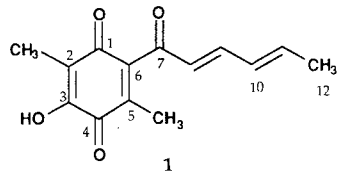
Isolation and Structure of Sorrentanone: A New Tetrasubstituted Quinone from *Penicillium chrysogenum*

RAYMOND F. MILLER* and STELLA HUANG

Bristol Myers-Squibb Pharmaceutical Research Institute, Wallingford, CT 06492-7660, U.S.A.

(Received for publication January 17, 1995)

As microorganisms develop resistance to current antibiotic therapy,[1~3] the search for new bioactive compounds becomes more important. As part of our natural products screening process to identify new leads, we have isolated and characterized a novel tetrasubstituted quinone from a fermentation broth of *P. chrysogenum* SC 13887. This compound, which has been named sorrentanone [3-hydroxy-2,5-dimethyl-6-(1′-oxo-2′,4′-dienylhexyl)-1,4-benzoquinone] (**1**) due to its distinctive sorrel color,[4] is active against both Gram-positive and Gram-negative microorganisms.



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Experimental

A culture of *P. chrysogenum* was fermented in the presence of SP-207 resin,[5] and the filter cake was extracted with *n*-BuOH. The crude butanol extract was concentrated at reduced pressure to afford a black oil, which was taken up in 9:1 MeOH-H_2O. The solution was washed with hexane (2 × 750 ml), extracted sequentially with CCl_4 (8 × 500 ml), and $CHCl_3$ (2 × 500 ml). The organic layers were combined and washed with H_2O (2 × 1 liter), were filtered with the aid of diatomaceous earth, and the solvent was removed at reduced pressure to afford a black solid. The material was taken up in 35% EtOAc in Hex and chromatographed on a silica gel 60 column (230~400 mesh, EM Science). Combination and concentration of the appropriate fractions at reduced pressure yielded 2.4 grams of a light orange solid, **1**.

Physico-chemical Characteristics

The physico-chemical properties of **1** are summarized in Table 1. Both the UV spectrum, with its strong K band at 272 nm, and the IR spectrum, with the carbonyl absorbance at 1654 cm^{-1}, are indicative of a quinone moiety. The structure of the quinone was determined using the NMR spectroscopic data summarized in Table 2. The ^1H NMR spectrum showed a spin system containing a methyl group (δ 1.80) and four vinyl protons (δ 6.11, 6.88, 6.16, and 6.17) suggesting the presence of a diene sidechain. The broad singlet peak at 8.06 ppm was assigned to the hydroxyl group based on its chemical shift, peak shape, and exchange experiments with D_2O. The two singlets appearing at 1.84 and 1.85 ppm represent the two independent methyl groups in the molecule.

In the ^{13}C NMR spectrum, fourteen carbon signals were observed. The three peaks at lowest field (δ 193.3, δ 186.1, and δ 183.4) are characteristic of unsaturated

Table 1. Physico-chemical properties of sorrentanone.

Appearance	Light orange solid
Molecular formula	$C_{14}H_{14}O_4$
FAB-MS (positive ion)	247 (M+H), 269 (M+Na), 285 (M+K)
HRFAB-MS (positive ion)	(M+H): Calcd: 247.0970 Found: 247.0958
UV (CH_3CN) λ_{nm} (ε)	194 (5,300), 272 (8,700)
IR ν_{max} (KBr) cm^{-1}	3376, 2856, 1654, 1632, 1596, 1436, 1392, 1382, 1362, 1318, 1236, 1220, 1144, 1070, 1006, 884, 824
Rf (silica gel 60)	Rf=0.44 in 5% MeOH/$CHCl_3$

Table 2. NMR chemical shifts data for sorrentanone.

Atom	^{13}C	HETCOR	COLOC	^1H	COSY
1	186.1		1.84	8.06	
2	117.1		1.84	6.88	6.11, 6.16
3	151.9		1.84	6.17	6.16, 1.80
4	183.4		1.85	6.16	6.17, 6.88
5	136.8		1.85	6.11	6.88
6	140.3		18.5, 6.11	1.85	
7	193.3		6.88, 6.11	1.84	
8	127.9	6.11	6.16	1.80	6.17
9	147.5	6.88			
10	130.1	6.16	6.11, 1.80		
11	142.8	6.17			
12	18.8	1.80			
13	7.7	1.84			
14	11.9	1.85			

Table 3. Antimicrobial activities of sorrentanone.

Strain No.	MIC (μg/ml)
Staphylococcus pneumoniae A9585	32
S. pyogenes A9604	16
Enterococcus faecalis A20688	128
S. aureus/Hetero MR A27218	32
S. epidermidis A24548	32
S. haemolytic A21638	64

quinone carbonyl carbons. The protonated carbon signals (APT, δ 147.5, 142.8, 130.1, and 127.9) represent the diene sidechain.

Sorrentanone displays activity against both Gram-positive and Gram-negative organisms. Table 3 shows MIC data against selected organisms.

Thus, a new bioactive quinone structure has been isolated from a fermentation broth containing *P. chrysogenum*. The structure and atom connectivity was established using 2D NMR techniques. The compound has weak to moderate activity against several Gram-negative and Gram-positive bacteria. Interestingly, the known compounds sorbicillin[6] and bisvertinolone[7] were also isolated from a similar fermentation broth and may share a common biogenetic precursor with **1**.

References

1) CHIN, G. J. & J. MARX: Resistance to antibiotics. Science 264: 359~393, 1994
2) SCHABERG, D. S.; D. CULVER & R. GAYNES: Major trends in the microbial etiology of nosocomial infections. Am. J. Med. 91: 5S~72S, 1991
3) PANLILO, A.; D. CULVER & R. GAYNES: Methicillin-resistant *Staphylococcus aureus* in US hospitals: 1975~1991. Infect. Control Hosp. Epidemiol. 13: 582~586, 1992
4) For related examples of this structural type, see: HORIUCHI, C. A. & Y. SUZUKI: A New synthesis of 3-hydroxy-2,5-dialkyl-1,4-benzoquinone from 3-halo-3,6-dialkyl-1,2-cyclohexanedione using iodine-copper (II) acetate. Bull. Chem. Soc. Jpn. 62: 2919~2922, 1989, and references therein
5) As the result of a media study, it was found that the addition of SP-207 resin enhanced production of **1**. For further details, see LAM, K. S.; J. A. VEITCH, G. A. HESLER, D. M. PIRNIK & S. FORENZA: manuscript in preparation
6) D. J. CRAM: Mold metabolites: The strucuture of sorbicillin, a pigment produced by the mold *Penicillium notatum*. J. Am. Chem. Soc. 70: 4240, 1948
7) TRIFONOV, L.; J. H. BIERI, R. PREWO, A. S. DREIDING, D. M. RAST & L. HOESCH: The constituners of vertinolide: A new derivative of tetronic acid, produced by *Verticillium interextum*. Tetrahedron 38: 397, 1982