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FUNGAL EXTRACTIVES—IV*

STRUCTURE OF A NOVEL SESQUITERPENE DIALDEHYDE FROM *LACTARIUS* BY SPECTROSCOPIC METHODS

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Abstract—The complete structure of a sesquiterpene dialdehyde ("velleral"), isolated from *Lactarius vellereus* and *L. pergamenus*, has been elucidated by means of IR, UV, ^{13}C-NMR spectroscopy, NOE measurements and computer simulation of the ^{1}H-NMR spectrum.

In recent publications we reported the structures for a pungent-tasting sesquiterpene dialdehyde, "isovelleral" (**2**),[1] and two sesquiterpene lactones.[2] In addition, a related crystalline, pungent-tasting dialdehyde, "velleral", was isolated[1] from *Lactarius vellereus* and *L. pergamenus* (Russulaceae), other workers[3] having isolated it from *L. vellereus*. We have now determined that velleral has the structure and relative configuration **1** (see Table 1) and the preferred conformation **1a** (see Fig 1).

Elemental analysis supplemented by ^{13}C-NMR (15 C; 20 H) and mass spectrometry (M^+ 232) gave the molecular formula for velleral ($C_{15}H_{20}O_2$). The presence of two conjugated aldehydic groups was indicated by CO stretching frequencies in the IR spectrum, (CCl_4, ν 1705 and 1693 cm^{-1}), and was supported by two aldehydic ^{1}H-NMR doublets at 9·49 ($J = 0·55$ Hz) and 9·47 ($J = 0·55$ Hz) ppm and two broad olefinic doublets at 7·02 ($J = 5·7$ Hz) and 7·07 ($J = 2·7$ Hz) ppm. Double irradiation experiments showed that each aldehydic proton appeared to be coupled to one only of the olefinic protons. The small long-range coupling constant (0·55 Hz) clearly excludes systems in which vinylic protons are alpha to the aldehydic groups.

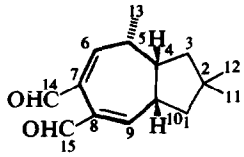
The UV spectrum (EtOH)(λ_{infl} 245 nm, ϵ 11,600 and λ_{max} 220 nm, ϵ 23,000) requires a more extended conjugation than is furnished by two isolated α,β-unsaturated aldehyde groups. In the ^{13}C-NMR spectrum of velleral the sp^2-carbons have similar chemical shifts in pairs reflecting a highly symmetrical system.[4] These facts (UV, NMR) and the fact that there is no apparent coupling between the olefinic protons leaves only one reasonable possibility for connecting the α,β-unsaturated aldehyde groups (**1**).

The fragmentation pattern in the mass spectrum of velleral shows a close resemblance to that of isovelleral (**2**) from the same species. Furthermore the ^{13}C-NMR spectra of these two dialdehydes have obvious similarities for the saturated portions of the molecules (Table 1). These observations are consistent with structure **1** for velleral.

In order to confirm structure **1** and to determine the stereostructure, a complete analysis of the seven proton spin system in the region 1·20–3·15 ppm was carried out. On irradiation of the vinylic protons the complex pattern in the allylic spectral region was simplified (Fig 1, I and II; H_6 and H_7 region). The two allylic protons were differentiated by irradiating the doublet of the Me group on the 7-membered ring (CH_3-13) to obtain the values $J_{6-8} = 2·7$ Hz and $J_{7-9} = 5·7$ Hz (*cf* above). The coupling constant $J_{6-8} = 2·7$ Hz requires a dihedral angle between H_6 and H_8 close to 90°. Inspection of Dreiding models of **1** in different conformations of *cis*- and *trans*-fused ring isomers revealed that this requirement is realized only for the *cis*-fused ring isomers in the conformation **1a**. The coupling constants for the seven proton spin system (H_1–H_7, **1a**) were estimated from bond angles measured in Dreiding models of velleral and also from known NMR data for the aforementioned closely related substance isovelleral (**2**).[1] These data together with approximate chemical shift values estimated

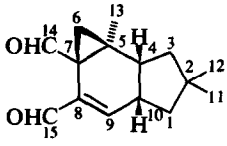
*Part III, see Ref. 2.

Table 1. ^{13}C-NMR data for velleral (1) and isovelleral (2) (25·2 MHz, $CDCl_3$)



1

Chemical shift (ppm from TMS)	Signal multiplicity[a]	Group	J_{C-H} (Hz)	Assignment (carbon nr.)
190·0	s	—CHO	187	14, 15
190·0	s	—CHO	187	
162·0	d	C=CH—	155	6, 9
161·0	d	C=CH—	155	
137·1	s	C=C—		7, 8
136·7	s	C=C—		
59·2	d	—CH—	133	4 or 5 or 10
48·3	t	—CH_2—	128	1, 3
47·3	t	—CH_2—	126	
40·7	d	—CH—	130	4, 5 or 4, 10 or 5, 10
37·7	d	—CH—	128	
37·7	s	—C—		2
29·4	q	—CH_3—	125	11, 12
27·2	q	—CH_3	128	
18·3	q	—CH_3	128	13



2

197·3	d	—CHO	180	14
191·9	d	—CHO	177	15
153·3	d	C=CH—	158	9
140·0	s	C=C—		8
46·9	t	—CH_2—	128	1,3
45·5	t	—CH_2—	124	
41·7	d	—CH—	127	4, 10
39·4	d	—CH—	123	
37·4	s	—C—		

Table 1. (*Continued*)

Chemical shift (ppm from TMS)	Signal multiplicity[a]	Group	J_{C-H} (Hz)	Assignment (carbon nr.)
34·4	s	>C<		2, 5, 7
34·1	s	>C<		
31·5	q	$-CH_3$	125	11, 12
31·0	q	$-CH_3$	125	
26·8	t	$-CH_2-$	162	6
18·6	q	$-CH_3$	127	13

[a]s = singlet, d = doublet, t = triplet, q = quartet; obtained by "off-resonance" decoupling.

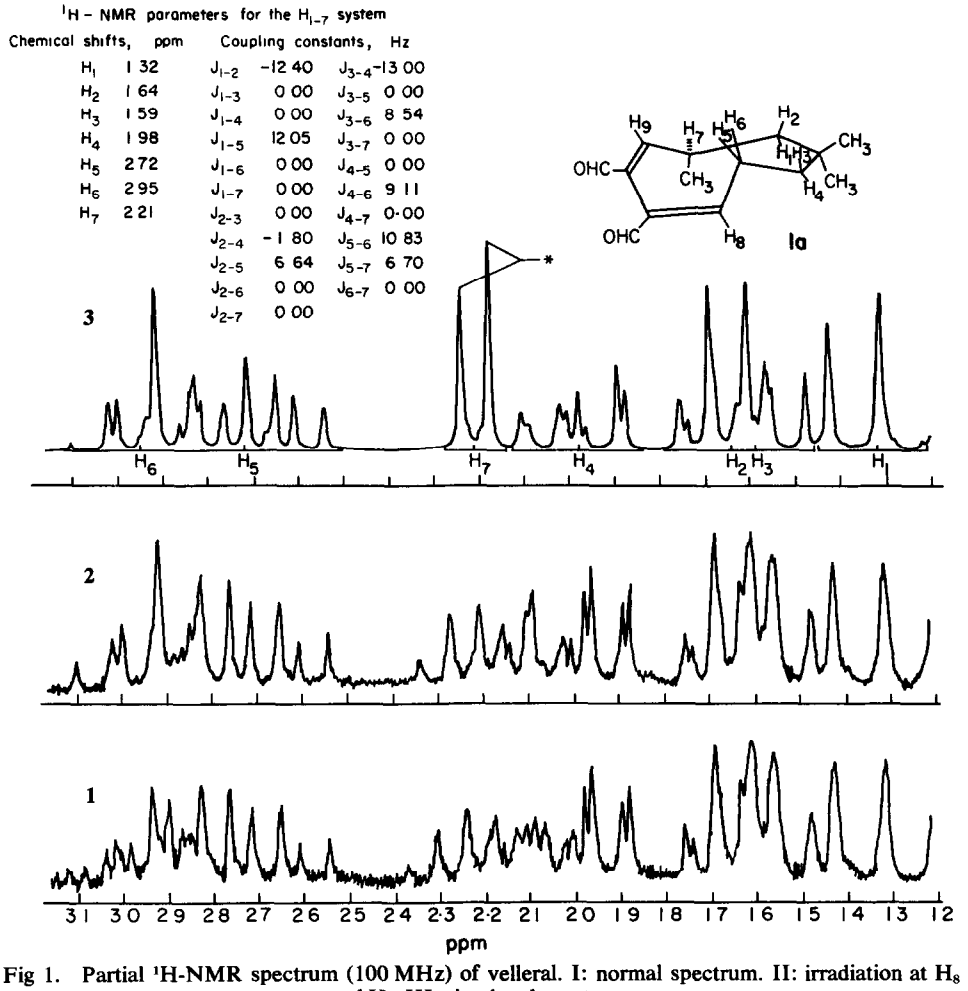


Fig 1. Partial ¹H-NMR spectrum (100 MHz) of velleral. I: normal spectrum. II: irradiation at H_8 and H_9. III: simulated spectrum.

*The coupling between H_7 and the methyl group protons could not be acommodated by the computer program (max. seven spins).

from the experimental spectrum were used as initial parameters in a theoretical simulation of the seven proton spectral region using the LAOCN 3 computer program.[5] Successive iterations resulted in fairly good agreement between the experimental (vinylic protons decoupled) and theoretical spectra (Fig 1, II and III). The calculated coupling constants agreed well with the expected values. Similar simulation of 60 MHz spectrum also showed good agreement with the experimentally obtained spectrum (same coupling constants; chemical shifts reduced with the factor 0·6), thereby providing further assurance for the coupling interpretation.

The *endo* position of the Me-13 group was deduced from the coupling constant $J_{5-7} = 6{\cdot}5$ Hz. The hypothetical *exo* position of the Me group would require a larger coupling constant (H_5 and H_7 antiperiplanar). The configuration at C-5 was confirmed by measuring NOE; complete saturation of the Me-13 protons resulted in increased integrated intensity for the vinylic protons (H_8: 13% NOE; H_9: 10% NOE) only consistent with the *endo* epimer. Irradiation of the vinylic protons gave 40% NOE for both aldehydic protons. This unusually large NOE effect is consistent with a state of rapid rotation between the two possible and approximately equally populated, intramolecularly H-bonded (6-membered, quasi planar ring) aldehyde group rotamers, where the aldehydic protons are sterically remote from other protons in the molecule. In order to verify these fine structural features, theoretical calculations of the NOE's were made under conditions for saturated Me-13.[6] All proton-proton distances for different aldehyde group and Me-13 rotamers were estimated from Dreiding models. In all cases the theoretical NOE for H_8 was too large and for H_9 too small compared with the experimental values. This discrepancy between theoretical and experimental values might be due to inversion of the heptadiene ring resulting in a conformation (present to a minor degree) in which the Me-13 group is bent away from the H_8 proton.

In conclusion it is significant that the relative configuration at C-5 in velleral is the same as that in isovelleral (2). The *cis*-ring junction is found not only in isovelleral but also in several characterised sesquiterpenoids of basidiomycetes origin.[7,8]

EXPERIMENTAL

The ^{1}H-NMR spectra were recorded on a Varian XL-100 instrument with ^{13}C-NMR capability with Fourier transform equipment. Mass spectra were recorded on a LKB 1100 instrument.

Isolation of velleral (1). Fresh fungi (*Lactarius vellereus* or *L. pergamenus*, Russulaceae) were ground with hexane and the mixture was pressed in a fruit press (Hafico). The hexane phase was separated, dried, evaporated, and the residue crystallised from hexane to remove *stearic acid*. The mother liquor was concentrated and chromatographed (silica gel, methylene chloride) to obtain a crude fraction which was rechromatographed (silica gel, methylene chloride) yielding almost pure velleral.

Velleral (1), m.p. 86·5–87·5° (from hexane); $[\alpha]_D^{19}$ −25° (*c* 2·1 in $CHCl_3$); UV (EtOH): λ_{infl} 245 nm (ε 11,600), λ_{max} 220 nm (ε 23,000); IR (CCl_4): ν 2720, 1705, 1693 (CHO), 1605 (C=C), 1360, 1355 (*gem* Me), 1207, 856, 714 cm^{-1}; NMR ($CDCl_3$, TMS): δ 9·49 (1H, d, J = 0·55 Hz; O*H*C—C=CH—), 9·47 (1H, d, J = 0·55 Hz; O*H*C—C=CH—), 7·07 (1H, d broad, J = 2·7 Hz; OHC—C=C*H*—CH—), 7·02 (1H, d broad, J = 5·7 Hz; OHC—C=C*H*—CHCH$_3$—), 1·20–3·15 (7H, m; for interpretation see Fig 1), 1·17 (3H, d, J = 6·6 Hz; —CH—C*H*$_3$), 1·13 (3H, s; —C—C*H*$_3$), 0·98 (3H, s; —C—C*H*$_3$) ppm; ^{13}C-NMR data see Table 1; MS (70 eV) *m/e*: 232 (M^+, 11%) ($C_{15}H_{20}O_2$), 119 (28%), 105 (54%), 91 (83%), 79 (51%), 77 (67%), 41 (100%; base peak). (Found: C, 77·7; H, 8·7. $C_{15}H_{20}O_2$ requires: C, 77·5; H, 8·7%).

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REFERENCES

[1]G. Magnusson, S. Thorén and B. Wickberg, *Tetrahedron Letters* 1105 (1972)
[2]G. Magnusson and S. Thorén, *Acta Chem. Scand.* Accepted for publication
[3]P. H. List and H. Hackenberg, *Arch. Pharmaz.* **302**, 125 (1969)
[4]G. C. Levy and G. L. Nelson, *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists* p. 67. Wiley-Interscience, New York, London, Sydney, Toronto (1972)
[5]S. Castellano and A. A. Bothner-By, *J. Chem. Phys.* **41**, 3863 (1964)
[6]R. E. Schirmer, J. P. Davis, J. H. Noggle and P. A. Hart, *J. Am. Chem. Soc.* **94**, 2561 (1972)
[7]T. C. McMorris, M. S. R. Nair, P. Singh and M. Anchel, *Phytochem.* **10**, 3341 (1971)
[8]T. Takeuchi, S. Takahashi, H. Iinuma and H. Umezawa, *J. Antibiotics* **24**, 631 (1971)