Structure of the Macrocyclic Bis-lactone Lepranthin from the Lichen *Arthonia impolita;* an X-Ray Analysis

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To Prof. Antonio G. González, IPNA-CSIC, La Laguna, Tenerife, celebrating his half-century of involvement with natural products chemistry

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The structure and relative stereochemistry of lepranthin from the lichen *Arthonia impolita* has been elucidated as 1 by NMR spectroscopy and X-ray analysis.

Introduction

Nearly 90 years ago Zopf [1] described a new neutral compound, m.p. 183 °C $[\alpha]_D$ + 71 and the molecular formula $C_{20}H_{40}O_{10}$ (440.52), from the crustaceous lichen *Arthonia impolita* (Ehrh.) Borrer (syn. *Leprantha impolita* (Ehrh.) Körber) and named it lepranthin. This compound was not investigated further until around 1980 when we carried out a NMR investigation (see below) which revealed lepranthin to be a macrocyclic bis-lactone. A private communication from Dr. M. M. Mahandru to S. H. in 1981 suggested that a compound lobarthidiol from an English *Arthonia* species could be identical with lepranthin. No details of lobarthidiol have been published. Unfortunately we were unable to define the size of the lactone ring. Recently we have revived our interest in this lichen substance and describe here the elucidation of its structure and relative stereochemistry by NMR spectroscopy and X-ray analysis.

Results and Discussion

The lepranthin (**1**) used in this investigation was from the Zopf collection of the Botanical Museum in Berlin-Dahlem. Recrystallization from benzene afforded plates of m.p. 185 °C and $[\alpha]_D^{24}$ +70 ($CHCl_3$), in good accordance with Zopf's data. The mass spectrum and elementary analysis gave the molecular formula $C_{32}H_{52}O_{14}$ (660.74), which was confirmed by the high-resolution value of the $[M-H_2O]$ peak of the lepranthin MS: 642.3249 for $C_{32}H_{50}O_{13}$.

Table I. ^1H NMR shifts (δ in ppm) and coupling constants (J in Hz) of lepranthin (**1**) and lepranthone (**2**).

	Lepranthin [δ]	Lepranthone [δ]
H		
2,2′	2.79 (dq, 7.3, 10.5)	3.60 (q, 7.0)
3,3′	3.71 (dd, 2.5, 10.5)	–
4,4′	1.9 (tq, 2.4, 7.0)	3.12 (quint., 7.0)
5,5′	5.21 (dd, 2.2, 8.5)	5.22 (ddd, 3.8, 6.4, 8.5)
6a,6′a	2.73 (dd, 4.0, 16.0)	*ca.* 2 (m)
6b,6′b	1.57 (ddd, 2.2, 8.6, 16.2)	*ca.* 2 (m)
7,7′	5.04 (dq, 3.5, 10)	5.09 (quint., 5.7)
8a, 8′a	1.68 (ddd, $J_{8a,9}$ 3.1, $J_{8a,7}$ 11.2, $J_{8a,8b}$ 14.6)	1.81 (t, 7.0)
8b, 8′b	1.63 (ddd, $J_{8b,7}$ 2.6, $J_{8b,9}$ 10.2, $J_{8b,8a}$ 14.6)	
9,9′	4.89 (ddq, 4.9, 6.2, 9)	4.88 (sext., 6.6)
Me		
10,10′	1.19 (d, 6.33)	1.21 (d, 6.9)
11,11′	1.27 (d, 7.2)	1.24 (d, 7.0)
12,12′	1.04 (d, 7.0)	1.09 (d, 7.2)

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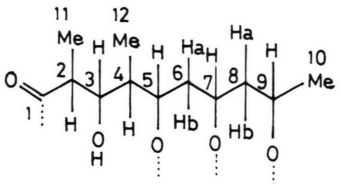
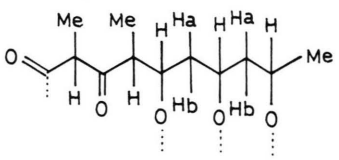
^1H and ^{13}C NMR spectroscopy led to the structure of a dimeric bis-lactone of the unit $C_{16}H_{26}O_7$ which contains a secondary hydroxyl group, two secondary acetates and three secondary methyls. The lactone terminus is also secondary. The ^1H and ^{13}C chemical shifts are listed in the Tables I and II.

Double irradiation experiments at 360 MHz enabled the structure of the monomeric unit to be assembled as follows. Irradiation of H-2 caused collapse of Me-11 and removed the major coupling from H-3. Irradiation of H-4 removed the minor couplings from H-3 and H-5 and collapsed Me-12. Irradiation of H-6a resulted in the removal of the major couplings from H-5, H-7 and H-6b while irradiation at H-6b removed a small coupling from H-7 and caused changes in H-6a. H-8a and H-8b have similar chemical shifts and form the AB part of an ABMX system with H-7 and H-9. Irradiation of H-8a and H-8b affects H-7 and H-9. The ^1H coupling constants are also shown in Table I. Irradiation of Me-11 and Me-12 confirmed their relationship with H-2 and H-4 respectively. Irradiation of Me-10 left H-9 as a doublet of doublets (due to coupling with H-8a and H-8b). These experiments account for all the carbons and hydrogens in partial structure A with the exception of the lactonic carbonyl group which must be placed as shown.

Oxidation of lepranthin with Jones' reagent afforded the diketone lepranthone (**2**). The ^1H NMR spectrum of **2** revealed H-2 as a quartet coupled only with Me-11 and H-4 as a quintet coupled with Me-12 and H-5. Both carbon atoms **2** and **4** are shifted downfield (by 7.34 and 12.73 ppm respectively) in **2** relative to **1.** The large shift of the lactone carbonyl carbon (+7.1 ppm) is due to removal of the hydrogen bonding. Thus the monomeric unit of lepranthone has structure A′.

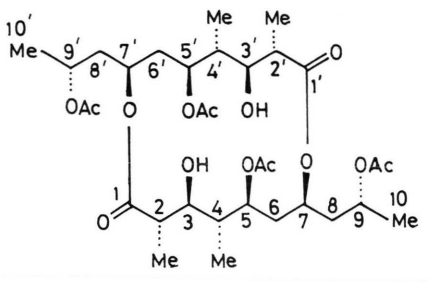


A

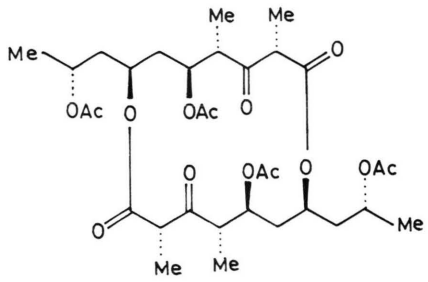


A′

The data presented do not define the positions of the acetates nor the size of the lactone ring. Therefore we carried out an X-ray analysis of lepranthin which led to structure **1** with a 16-membered bis-lactone ring (Fig. 1).



1



2

Table II. ^{13}C NMR shifts (δ in ppm) and $\Delta\delta$ values of lepranthin (**1**) and lepranthone (**2**).

Carbon atoms	Lepranthin [δ]	Lepranthone [δ]	$\Delta\delta$ (**1**–**2**)
1,1′	175.57 (s)	168.47 (s)	7.10
2,2′	44.37	51.71	−7.34
3,3′	75.83 (d)	–	–
4,4′	36.42 (d)	49.15 (d)	−12.73
5,5′	69.47 (d)	70.31 (d)	–
6,6′	33.54 (dd)	34.79 (t)	−1.25
7,7′	68.74 (d)	69.24 (d)	–
8,8′	38.16 (t)	40.23 (t)	−2.07
9,9′	67.10 (d)	66.83 (d)	–
10,10′	20.45 (q)	20.30 (q)	0.15
11,11′	13.91 (q)	12.66 (q)	1.25
12,12′	11.15 (q)	12.55 (q)	−1.40
13,13′,	170.12 (s),	170.25 (s),	−0.12,
15,15′	170.19 (s)	170.33 (s)	−0.14
14,14′,	20.96 (q),	20.77 (q),	0.19,
16,16′	21.29 (q)	21.00 (q)	0.29

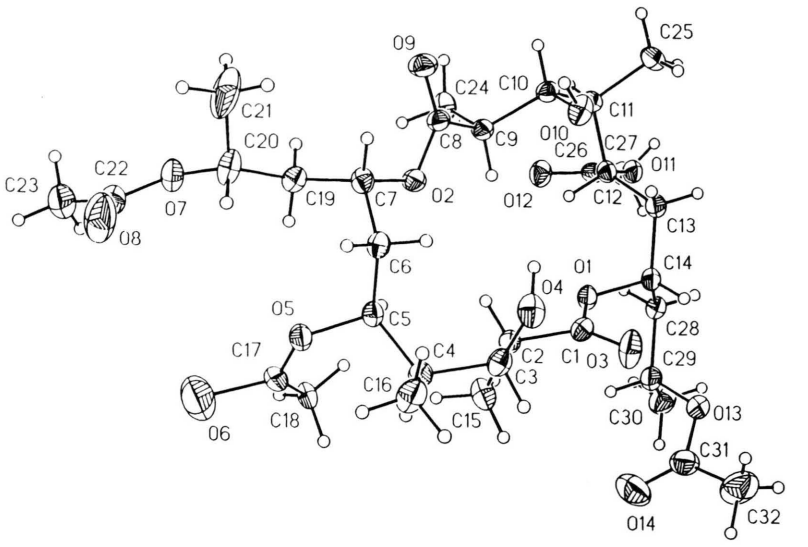


Fig. 1. Computer drawing of a lepranthin molecule (note the different numbering system to formulae **1** and **2.**

Table III. Crystal data of lepranthin.

Molecular formula	$C_{32}H_{52}O_{14} \cdot C_6H_6$
MW	738.84
Temperature [K]	296(1)
Colour, form	colourless plate
Size [mm]	23, .43, .47
Crystal system	orthorhombic
Space group	$P2_12_12_1$ (No. 19)
Unit cell [in Å]	a = 11.429(3) b = 11.933(3) c = 30.704(6)
[in °]	α = 90.00(2) β = 90.00(2) γ = 90.00(2)
	V= 4188(2) Å^3
Radiation Mo–K_α	λ = 0.71069 Å Z = 4 F(000): 1592
Density	ϱ [mg/m^3] = 1.172 absorption coefficient μ [mm^{-1}] = 0.089
ω-Scan data collection	θ_{max} = 21.98
Reflections measured	5462 $0 \leq h \leq 12$
Unique reflections	4944 $0 \leq k \leq 12$
	$-36 \leq l \leq 36$
Methode used	full matrix least squares on F^2
Data/refined parameters/ restraints	4944/469/36
SHELXL-93	$R1$: 0.0508[F^2] $wR2$: 0.1441 $I > 2\sigma(I)$
	$R1$: 0.0585[F^2] $wR2$: 0.1516[F^2] all data
Weight	$w = 1/[\sigma^2F_o^2 + 0.1141P^2 + 1.66P]$ where
	$P = (\max(F_o^2, 0) + 2F_c^2)/3$
Goodness of fit	0.920 computer: PC(486)
Difference electron density [e/Å^3]	0.281/–0.237
Absolute structure parameter	0.8 (1.4)
Programs used	SHELXS-86, SHELXL-93

Table III contains the crystal data of lepranthin. The full data of the X-ray analysis are deposited at the Fachinformationszentrum Karlsruhe, Eggenstein-Leopoldshafen.

The absolute configuration of **1** has yet to be determined. Lepranthin with 12 chiral centres is the first macrocyclic bis-lactone from a lichen. The biosynthesis of lepranthin arises either by twofold

methylation, reduction and acetylation of a pentaketide, followed by cyclization, or by condensation of 3 molecules of acetyl-CoA with 2 molecules of propionyl-CoA, reduction and acetylation of the corresponding 2,4-dimethyl-3,7-dihydroxy-5,9-diacetoxydecanoic acid and subsequent lactonization to **1.**

Colletallol, colletoketol, colletol, grahamimycin A_1, pyrenophorin, and vermiculin are bis-lactone from fungi [2].

Experimental

Lepranthin

From *Arthonia impolita* from an old oaken barn door near Eckern (Oldenbourg, Germany); leg. H. Sandstede, *ca.* 1904. Lepranthin (Zopf's collection), from benzene rectangular plates with crystal benzene (for the X-ray analysis) of m.p. 185 °C; from MeOH–H_2O flat needles of m.p. 183–185 °C; CD (EtOH): $\Delta\varepsilon$ −4.17 (216 nm). IR, γ_{max}^{KBr}: 770, 815, 894, 974, 1000, 1032, 1076, 1115, 1178, 1250, 1308, 1338, 1380, 1436, 1464, 1720, 2996, 3550 cm^{-1}. MS (+), *m/z* 642 (33%, M–H_2O), 600 (19, M–AcOH), 582 (54, M–H_2O–AcOH), 572 (9), 540 (29), 527 (24), 522 (10), 514 (11), 480 (9), 460 (16), 433 (26), 415 (26), 373 (37), 355 (52), 331 (60), 313 (60), 306 (27), 299 (45), 295 (27), 271 (74), 270 (36), 266 (26), 257 (98), 253 (49), 229 (56), 228 (49), 210 (82), 197 (67), 193 (65), 192 (56), 169 (100), 168 (87), 157 (87), 143 (52), 140 (88), 137 (90).

Lepranthone

By oxidation of lepranthin (0.02 g) in acetone (20 ml) with Jones' reagent in 4 min at 20 °C and usual work up; from CH_2Cl_2–*n*-hexane needles of m.p. 200–201 °C. $C_{32}H_{48}O_{14}$ (656.70). IR, γ_{max}^{KBr}: 804, 940, 970, 1000, 1026, 1044, 1092, 1110, 1122, 1142, 1176, 1190, 1240, 1320, 1374, 1450, 1724, 2940, 2998 cm^{-1}. MS (+), *m/z* 656 (38%, M), 596 (58, M–AcOH), 583 (12), 554 (30, M–AcOH–CH_2=C=O), 536 (100, M–2AcOH), 492 (41) 481 (40), 476 (M–3AcOH)), 432 (39), 421 (26), 416 (8, M–4AcOH), 396 (31), 329 (82), 324 (37), 282 (62), 273 (62), 269 (87), 251 (51), 225 (40), 213 (82), 209 (82), 191 (62), 164 (62), 153 (72), 135 (98).

Acknowledgements

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[1] W. Zopf, Liebigs Ann. Chem. **336,** 46 (1904).

[2] W. B. Turner, D. C. Aldrige, Fungal Metabolites. Academic Press, London, New York (1983).