Tetrahedron Letters No. 42, pp 4189 - 4192, 1973. Pergamon Press. Printed in Great Britain.

CUSPIDIOL: A NEW MONOMERIC PHENYL PROPANOID

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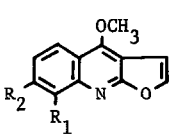
(Received in Japan 9 July 1973; received in UK for publication 11 September 1973)

As a part of our study on the alkaloids of Rutaceous Plants,[1] we have now examined the Formosan species, *Xanthoxylum cuspidatum* Champ (*Fagara cuspidata* Engl.). From the heart-wood, we isolated a new "C_6-C_3 unit", product (1), having an isoprenoid residue as an ether group (0.0408 %) together with β-sitosterol (2) (0.0068 %), γ-fagarine (3) (0.0212 %), skimmianine (4) (0.0067 %), dictamnine (5) (0.0067 %), and nitidine (6) (0.0052 % as chloride). We wish to designate this new compound as cuspidiol and report here its structural elucidation.

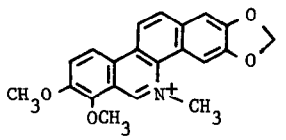


(3): R_1=OCH_3, R_2=H

(4): R_1=R_2=OCH_3

(5): R_1=R_2=H

Scheme 1



(6)

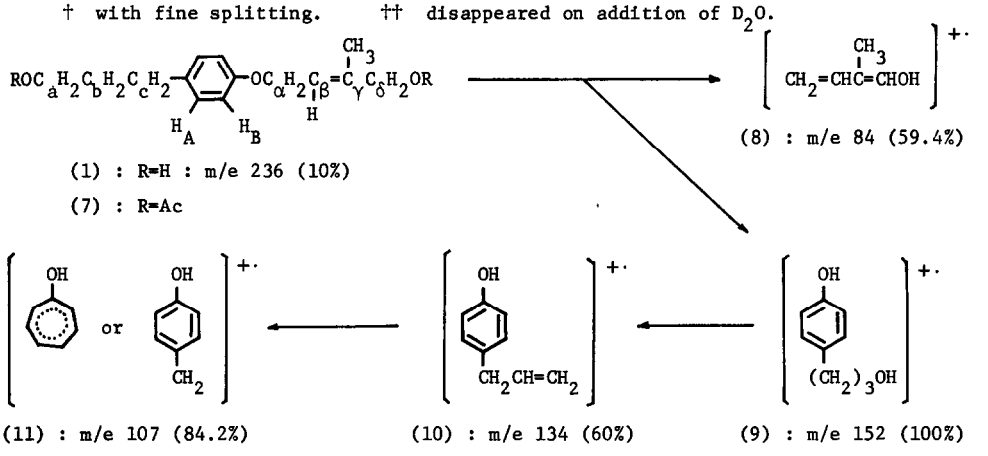
Cuspidiol (1), colorless needles, mp 65-67° (from benzene·ether), $C_{14}H_{20}O_3$* (M^+: at m/e 236), shows the following spectral data: IR ν_{max}^{Nujol} cm^{-1}: 3330, 3270(OH); UV λ_{max}^{EtOH} mμ(log ε): 278.5 (3.42), 286(3.35); NMR: see Table 1. Inspection of the NMR spectrum of (1) allowed us to recognize the existence of the following structural components. A 1,4-disubstituted phenyl ring, deduced from the appearance of A_2B_2 type signals in the aromatic region, and from the UV spectral data of (1): a sequence $-OCH_2CH_2CH_2Ph$, from decoupling experiments in which irradiation at δ 1.86 (C_b-H) caused two 2H triplets at δ 3.61 and 2.62 (C_a-H_2 and C_c-H_2) to change to singlets, and irradiation at either δ 2.62 or 3.61 changed a 2H multiplet at δ 1.86 (C_b-H_2) to a 2H triplet (J=7.5 Hz and J=7.0 Hz, respectively): a partial structure $-OCH_2CH=C(CH_3)CH_2O-$, concluded from other decoupling experiments in which irradiation at 5.74 (C_β-H) caused the 2H doublet at δ 4.54 (C_α-H_2) to collapse to a singlet, and the 3H doublet at δ 1.76 (C_γ-CH_3) to a singlet, and *vice*

* The compound gave satisfactory elemental analysis for the formula given.

Table 1 : NMR and Mass spectra of Cuspidiol (1)

		Cuspidiol (1)	Diacetyl Cuspidiol (7)	Dehydrocuspidiol (12)
$-CH_2CH_2CH_2O-$	C_a-H_2	3.61(t, J=7.0 Hz)	4.07(t, J=7.0 Hz)	3.65(t, J=7.0 Hz)
	C_b-H_2	1.86(m)	1.90(m)	1.86(m)
	C_c-H_2	2.62(t, J=7.5 Hz)	2.63(t, J=7.5 Hz)	2.65(t, J=7.5 Hz)
phenyl	2 x H_A	7.09(d, J=8.5 Hz)	7.08(d, J=8.5 Hz)	7.14(d, J=8.0 Hz)
	2 x H_B	6.79(d, J=8.5 Hz)	6.81(d, J=8.5 Hz)	6.84(d, J=8.0 Hz)
isoprenoid	$C_\alpha-H_2$	4.54(d, J=6.0 Hz)	4.55(d, J=6.0 Hz)	4.45(d, J=6.0 Hz)
	$C_\beta-H$	5.74(t†, J=6.0 Hz)	5.77(t†, J=6.0 Hz)	6.66(t†, J=6.0 Hz)
	$C_\gamma-CH_3$	1.76(d, J= ∿1 Hz)	1.77(d, J=ca 0.5 Hz)	1.83(d, J= ∿1 Hz)
	$C_\delta-H_2$	4.06(s)	4.53(s)	
others		2 x OH: 1.80(2H, s)††	2 x $COCH_3$: 2.05 & 2.08(3H, s)	OH : 1.43(1H, br. s)†† $C_\gamma-C_\delta HO$: 9.47(1H, s)

† with fine splitting. †† disappeared on addition of D_2O.



Scheme 2

versa.

The modes of linkage of these three structural moeties were determined by comparison of the NMR spectrum of (1) with that of diacetyl cuspidiol (7). Acetylation of (1) with Ac_2O-pyridine at room temperature for 24 hr. gave diacetyl cuspidiol (7), colorless oil, bp 150-160° (2 x 10^{-4} mmHg), $C_{18}H_{24}O_5$, which shows no hydroxy absorption band in its IR spectrum ($CHCl_3$) but shows a carbonyl at 1734 cm^{-1}. In the NMR spectrum of (7), a 2H triplet at δ 4.07 (C_a-H_2) and a 2H singlet at δ 4.53 ($C_\delta-H_2$) were observed at a field lower by 46-47 cps than the corresponding

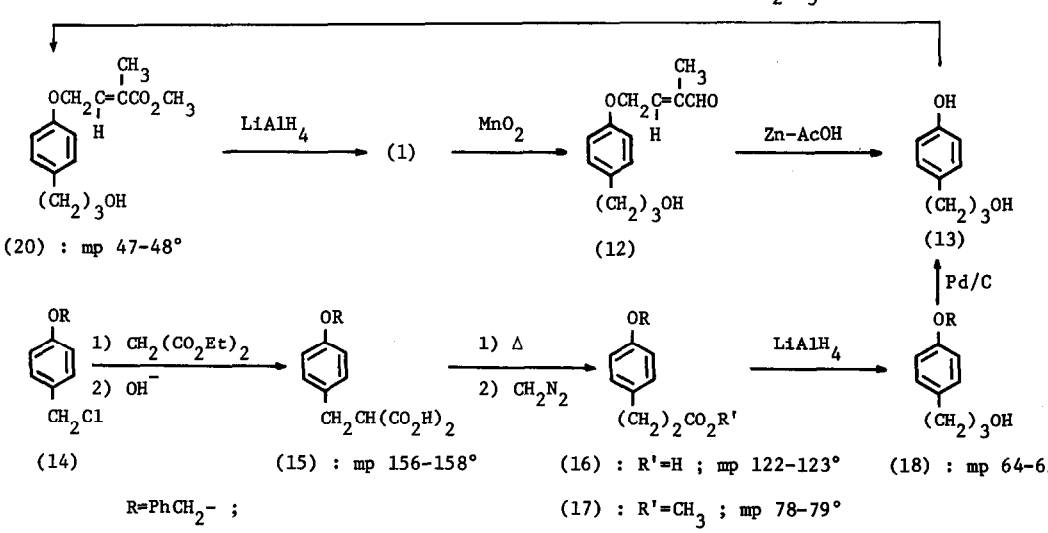
signals of (1). These data indicate that the oxygen atoms at the C_a and C_δ positions exist as primary alcohols. In other words, the oxygen atom at the C_α position can be allocated to an ether linkage at which the isoprenoid unit is connected with the phenyl propanoid unit. This formulation is also supported by the fact that the mass spectrum of (1) can be reasonably explained by the fragmentation pathway from this structure shown in Scheme 2.

This conclusion deduced from the spectral data was confirmed by the following chemical means. Oxidation of (1) in $CHCl_3$ with active MnO_2 gave an α,β-unsaturated ketone, dehydrocuspidiol (12), colorless oil, bp 130-135° (1.9×10^{-4} mmHg), $C_{14}H_{18}O_3$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620(OH), 1693(C=O). This experiment gave proof of the presence of an allylic alcohol group in the structure of (1). Treatment of (12) with zinc dust in acetic acid afforded dihydro-p-coumaryl alcohol[2] (13) which was identified with a synthetic specimen prepared from p-benzyloxybenzyl chloride[3] (14). (Scheme 3). Such a degradation under the above conditions can be rationalized only as transformation of a vinylogous derivative of an α-aryloxycarbonyl group.

Finally, in order to confirm the configuration about a double bond of (1), an NOE experiment and a total synthesis of (1) were attempted. In the NMR spectrum of (1), an increase (15 %) of integration of the olefinic proton (C_β-H) was observed on irradiation at δ 4.06 (C_δ-H) but not by irradiation at δ 1.76 (C_γ-CH_3). Furthermore, treatment of (13) with methyl 4-bromo-2-methylcrotonate[4] (19) gave an aryloxy ester (20), colorless needles, mp 47-48°, bp 130-135° (1.9×10^{-4} mmHg), $C_{15}H_{20}O_4$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3680, 3615(OH), 1718(C=O), NMR ($CDCl_3$) δ: 1.59(1H, s, OH)††,

Scheme 3

methyl 4-bromo-2-methylcrotonate (19) in acetone with K_2CO_3



1.85(2H, m, CH_2), 1.92(3H, d, J=1.0 Hz, vinyl CH_3), 2.66(2H, t, J=7.5 Hz, $ArCH_2CH_2$), 3.66(2H, t, J=7.0 Hz, $-CH_2CH_2OH$), 3.77(3H, s, CO_2CH_3), 4.68(2H, d, J=5.5 Hz, $-C=CHCH_2OAr$), 6.91(1H, t, J=5.5 Hz, olefinic H), 6.78(1H, d, J=8.0 Hz, aromatic H), 7.15(1H, d, J=8.0 Hz, aromatic H). Since the (E)-configuration of methyl 4-bromo-2-methylcrotonate (19) has been confirmed by its use in syntheses of crocetin[4b] and zeatin[4c], we may safely assign the structure of the aryloxy ester (20) to (E)-methyl 4-[p-(3-hydroxypropyl)phenoxy]-2-methylcrotonate. Reduction of the aryloxy ester (20) with $LiAlH_4$ then gave cuspidiol (1), which was idnetified with the natural specimen by comparison of IR spectra and by mixed melting point. These results conclusively indicate the (E)-configuration of cuspidiol.

Consequently, we can depict the structure of cuspidiol as the structural formula (1).

In 1966, Oksanen[5] claimed the presence of dihydro-p-coumaryl alcohol itself with p-coumaryl alcohol in *Pynus sylvestris*. As far as we know, this is the only report of the natural occurrence of a monomeric phenyl propanoid as the dihydro-p-coumaryl alcohol. Therefore, it is important that our result shows the presence of another monomeric derivative of dihydro-p-coumaryl alcohol in nature.

Acknowledgement: We express our sincere thanks to Prof. Sheng-Teh Lu, Kaohsing Medical College, Taiwan, for providing convenience for our research.

References

1. Preceeding papers: Part XIX, H. Ishii, H. Ohida and J. Haginiwa, Yakugaku Zasshi, 92, 118 (1972). H. Ishii and K. Hosoya, Chem. Pharm. Bull. (Tokyo), 20, 860(1972). H. Ishii, T. Ishikawa, H. Sekiguchi and K. Hosoya, *ibid.*, in press.
2. I. A. Pearl, J. Org. Chem., 24, 736(1959).
3. R. S. Shelton, M. G. Van Campen, Jr., D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen and K. K. Wyckoff, J. Am. Chem. Soc., 75, 5491(1953).
4. a) A. Löffler, R. J. Pratt, H. P. Rüesch and A. S. Dreiding, Helv. Chim. Acta, 53, 383(1970). b) R. S. Ratney and J. English, J. Org. Chem., 25, 2213(1960). c) G. Shaw, B. M. Smallwood and D. V. Wilson, J. Chem. Soc., 1966, 921.
5. H. Oksanen, Soumen Kemistilehti, B39(3), 56(1966). [Chem. Abstr., 65, 5876d(1966)].