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Phenarctin, a Fully Substituted Depside from *Nephroma arcticum* *

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On the basis of physical data formula *2* is suggested for phenarctin.

Nephroma arcticum (L.) Torss. is a foliose lichen, fairly common in Norway. It has been investigated by Hesse [1] and by Zopf [2] who reported the presence of usnic acid, zeorin, and a substance named nephrin. Recently Nuno *et al.*[3] isolated a depside to which they gave the name nephroarctin and the structure (*1*). An investigation of *N. arcticum* had been undertaken in this laboratory also, and the same substance had been found. The physical data are in agreement with those reported by Nuno *et al.*, and the same conclusions had been drawn from them. However, the distinction between the various possibilities for the "A-fragment" was achieved by a synthetic study of the possible *m*-methoxytrimethylphenols.

In contrast to the common depsides nephroarctin was very resistant to alkaline hydrolysis, and was not attacked by methoxylate ion in methanol at room temperature (72 h). Refluxing 50 % aqueous potassium hydroxide nevertheless afforded a sufficient amount of degradation products to permit identification of the two main fragments. One substance was 2,4-diformyl-3,5-dihydroxytoluene (*3*) identical with a synthetic [4] sample. The other substance was identical with 3-methoxy-2,5,6-trimethylphenol(*4*),[5] confirming the conclusion of Nuno *et al.*[3]

By chromatography a further substance, m.p. 167 – 168°, was isolated from the lichen. NMR (Table 1) and mass spectral data (Table 2) indicated that it might be a carboxylic derivative of nephroarctin. The methoxyl signal in the NMR spectrum *a priori* could be due to either an ester or an ether grouping. The position of the new hydroxylic proton in the NMR spectrum (see Table 1) does not allow a distinction between a hydrogen bonded hydroxyl group and a carboxylic acid. The fact that the mass spectrum of phenarctin contains the fragments *m/e* 210 ($C_{11}H_{14}O_4$) and 178 ($C_{10}H_{10}O_3$) indicating loss of CH_4O,

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Table 1. NMR values for $CDCl_3$ of various substances, δ ppm. [a] Data from Ref. 3; [b] isolated; [c] synthetic; [d] *cf.* Ref. 5. Figures in parentheses give the number of methyl groups if more than one.

Subst.		Ar–CH_3			–O–CH_3	–O–CH_2–		Ar–H	Ar–C(H)=O			OH	
1	a	2.11(2)	2.28	2.73	3.80			6.61	10.18	10.33		13.43	13.79
	b	2.12(2)	2.28	2.73	3.83			6.62	10.18	10.33		13.40	13.78
2	b	2.15(2)	2.43	2.70		3.95			10.13	10.28	10.93	13.42	13.77
3	b			2.55				6.27	10.05	10.30		12.65	13.55
	c			2.55				6.33	10.10	10.32		12.70	13.60
4	b	2.08(2)	2.23		3.76			6.29			4.60		
	c,d	2.10(2)	2.25		3.78			6.35			4.66		
5	c,d	2.12	2.16(2)		3.68			6.41			4.74		
6	c,d			2.56		3.95			10.19	10.33		13.15	13.75
9	c,d	2.16(2)	2.42		3.70	3.95					11.00		
10	c,d	2.12	2.15(2)		3.73	3.90					5.04		
11	c,d	2.18(2)	2.44			3.96	4.80						
12	c,d		2.20(3)		3.76	3.95	4.78						

Table 2. Some mass spectral data.

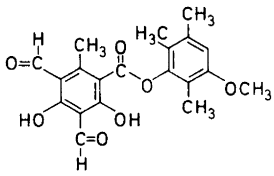
Subst.	Found	RI (%)	Calc.	Formula	
	372.124	(6)	372.1209	$C_{20}H_{20}O_7$	
	207.0826	(30)	207.0293	$C_{10}H_7O_5$	
1	166.0988	(100)	166.0994	$C_{10}H_{14}O_2$	166 → 151
	151.0759	(20)	151.0759	$C_9H_{11}O_2$	
	416.1107	(5)	416.1107	$C_{21}H_{20}O_9$	
	210.0887	(60)	210.0892	$C_{11}H_{14}O_4$	
2	207.0286	(75)	207.0293	$C_{10}H_7O_5$	
	178.0630	(100)	178.0630	$C_{10}H_{10}O_3$	178 → 150
	150.0680	(70)	150.0681	$C_9H_{10}O_2$	
	180.0428	(100)	180.0423	$C_9H_8O_4$	180 → 152
	152.0472	(93)	152.0473	$C_8H_8O_3$	152 → 134
	151.0397	(70)	151.0395	$C_8H_7O_3$	151 → 133
3	134.0368	(2)	134.0368	$C_8H_6O_2$	134 → 106
	133.0289	(4)	133.0290	$C_8H_5O_2$	
	106.0418	(14)	106.0419	C_7H_6O	

might be taken to suggest the presence of a methyl ester. However, it was felt desirable to obtain additional evidence. This was achieved by solvent induced shift.[6] In benzene solution the signal from the methoxy group was found at δ 3.40, corresponding to a large Δ-value of 0.52 [$\Delta = \delta(CDCl_3) - \delta(\text{benzene})$], too large for a methoxyl group flanked by two *ortho* substituents (*cf.* Table 3).

It was concluded that the new substance, for which the name phenarctin is suggested, could have the constitution *2*. Again this was supported by a

Table 3. Some NMR data in benzene and [$\Delta = \delta(CDCl_3) - \delta(\text{benzene})$] (*cf.* also Table 1).

Subst.	$-OCH_3$		Δ		$-O-CH_2-$	Δ
1	3.40		0.43			
2	3.43		0.52			
5	3.40		0.28			
9	3.36	3.42	0.34	0.53		
			or			
			0.28	0.59		
10	3.63		0.10	0.27		
11	3.38		0.58		4.58	0.22
12	3.62	3.66	0.14	0.29	4.54	0.24
			or			
			0.10	0.33		



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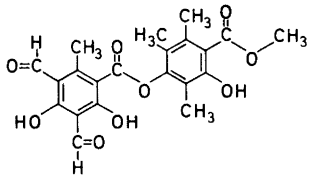

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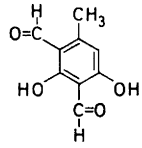

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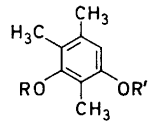
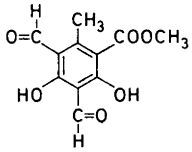


4. R = H, R' = CH_3
5. R = CH_3, R' = H



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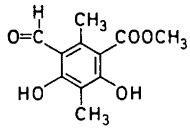

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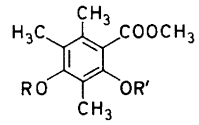
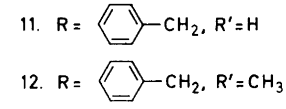
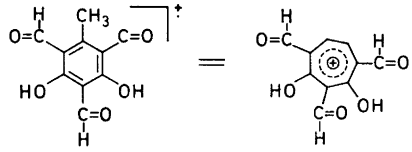


8. R = R' = H
9. R = CH_3, R' = H
10. R = H, R' = CH_3



11. R = $C_6H_5CH_2$, R' = H
12. R = $C_6H_5CH_2$, R' = CH_3



13

study of the compounds *6* and *9*.[5] It will be seen (Table 1) that the NMR signals match quite well. It will be noticed that the signal related to the methyl group of the aldehyde portion of the phenyl esters *1* and *2* occurs in the same narrow range as the corresponding methyl signal of the methyl ester *7*, but at slightly lower field compared with the methyl ester *6*.

Table 4. UV absorption data, in ethanol if not stated, and carbonyl frequencies in cm^{-1}. [a], isolated; [b], synthetic; [c], in hexane; [d], shoulder.

Subst.	λ_{max}	λ_{min}	$\lambda_{infl.}$	ε	CO
	3790			3 500	
		3600		3 000	1740
	3150			10 000	1630
1[a]		3015		8 500	
	2810			12 500	
			2590	9 500	
	2380			6 500	
	3765			10 500	1750
		3590		10 000	1655*d*
	3135			29 500	1630
2[a]		2990		26 500	
	2830			29 000	
		2710		28 500	
	2540			31 000	
		2355		22 000	
	3455			8 500	
		3135		3 500	1655*d*
3[a,c]			2720	22 000	1635
	2595			32 500	
		2235		1 570	
	3455			9 000	
		3135		4 500	1655*d*
3[b,c]			2720	23 000	1630
	2595			33 500	
		2235		1 640	
	3440			6 500	
		3150		4 500	
3[b]			2720	19 500	
	2610			24 000	
		2270		2 000	
	2910			1 070	
		2900		1 060	
4[a]	2780			1 100	
		2750		1 040	
	2735			1 050	
		2500		210	
	2920			908	
		2910		900	
	2785			930	
4[b]		2755		880	
	2740			895	
		2500		235	

In Table 1 are found also the NMR data of the degradation products *3* and *4*, and those of their synthetic counterparts.

Table 4 contains the UV data and carbonyl frequencies in the IR of the compounds.

The mass spectra of nephroarctin and phenarctin (Table 2) indicate that they mainly split off the aldehyde portion as a neutral fragment, the charge remaining predominantly with the fragments corresponding to the molecular ions of *4* and *8*, respectively, the fragmentations of which (*cf.* also Ref. 5) dominate the spectra. To a minor extent the charge seems to be retained by an apparently energetically favourable fragment, possibly (*13*).

EXPERIMENTAL

M.p.'s are uncorrected. Mixed m.p. determinations were done by observing the m.p.'s of the two substances and their mixture at the same time. Petroleum ether refers to a fraction of b.r. 40 – 50°, whilst petroleum refers to one of b.r. 60 – 70°. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer in potassium bromide discs. Ultraviolet spectra were measured in ethanolic solutions, unless specified, with a Coleman-Hitachi Model 124 spectrometer. NMR spectra were run on a Varian A-60A instrument in deuterochloroform solutions, unless specified. Signals stated to be due to OH were shown to disappear on exchange with deuterium oxide.

Air dried *Nephroma arcticum* (217 g) collected in the Oppdal region, south of Trondheim, was extracted in a Soxhlet apparatus for 45 h. On concentrating the filtered extract a total of 6.5 g of a mixture of substances were obtained. Treatment with benzene left 1.0 g undissolved. This appeared to be a mixture of zeorin [1,2] and arabitol.[7] The dissolved material was chromatographed (Mr. Jan Øveraas) on a column prepared from 650 g of silica gel and 1 l of 0.5 N oxalic acid and dried at 105°, each fraction = retention volume = 950 ml. The first two fractions eluted with benzene contained traces of material, whilst the next two each contained 0.3 g, which was shown to be (+)-usnic acid, $[\alpha]_D + 438°$ (*c*, 1.98 in chloroform, 1 dm tube). Fractions 5 and 6 each contained 1.3 g, and on crystallisation from acetone they afforded nephroarctin, m.p. 200 – 201°. The next three fractions, eluted with benzene-chloroform 9 : 1, contained 1.0, 0.2, and 0.1 g, respectively. The last of these three fractions was a mixture, whilst the two others appeared fairly pure. Crystallisations from acetone furnished 0.6 g of *phenarctin*, m.p. 167 – 168°. M^+, see Table 2.

Alkaline degradation of nephroarctin. Nephroarctin (1 g) was refluxed for 4 h with potassium hydroxide (150 g) in water (150 ml). After acidification with sulphuric acid organic material was extracted with ether. The ether solution was concentrated to about 100 ml, and petroleum (200 ml) was added. Solvent was distilled off until 25 ml remained, when a further 100 ml of petroleum were added. On cooling a precipitate appeared (615 mg) whilst 315 mg remained in solution. The precipitated material was unchanged starting material by m.p. and mixed m.p.

The dissolved material was chromatographed on silica gel (30 g) and oxalic acid, prepared as above. Elution with petroleum-benzene 1 : 1 (each fraction = retention volume) afforded 8 mg in the two first fractions, whilst the next four contained 25, 83, 46, and 34 mg, respectively. Thin layer chromatograms of these four fractions on oxalic acid coated silica gel [8] in benzene-chloroform 1 : 1 and with a modified anisaldehyde spraying agent [9] contained only one spot. The four fractions, therefore, were combined and crystallised from petroleum ether. The crystalline material, however, melted over a wide range. It was possible to separate manually two sorts of crystals, one "light" and one "dense". The former was crystallised from carbon tetrachloride to m.p. 123 – 124°, identical with 2,4-diformyl-3,5-dihydroxytoluene [4] (*3*) (m.p. and mixed m.p., UV and IR, NMR and mass spectra); the latter crystallised from petroleum ether, m.p. 71 – 72°, and was identical with 3-methoxy-2,5,6-trimethylphenol [5] (*4*) by the same criteria.

When the pure degradation compounds became available, it appeared that 2,4-diformyl-3,5-dihydroxytoluene did not give a colour with the spraying agent.

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