis, and lowers the rectal body temperature in normothermic, but not in hyperthermic rats.

In acute toxicity tests on rats, **1** had a LD_{50} of 28 mg/kg per os and 51.5 mg/kg i.p. **1** is much more toxic after repeated application or on adrenalectomized rats. In Rhesus monkeys a single subcutaneous dose of 1 or 3 mg/kg caused weakness, decreased motility, incoordinated behaviour and anorexia.

In Table II the results of some analogues of **1** are summarized. Interesting is the fact that the introduction of a corticoid side chain (**4** and **5**) caused a complete loss of the antiphlogistic activity.

Zusammenfassung. 11-Desacetoxy-wortmannin (**1**) ist ein neuer Pilzmetabolit aus *Penicillium funiculosum* Thom, der durch seine starke entzündungshemmende Wirkung bei verschiedenen Tiermodellen auffällt. Die Einführung einer Corticoid-Seitenkette in das Molekül führt zum vollständigen Verlust der Aktivität.

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