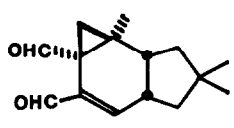
Tetrahedron Letters No. 12, pp 1105 - 1108, 1972. Pergamon Press. Printed in Great Britain.

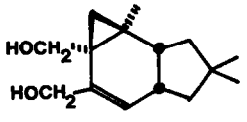
FUNGAL EXTRACTIVES I. STRUCTURE OF A SESQUITERPENE DIALDEHYDE FROM LACTARIUS BY COMPUTER SIMULATION OF THE NMR SPECTRUM

Göran Magnusson, Svante Thorén and Börje Wickberg
Organic Chemistry 2, Chemical Center, The Lund Institute of Technology
Box 740, S-220 07 Lund 7, Sweden
(Received in UK 24 January 1972; accepted for publication 10 February 1972)

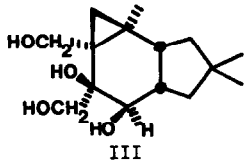
The isolation of a number of sesquiterpenoids of incompletely known structure from Lactarius species has recently been described[1,2]. We therefore report here our own results and evidence assigning structure I to a sesquiterpene dialdehyde from L.vellereus and L.pergamenus* (Russulaceae). Two further aldehydes and two lactones of sesquiterpene type were also isolated. Compound I and one of the other aldehydes are apparently identical with the substances "isovelleral" and "velleral" of unknown structure from L.vellereus[1].



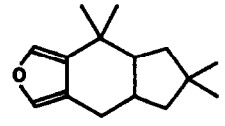
I



II



III



IV

In the present investigation, the sesquiterpenes were isolated by grinding fresh fungus with hexane, partitioning the hexane extract against aqueous methanol and chromatographing the extract on silica. Compound I**, $C_{15}H_{20}O_2$ (M^+ 232) has m.p. 105-106°, $[\alpha]_D^{19}$ +293° (c 2.0, $CHCl_3$). Two down-field one proton singlets at δ 9.48 and 9.74 indicate the presence of two aldehyde groups (ν_{max}^{CCl4} 2826, 2725 cm^{-1}), one of which should be α,β-unsaturated (ν_{max}^{CCl4} 1685, 1630 cm^{-1}; λ_{max}^{EtOH} 249 nm, ε 7300). Only one vinyl proton is indicated (δ 6.47,m, 1H). On irradiation at δ 2.74, the vinyl proton multiplet changes to a singlet indicating coupling with two allylic protons ($|J|$ =1.9, 1.0 Hz). IR data (ν_{max}^{CCl4} 1710 cm^{-1}) show that the second aldehyde group might be attached to a cyclopropyl carbon, which should then be quaternary. A proton at δ 0.95 (d, 1H, $|J|$ =4.5 Hz) coupled with a proton at δ 1.88 gives further indication for a cyclopropane ring (see also below). NMR also shows the presence of three quaternary methyl groups (1.07, 1.09, 1.14 s, 3 H each), two of which should be geminal (ν_{max}^{CCl4} 1385, 1366 cm^{-1}).

Reduction of compound I affords the diol II, $C_{15}H_{24}O_2$, m.p. 110-111° and 117-118° (dimorphous), $[\alpha]_D^{22}$ -2° (c 2.1, $CHCl_3$). The presence of two cyclopropane hydrogens is apparent from an AX quartet (doublets at δ 0.58 and 0.86, $|J|$ =4.5 Hz). A trisubstituted ethylene group

*Frequently confused with L.piperatus

**All compounds have given satisfactory analyses. Mass spectra were recorded on a LKB 1100 mass-spectrometer and NMR spectra on Varian A-60 A and Varian XL-100 NMR spectrometers.

(δ 5.19, s broad, $-\underset{|}{\overset{|}{C}}=C\underline{H}$; ν_{max}^{CCl4} 1645 cm^{-1}, weak) must be conjugated with the cyclopropane ring (strong end absorption in the UV region, $\varepsilon_{220nm}^{EtOH}$ 4540)[3]. The NMR spectrum exhibits further signals at δ 1.01 (s, 6H, overlapping methyl singlets), 1.27 (s, 3H, methyl), 2.41 (m, 2H, allylic type protons), 3.49 and 4.06 (ABq, |J| =12.5 Hz, $-\underset{|}{C}-C\underline{H}_2OH$), 4.21 (s broad, 2H, $C=\underset{|}{C}-C\underline{H}_2OH$).

Diol II reacts rapidly with OsO_4 in pyridine to give a single tetraol (III) in remarkably high yield (97 %). Compound III, $C_{15}H_{26}O_4$, m.p. 158.5-159.5°, $[\alpha]_D^{22}$ -73° (c 2.0, EtOH), shows no significant UV absorption at or above 220 nm. It resists hydrogenation over platinum in acetic acid. Since it does not show any signs of unsaturation it was concluded that compounds I - III are tricyclic. Compound III exhibits NMR signals at δ 0.22 and 1.00 (AXq, |J| =4.7 Hz, 1H each, cyclopropane protons), 1.04, 1.15, 1.22 (s, 3H each, methyls), 3.20, 4.26 (AXq, |J| =12.2 Hz, 1H each, $-C\underline{H}_2OH$), 3.55, 3.83 (ABq, |J| =11.2 Hz, 1H each, $-C\underline{H}_2OH$), and 3.66 (d, |J| =11.0 Hz, 1H, $\underset{|}{C}H-\underset{|}{C}\underline{H}-OH$).

Conclusive evidence of the structure of the cross-conjugated system of compound I was obtained by partial hydrogenation over a palladium catalyst (1 equiv. H_2 uptake) and subsequent reduction with excess potassium borohydride in dioxan-water, which afforded a 50 % yield of a furan derivative (IV). Compound IV, $C_{15}H_{22}O$ (M^+ 218), an oil, has $[\alpha]_D^{25}$ +21° (c 0.6, $CHCl_3$); λ_{max}^{EtOH} 216 nm (ε 7700); ν_{max}^{CCl4} 3090 and 895 cm^{-1} (furan); δ 0.90 (s, 6H, overlapping methyls), 1.15 and 1.12 (s, 3H each, methyls) and 7.15 (s, 2H, 3,4-disubstituted furan). Formation of a furan ring implies that the formyl groups of compound I are vicinal and the formation of a new methyl group shows that the cyclopropane hydrogens of I-III are geminal. The attachment of at least one methyl group to a "benzylic" carbon atom of IV is indicated by a prominent M^+-15 base peak in its mass spectrum.

Attempts to reconstruct the entire structure of I must accomodate the presence of a strongly coupled 6-proton system in the NMR spectrum of I and the coupling of that system with the vinyl proton. This restriction and obvious biogenetic analogies* make I the structure of choice. The 5/6 ring cis-fusion gains support from the exclusive formation of one tetraol from diol II, since osmium tetroxide oxidations are normally not very stereoselective. Dreiding models show that the observed stereoselectivity would only be expected with cis-fused rings. The observation that one cyclopropane signal of tetraol III is shifted significantly down-field as compared to the NMR spectrum of the diol II points to an interaction between one of the cyclopropane protons and the secondary hydroxyl group of III. This leaves the stereoisomers depicted in formulas I-III as the most plausible alternatives.

Definite structural proof was obtained by using the LAOCN 3 computor program[7] to construct the partial 100 MHz NMR spectrum of I as obtained on decoupling of the vinyl proton (Fig. 1a). The spectrum consists of a 2 proton A part and a 4 proton X part. The initial coupling parameters were estimated[8] from bond angles of reasonable conformers of structure I using Dreiding models. Iteration procedures eventually led to the set of parameters shown in table, Fig. 1a, which gave a very satisfactory fit (Fig. 1b) with the experimental spectrum. Only lines with

*Marasmic acid[4,5] as well as a number of other fungal sesquiterpenes[6] all contain an analogously substituted cyclopentane ring.

an intensity >0.03 were considered. It should be noted that the apparent deviations in the A part may be referred to errors in long range coupling constants of the order of 0.1 Hz, which are of little importance for the structural conclusions.

The computed parameters are consistent with the presence of two vicinal protons (H_5 and H_6) of allylic type. These protons are coupled with two inherently separate sets of geminal hydrogen atoms. This leads unequivocally to structure I, and specifically to the conformation indicated in Fig. 1a. Dreiding models show that in this conformation the angles between H_6 and H_4, and between H_6 and the vinylic proton are close to 90°, respectively, as is required by the very low coupling constants. The corresponding angles in the 5/6 ring trans isomer of I require larger coupling constants. Additional proof of the assignments was obtained by using the parameters above to construct a 60 MHz spectrum, which showed an equally good fit with an experimental 60 MHz spectrum. Where possible, proton couplings and peak assignments were confirmed by double irradiation experiments.

In the NMR spectrum of compound I, the geminal cyclopropane protons give rise to an unusual AX quartet with doublets at δ 0.95 and 1.88 ($|J|$ =4.5 Hz). A similar pattern has been observed with methyl marasmate[4] (doublets at δ 1.18 and 2.34). The proton at δ 1.88 in I might be that cis to the bridgehead aldehyde group, which could be subject to rotational restriction. However, attempts to confirm this assignment by nuclear Overhauser experiments were inconclusive.

Acknowledgement. The authors are grateful to Dr. Torbjörn Drakenberg, Lund for helpful discussions and for recording the 100 MHz spectra. This work has been supported by Swedish Natural Science Research Council.

References

1. P.H. List and H. Hackenberg, Arch.Pharmaz. 302, 125 (1969)
2. W.M. Daniewski and M. Kocór, Bull.Acad.Pol.Sci. 18, 585 (1970)
3. T. Norin, Acta Chem.Scand. 15, 1676 (1961)
4. J.J. Dugan, P. deMayo, M. Nisbet, J.R. Robinson and M. Anchel, J.Amer.Chem.Soc. 88, 2838 (1966)
5. P.D. Cradwick and G.A. Sim, Chem.Commun. 431 (1971)
6. See e.g. T.C. McMorris, M.S.R. Nair and M. Anchel, J.Amer.Chem.Soc. 89, 4562 (1967) /illudol/; F.W. Comer et al., Chem.Commun. 310 (1965) /hirsutic acid/; J.A. Kepler et al., J.Amer.Chem.Soc. 89, 1260 (1967) /fomannosin/; S. Nozoe et al., Tetrahedron Letters, 3125 (1971) /Fomitopsis sesquiterpenes/.
7. S. Castellano and A.A. Bothner-By, J.Chem.Phys., 41 3863 (1964)
8. L.M. Jackman and S. Sternhell, Applications of nuclear magnetic resonance spectroscopy in organic chemistry, Pergamon Press, Braunschweig, 1969.

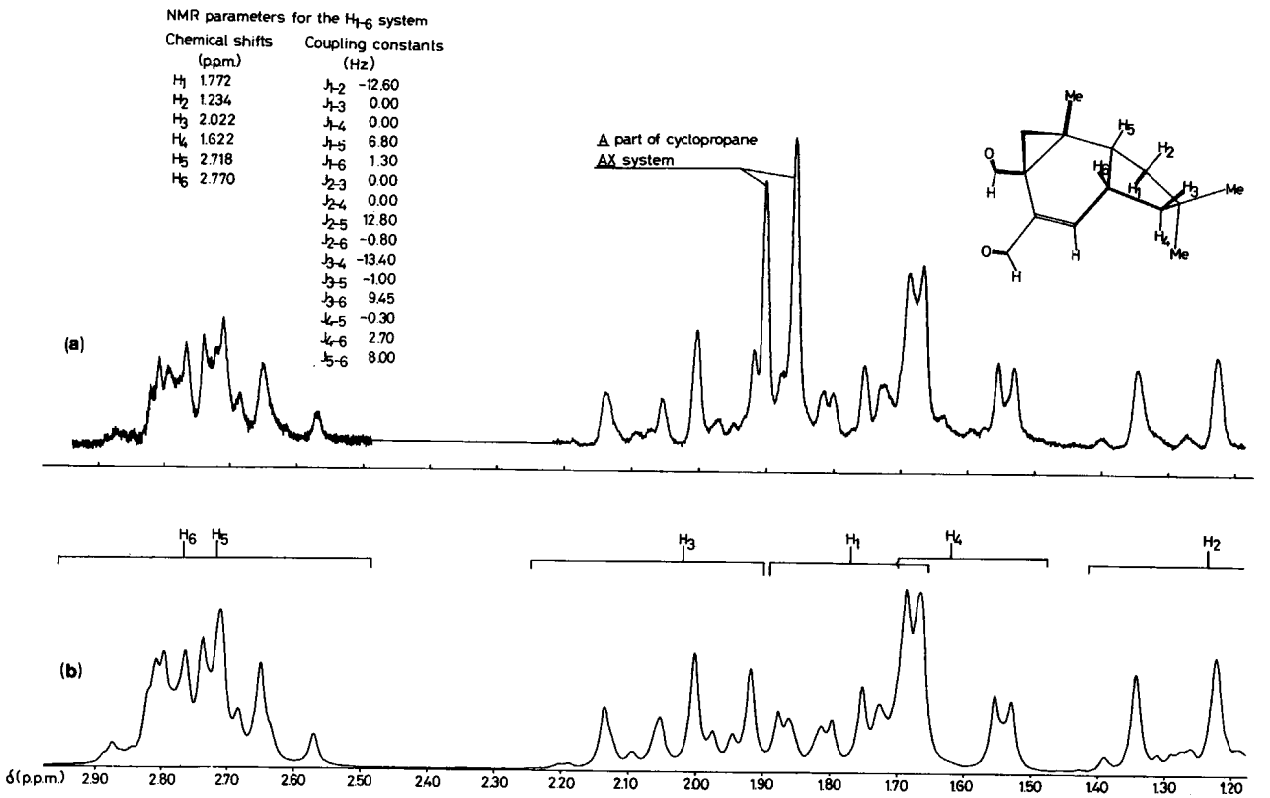


Fig. 1. Part of 100 MHz nmr spectrum of compound I; (a) experimental spectrum, (b) calculated spectrum.