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TRICHODERMADIENE: A NEW TRICHOTHECENE

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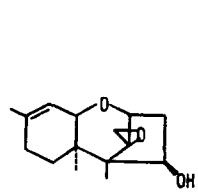
A new trichothecene, trichodermadiene (3), possessing a dienic ester side chain has been isolated and characterized.

We wish to report the isolation of a new class of trichothecene[1,2] which has a Z, E-dienic ester function typical of the macrocyclic trichothecenes [as in roridin A(2)] but is not macrocyclic. The compound is called trichodermadiene (3) after trichodermol (1) which 3 gives upon hydrolysis.

Trichodermadiene (3) was isolated by a methanol extraction of the mycelium of a fermentation of Myrothecium verrucaria (ATCC #24571).[4] Chromatography on silica gel gave a series of the less polar trichothecenes (roridin H and verrucarins B and J) and a previously uncharacterized trichothecene which had a Rf value higher than any heretofore reported macrocyclic trichothecene. Crystallization from ether gave needles, mp 145-146°; $[\alpha]_D^{27°}$ +17.7 (c3.2, $CHCl_3$), M^+ 386; UV (EtOH) 264 nm (log ε = 4.41); IR ($CHCl_3$) 1700 cm^{-1}, 1640 cm^{-1} and 1600 cm^{-1}, and an analysis which fits $C_{23}H_{30}O_5$, requiring nine units of unsaturation. The proton NMR spectrum clearly showed the presence of the dienic ester system typical of the macrocyclic trichothecenes.[3] However, unlike the ^1H NMR spectra of the macrocyclic trichothecenes, the ^1H NMR spectrum of the unknown exhibited two quaternary methyl groups, and the region around 4 ppm was unusually uncluttered; there were present only two sets of doublets, H-2 (δ3.85, J = 5.0 Hz) and H-11 (δ3.65, J = 5.5 Hz).



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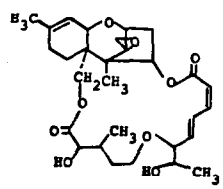
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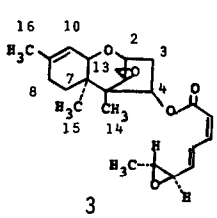
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The trichodermol and dienic ester systems account for eight of the nine units of unsaturation and leave the fragment C_3H_5O unaccounted for. Proton noise-decoupled and single-frequency off-resonance decoupled carbon-13 NMR spectra demonstrated that one of the remaining carbon atoms is a methyl carbon, which appears as a 5-Hz doublet in the proton NMR spectrum, while the other two carbon atoms are both methine carbons attached to an oxygen.[5] These facts are accommodated by placement of a 1,2-disubstituted epoxide group at C-5'. The 2.1-Hz coupling constant observed between H-6' and H-7' suggests a trans configuration for this epoxide system.[6] The ^1H and ^{13}C spectral data for 3 are given in Table 1.

We have preliminary data to suggest that this class of compound may exhibit interesting biological activity. Trichodermadiene (3) has been tested *in vivo* against P388 mouse leukemia (PS)[7] and has shown a T/C = 143 at 16 mg/Kg.[8] It will be interesting to see what the change in PS activity will be upon epoxidation of the C9, C10 double bond, since epoxidation of this bond in the macrocycles results in marked increase in PS activity,[9] whereas similar epoxidation in the PS active simple trichothecenes (e.g., anguidine) results in a great diminution of activity.[10]

Finally, it should be noted that the biosynthetic sequence leading to the lactone formation in the macrocycles is obscure.[11] Investigation of the metabolic fate of 3 *in vivo* may shed light on this point.

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Table 1. ^{13}C and ^{1}H NMR Data for Trichodermol (1, R=OH) and Trichodermadiene (3)[a]

Position	Trichodermol (1, R=OH)[c,d]	Trichodermadiene (3)[e]
2	79.3d (3.81d)[5]	79.2d (3.83d)[5]
3	40.2t (1.9dd)[3.5,15] (2.60dd)[8,15]	36.9t (2.1m) (2.6dd)[7.5,15]
4	74.2d (4.32dd)[3.5,8]	75.0d (5.7dd)[4,7.5]
5	49.6	49.2
6	40.4	40.5
7	24.9t (1.35m)	24.6t (2m)
8	28.4t (2m)	28.1t (2m)
9	140.5	140.0
10	119.4d (5.41d)[5.5]	118.9d (5.43d)[5.5]
11	70.8d (3.51d)[5.5]	70.6d (3.64d)[5.5]
12	66.2	65.5
13	47.9t (2.95AB)[4]	47.8t (2.97AB)[4]
14	6.4q (0.80)	6.0q (0.74)
15	16.0q (0.85)	16.1q (1.0)
16	23.4q (1.70)	23.2q (1.72)
1'		165.8
2'		118.4d (5.7d)[11]
3'		143.1d (6.57t)[11]
4'		130.3d (7.83dd)[11,15.5]
5'		140.4d (5.7dd)[8,15.5]
6'		58.8d (3.21dd)[2,8]
7'		56.8d (2.97dq)[2,5]
8'		17.5q (1.36d)[5]

[a]In $CDCl_3$, parts per million from TMS (0.0 ppm). ^{13}C NMR spectra were determined on Varian CFT-20 and FT-80A spectrometers operating at 20 MHz. ^{13}C NMR signals were assigned using SFORD techniques, [b]chemical shift relations, [a]and by comparison with literature data. [c,d] ^{1}H NMR spectra were determined on a Varian EM-390 spectrometer operating at 90 MHz in the TMS-locked mode. [b]F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra," Heyden & Son, Ltd., Philadelphia, Pennsylvania, 1978. [c] ^{13}C NMR data: J. R. Hanson, T. Marten, and M. Siverns, J. Chem. Soc. Perkin 1, 1033 (1974). [d] ^{1}H NMR data: J. R. Bamburg and F. M. Strong, "12,13-Epoxytrichothecenes," Chapter 7, in S. Kadis, A. Ciegler, and S. J. Ajl, Eds., "Microbial Toxins, Vol. VII," Academic Press, New York, New York, 1971. [e]Comparative ^{13}C and ^{1}H NMR data for the dienic part of roridin A, W. Breitenstein and Ch. Tamm, Helv. Chim. Acta, 58, 1172 (1975) and footnote d: 1', 166.3; 2', 117.2d (5.78d)[11]; 3', 143.6d (6.66t)[11]; 4', 126.0d (7.68dd)[11,15.5]; and 5', 139.0d (6m)[15.5].

References and Footnotes

(1) (a) J. R. Bamburg and F. M. Strong in "Microbial Toxins," Edited by S. Kadis, A. Ciegler and S. J. Ajl, Vol. 7, Academic Press, New York, New York, 1971; (b) J. R. Bamburg in "Mycotoxins and Other Fungal Related Food Problems," Edited by J. V. Rodricks, Advances in Chemistry Series, Vol. 149, American Chemical Society, 1976.
(2) Y. Ueno, Pure and Appl. Chem., 49, 1737 (1977).
(3) Ch. Tamm, Fortschr. Chem. Org. Naturst., 31, 63 (1974).
(4) This fermentation (200 gal) was carried out under the direction of Mr. Richard Geoghegan, Frederick Cancer Research Center, Frederick, Maryland. Details of this procedure will be presented in a full paper.
(5) F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 Spectra," Heyden & Son Ltd., Philadelphia, Pennsylvania, 1978, p. 37.
(6) (a) J. M. Lehn and J. J. Riehl, Mol. Phys., 8, 33 (1964); (b) D. D. Elleman, S. L. Manatt and E. D. Pearce, J. Chem. Phys., 42, 650 (1965); (c) S. L. Smith and R. H. Cox, ibid., 45, 2848 (1966); (d) F. Taddei et al., Org. Magn. Reson., 5, 385, 391, 393 (1973).
(7) We thank Dr. T. W. Doyle, Department of Medicinal Chemical Research, Bristol Laboratories Syracuse, New York for making the results available to us.
(8) Compound 3 was inactive at a dose level of 4 mg/Kg and was toxic at 64 mg/Kg. The macrocyclic trichothecenes are typically inactive in PS (see, however, B. B. Jarvis, G. P. Stahly and C. R. Curtis, Cancer Treat. Rep., 62, 1585 (1978) and references therein) and toxic at dose levels much above a few mgs/Kg.
(9) Epoxidation of the 9,10-double bond in both verrucarin A and roridin A converts these PS inactive (T/C < 130) compounds into β-9,10-epoxides which show potent activity (T/C > 200 against P388 mouse leukemia: B. B. Jarvis and G. P. Stahly, unpublished results; see also reference given in footnote 8 above.
(10) T. W. Doyle, personal communication.
(11) Ch. Tamm in "Mycotoxins in Human and Animal Health," Edited by J. V. Rodricks, C. W. Hesseltine and M. A. Mehlman, Pathotox Publishers, Inc., Park Forest South, Illinois, 1977.

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