Tetrahedron Letters No. 52, pp 4989 - 4992.
0040-4039/79/1222-4989$02.00/0

STRUCTURES OF XANTHOVIRIDICATIN D AND XANTHOVIRIDICATIN G, METABOLITES OF PENICILLIUM VIRIDICATUM: APPLICATION OF PROTON AND CARBON-13 NMR SPECTROSCOPY

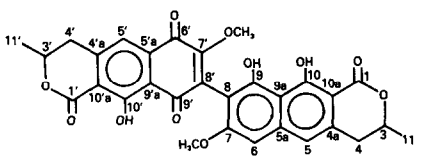
Michael E. Stack, Eugene P. Mazzola*, and Robert M. Eppley
Division of Chemistry and Physics, Food and Drug Administration,
Washington, D.C. 20204

The structures of xanthoviridicatin D and xanthoviridicatin G, toxic metabolites of Penicillium viridicatum, have been shown to be 3 and 4a, respectively by spectroscopic studies.

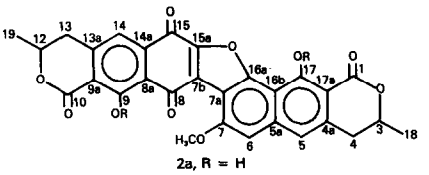
In a continuing search for naturally-occurring food contaminants, we have isolated several metabolites of the mold Penicillium viridicatum.[1] Four of these metabolites were found by ir, uv, pmr, and mass spectral examination to be xanthomegnin, viomellein 1, rubrosulphin 2a, and viopurpurin.[2-4] We now describe spectral studies which show that the structures of two new P. viridicatum metabolites, whose isolation is described in reference 1 and which have been designated xanthoviridicatins D and G, are 3 and 4a, respectively.

Ms, uv, ir, and ^{1}H and ^{13}C nmr data of 3 ($C_{26}H_{20}O_9$: M^{+}·476, m.p. 133-136°C, λ_{max}^{MeOH} 225, 264, 384 nm (ε 11,400; 23,100; 8100), ν_{max}^{KBr} 3420, 1725, 1664, 1590 cm^{-1}) were similar to those of 1[3-6] (Tables I and II). The appearance of only one C-methyl group in the pmr spectrum of 3, versus two in 1, and other data indicated that 3 was a lower molecular weight congener of 1, possessing only one lactone ring. The presence in 3 of pmr signals at δ6.58 and 6.95 ppm (later assigned to H-6 and H-5, respectively) and the absence of a singlet at δ7.50 ppm (assigned to H-10' in 1) suggested that the naphthoquinonyl lactone ring was absent in 3.

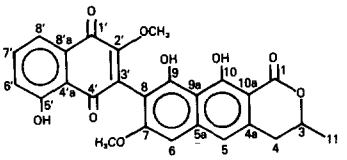
Proton noise-decoupled and single-frequency off-resonance decoupled cmr spectra revealed the presence of 26 carbons in 3 (versus 30 in 1) and only one signal each which could be attributed to a C-methyl, methylene, lactonic carbonyl, and an aliphatic methine group. Examination of the cmr data of 1, 3, and 5a (Table II) identified carbons in 3 whose shifts are virtually identical to those of carbons 1-10a in 1 and 4'a-8'a in 5a.



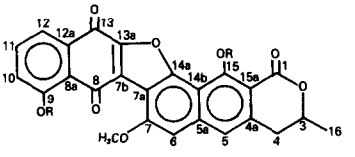
1



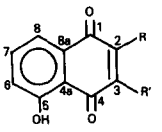
2a, R = H
2b, R = CH_3
2c, R = Ac



3



4a, R = H
4b, R = Ac



5a; R = R' = H
5b; R = OCH_3, R' = H
5c; R = H, R' = OCH_3

Table I. ^1H NMR Data[a] of Viomellein (1), Di-O-acetylrubrosulphin (2c), and Xanthoviridicatins D (3) and G-diacetate (4b)

Position	1[b]	3[c]	Position	2[c]	4[b]
3	4.63	4.74 m	3	4.76	4.72 m
4	3.02	2.98d(6)	4	3.07	2.98 d (6)
5	6.96	6.95	5	7.44	7.37
6	6.66	6.66	6	6.90	6.87
11	1.56	1.50d(6)	10		8.19dd(1.2,7.5)
3'	4.63		11		7.80 t (7.5)
4'	3.02		12	4.68	7.44dd(1.2,7.5)
5'	7.50		13	3.02	
6'-8'		7.2-7.8	14	7.99	
11	1.34		3-CH_3	1.56	1.53 d (6)
OCH_3	3.84,3.90	3.83,3.89	12-CH_3	1.56	
9-OH	9.80	9.78	7-OCH_3	4.07	4.10
5'-OH		12.30	OAc	2.51,2.61	2.51,2.69
10'-OH	13.44				
10-OH	13.88	13.92			

[a]In $CDCl_3$, parts per million from TMS. $J_{H,H}$ in parentheses. [b]Spectra recorded at 100 MHz, reference 3. [c]Spectra recorded on a Varian EM-390 spectrometer operating at 90 MHz.

Table II. ^{13}C NMR Data[a] of Viomellein (1), Di-O-methylrubrosulphin (2b), Xanthoviridicatins D (3) and G-diacetate (4b), and Juglone (5a)

Position	1[b]	Position	3[c]	5a[c]	Position	2b[b]	Position	4b[c]
1	171.2	1	171.4		1	161.7	1	161.3[d]
3	76.5d	3	76.6d		3	74.2d	3	74.2d
4	34.6t	4	34.7t		4	36.5t	4	36.1t
4a	134.0	4a	133.9		4a	138.6	4a	138.3
5	116.0d	5	116.2d		5	119.7d	5	122.3d
5a	140.5	5a	140.6		5a	138.9	5a	138.9
6	97.8d	6	97.9d		6	101.9d	6	102.3d
7	160.1	7	160.6		7	155.1	7	155.8
8	99.9	8	99.9		7a	113.3	7a	111.2[e]
9	161.3	9	161.2		7b	126.2	7b	126.6
9a	105.1	9a	105.8		8	176.8	8	177.4
10	155.3	10	155.5		8a	124.8	8a	124.9
10a	107.9	10a	108.2		9	162.7	9	161.5[d]
1'	162.4				9a	125.6	10	124.8d
3'	74.1d				10	160.1		
4'	36.3t				12	74.2d		
4'a	147.9	7'	135.2d	136.6d	13	36.5t		
5'	116.4d	8'	124.6d	124.5d	13a	147.1	11	134.4d
5'a	134.4	8'a	131.8	131.9	14	120.4d	12	130.9d
6'	180.1	1'	180.8	184.2	14a	136.1	12a	133.7
7'	158.2	2'	159.2		15	172.5	13	173.3
8'	123.6	3'	123.2		15a	150.8	13a	150.7
9'	188.3	4'	189.7	190.3	16a	154.9	14a	152.2[f]
9'a	114.8	4'a	114.8	115.0	16b	111.7	14b	114.1[e]
10'	162.8	5'	162.8	161.5	17	159.5	15	152.1[f]
10'a	117.6	6'	119.1d	119.2d	17a	113.9	15a	118.6[e]
3-CH_3	20.7q	3-CH_3	20.7q		3-CH_3	20.8q	3-CH_3	20.8q
3'-CH_3	20.7q				12-CH_3	20.8q		
7-OCH_3	55.9q	7-OCH_3	55.9q		7-OCH_3	55.8q	7-OCH_3	56.2q
7'-OCH_3	60.3q	2'-OCH_3	60.4q		9-OCH_3	63.4q		
					17-OCH_3	62.7q		
							$\underline{CH_3CO}$	21.1,21.2
							$CH_3\underline{CO}$	169.5,169.9

[a]In $CDCl_3$, parts per million from TMS. [b]Spectra recorded at 25.2 MHz, reference 5. [c]Spectra recorded on a Varian CFT-20 spectrometer operating at 20 MHz. Signals assigned using SFORD experiments, chemical shift correlations[9], and by comparison with each other. [d,e,f]These signals could not be more specifically assigned.

A question remained concerning the location of the hydroxyl group in the phenyl ring of the naphthoquinone system of 3, i.e. whether this hydroxyl group was positioned at C-5' or C-8'. Scheuer has investigated the proton nmr spectra of the naphthoquinones 5b and 5c and found that the chemical shifts of the phenolic protons are sensitive to the location of the methoxyl group.[8] Specifically, in 5b the chemical shift of the phenolic proton is δ11.70 ppm. Two of the observed phenolic proton chemical shifts of 3 are nearly identical to two resonances reported for 1, viz. those at δ9.8 and 13.9 ppm which were assigned to 9-OH and 10-OH, respectively.[3] This leaves the signal at δ12.26 ppm due to 5'-OH, a chemical shift value which is essentially the same as that found for the hydroxyl proton of 5b. A structure for 3 corresponding to 5c is, therefore, eliminated.

Ms, uv, ir, and ^{1}H and ^{13}C nmr data of 4a ($C_{25}H_{16}O_8$: M^{+}·444, m.p. 318-320°C, λ_{max}^{MeOH} 280, 355, 440 nm (ε 29,200; 3200; 4400), ν_{max}^{KBr} 3390, 1737, 1664, 1580 cm^{-1}) and 4b resembled those of 2 (Tables I and II). The fact that 4a was obtained from 3 on refluxing in K_2CO_3 and acetone in the same manner as 2a was formed from 1[3] established the structure of xanthoviridicatin G as 4a. Like compound 2b, C-7, C-8, C-13, C-13a, and C-14 show upfield shifts relative to the corresponding carbons in the naphthalene-naphthoquinone systems (1 and 3) due to steric compression effects resulting on formation of the furanoid ring.[9]

REFERENCES

1. M.E. Stack, R.M. Eppley, and A.E. Pohland, "Metabolites of Penicillium viridicatum," p. 543. In J. Rodricks, C.W. Hesseltine, and M. Mehlman, eds., "Mycotoxins in Human and Animal Health," Pathotox Publishers, Inc., Park Forrest South, Ill., 1977.
2. G. Just, W.C. Day, and F. Blank, Canad. J. Chem., 41, 74 (1963); A.S. Ng, G. Just, and F. Blank, ibid., 47, 1223 (1969).
3. R.C. Durley, J. MacMillan, T.J. Simpson, A.T. Glen, and W.B. Turner, J. Chem. Soc. Perkin I, 163 (1975).
4. M.E. Stack, R.M. Eppley, P.A. Dreifuss, and A.E. Pohland, Appl. Environ. Microbiol., 33, 351 (1977).
5. T.J. Simpson, J. Chem. Soc. Perkin I, 592 (1977).
6. G. Hofle and K. Roser, J. Chem. Soc. Chem. Comm., 611 (1978). These authors offer strong evidence for a linear structure for members of the xanthomegnin family, i.e. the naphthoquinone moiety, based on 3-bond proton-carbon coupling constants in xanthomegnin and model naphthoquinones.[7]
7. G. Hofle, Tetrahedron, 33, 1963 (1977).
8. R.E. Moore and P.J. Scheuer, J. Org. Chem., 31, 3272 (1966).
9. F.W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra," Heyden, New York, 1976, Chap. 2.

(Received in USA 17 August 1979)