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IRIDOIDS. I. HARPAGIDE ACETATE FROM MELITTIS MELISSOPHYLLUM (+)

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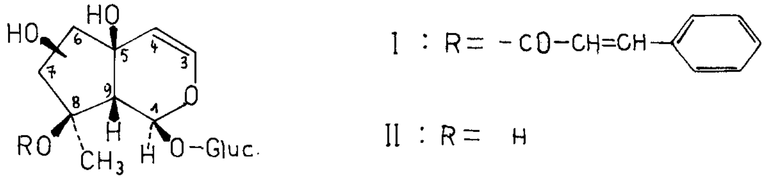
The structure of harpagoside (I), a cinnamic ester of harpagide (II), isolated from Harpagophytum procumbens, has recently been established by Lichti and von Wartburg (1).



In this structure the position of the secondary OH, which could be either on C_6 or on C_7, was not assigned.

We have now isolated two iridoid substances from Melittis melissophyllum, one of which, $C_{15}H_{24}O_{10}$, has been identified as harpagide (II), by direct comparison with an authentic sample(++) (by chromatography and NMR spectroscopy).

In this note we wish to give evidence that the second substance, isolated from Melittis m., is 8-O-acetyl-harpagide and that the secondary OH, in compounds (II) and (III), is

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(++) The authors are greatly indebted to Lichti and von Wartburg for providing this sample.

located at C_6.

Compound (III) is a crystalline substance, $C_{17}H_{26}O_{11}$, [m.p. 154-156°; $[\alpha]_D^{17} = -132°$ (CH_3OH)]. It contains an acetoxyl group, as shown by acetyl group quantitative determination and by the presence of a NMR signal at 2.07 ppm.

Compound (III) is converted into harpagide (II) by alkaline hydrolysis. This fact, coupled with foregoing data, indicates that (III) in an O-acetyl-harpagide.

The position of the acetoxyl group is revealed by a comparison of the NMR spectra of(II) and (III) (measured in D_2O at 60 Mc, internal reference sodium 2,2-dimethyl-2-silapen=tane-5-sulfonate).

The signals of the methyl protons at C_8 and of the neighbouring protons at $C_9$and C_1, which lie at 1.27, 2.58, 5.75 ppm respectively in (II), are displaced to 1.45, 2.88 and 6.11 ppm respectively in (III). This indicates that the acetoxyl group is located at C_8. Also L. and von W. reported that the C_8 methyl peak is at lower field in (I) then in (II), due to the presence of the cinnamoyl group at C_8.

Periodic acid oxidation(+) of (III), made in order to assign the position of the secondary OH, led to a crystalline, water insoluble substance (IV), $C_9H_8O_3$, (m.p. 95-96° subl.)(++).

This compound is a phenolic aldehyde, as shown by its chemical properties and UV - Vis. spectrum

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(+) The oxidation was carried out at room temperature with an aqueous solution of $NaIO_4$ (M/10, pH 5.0).

(++) More than five molecules (5.3-5.5) were used up in the process, instead of the expected three (for OH on C_6) or two (for OH on C_7).

In HCl N/10 λ_{max} (m μ)		In NaOH N/10 λ_{max} (m μ)	
202	10,000	220	22,700
244	28,600	242	21,400
346	6,400	269	8,600
-	-	414	10,900

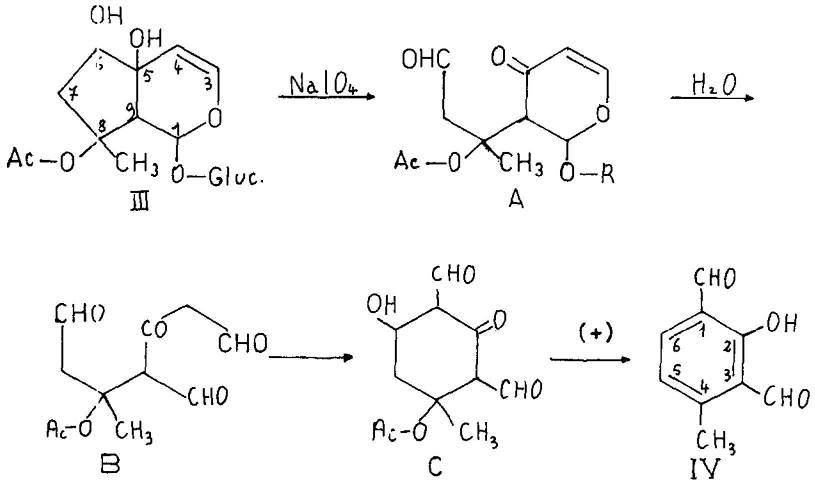
Details of the NMR spectrum of (IV), measured in $CDCl_3$ at 60 Mc (internal reference TMS) are given in table I

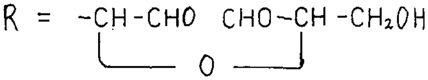
TABLE I

Chemical Shift (δ)	Molteplicity and J	Relative Intensity	Assignment
2.66	1	3	$C\underline{H}_3$ (C_4)
6.84	2 (8 cps)	1	H (C_5)
7.83	2 (8 cps)	1	H (C_6)
10.23	1	1	$C\underline{H}O$ (C_1,C_3)
10.43	1	1	
12.30	1	1	$O\underline{H}$ (C_2)

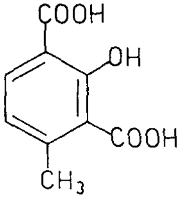
The four substituents on the aromatic ring (CH_3, CHO, CHO, OH) are all vicinal, as is shown by the two doublets, with J = 8 cps, corresponding to two ortho aromatic protons. The signal at 12.30, that disappears on deuteration, is a sharp singlet lying at very low field. This indicates that the hydroxyl group is intramolecularly hydrogen-bonded to one of the aldehyde groups. The resonance of the methyl protons also lies at rather low field through the presence of an ortho aldehyde group.

Formation of (IV) from (III) may proceed by the following postulated reaction-path, as seems likely seeing the ease of hydrolysis of β-ketoenolethers.




$$R = \underbrace{-CH-CHO \quad CHO-CH}_{O}-CH_2OH$$

Structure (IV) was ascertained by oxydizing the substance with Ag_2O to the dicarboxylic acid (V) and by comparing (V) with a synthesized (2) sample.



V

(+) Elimination of acetic acid, postulated during the last stage, might occur from the intermediates A or B instead.

Periodic oxidation of harpagide (II) also led to the dialdehyde (IV).

Formation of (IV) from (III) shows that cyclopentane ring cleavage occurs between C_5 and C_6, and consequently that the secondary OH is attached at C_6. At the same time these results prove that the hydroxyls on C_5 and C_6 are not acetylated(+), in accordance with the spectroscopic evidence of the presence of an acetyl group on C_8.

Melting points are uncorrect. UV and Vis. spectra are determined with an Infracord 137 UV spectrometer (Perkin Elmer), NMR spectra with a Varian A 60 instrument.

REFERENCES

(1) H.Lichti and A. von Wartburg, Tetrahedron Letters, **15**, 835 (1964

(2) V.Prelog, O.Metzler and O.Jeger, Helv., **30**, 675 (1947)

(+) A sample of (III), in an aqueous solution of NaH_2PO_4 (m/5, pH 4,7) was completely unchanged after 12 hours at room temperature. This result excludes the possibility that the periodate solution (pH 5.0) could have hydrolyzed the acetyl group before the cleavage of cyclopentane ring.