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STRUCTURE OF THE FURTHER NORDITERPENOIDS OF PODOCARPUS MACROPHYLLUS. INUMAKILACTONE A GLUCOSIDE, A PLANT GROWTH INHIBITOR AND INUMAKILACTONE E

Teruo Hayashi and Hiroshi Kakisawa*

Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo

Shô Itô

Department of Chemistry, Tohoku University, Sendai, Japan

Yuh Pan Chen and Hong-Yen Hsü

Bristol Research Institute of Taiwan, Chung Ching South Road, Taipei, Taiwan

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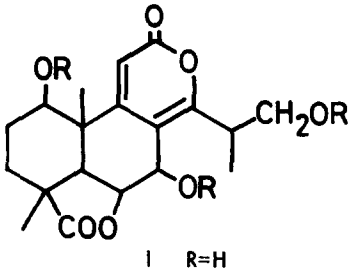
Podocarpus species is known to produce nor- and bisnor-diterpenoid lactones (1-5), some of which are potent inhibitors of expansion and mitosis of plant cells (3, 5, 6). We have isolated two more new compounds of this type, inumakilactone E (7) and inumakilactone A glucoside, from the stem of Podocarpus macrophyllus D. Don, together with inumakilactone A (1a) and nagilactones C (2a) and F (8). The present communication deals with the structure determination of these new compounds to which we assigned structures I and VII, respectively.

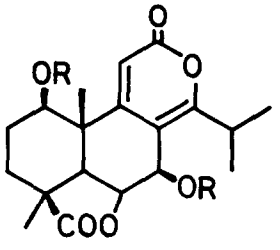
The i.r. and u.v. spectra of I, $C_{19}H_{24}O_7$, m.p. 220-225°, show the presence of an α-pyrone [λmax (EtOH), 300 nm (ε 5600); ν_{max} (KBr), 1685, 1620 and 1535 cm^{-1}], a γ-lactone [ν_{max} (KBr), 1770 cm^{-1}] and hydroxyl groups [ν_{max} (KBr), 3400 and 3200 cm^{-1}]; very similar spectral properties to those of nagilactone A (III) (2a). The presence of three hydroxyl groups in the molecule, suggested by the molecular formula was verified when I with acetic anhydride and pyridine afforded the triacetate (II), $C_{25}H_{30}O_{10}$, M^+ 490.191, calcd. 490.184, with no hydroxyl group. The n.m.r. spectrum (TABLE) of II is very similar with that of nagilactone A diacetate (IV) (2a), revealing their structural resemblance. Significant differences are seen only in the signals due to the side chains: Methyl signals of the isopropyl group, which always appear as two doublets (2a) in the spectra of derivatives of III, are displaced in the spectrum of II by a three-proton

doublet at δ 1.25 and a two-proton multiplet at δ 4.15. Thence the presence of the group CH_3-$\overset{1}{C}$H-CH_2-OAc is evident. The large up-field shift (Δδ 1.42 ppm) of H_{11} upon acetylation indicates the presence of a hydroxyl group at C_1 in I. From these physical evidences the structure I was assigned to inumakilactone E.

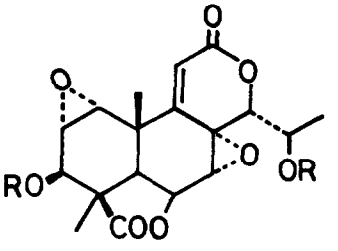
Inumakilactone A glucoside (VII), $C_{24}H_{30}O_{13}$, m.p. 296-300°, has the following spectral properties: ν (KBr), 3450, 3350, 1780, 1710 and 1640 cm^{-1}; λmax (EtOH), 222 nm (ε 9500), revealing the presence of hydroxyl, γ-lactone and α,β-unsaturated δ-lactone groupings. VII gave on acetylation the pentaacetate (VIII), $C_{34}H_{40}O_{18}$, m.p. 146°, M^+ 736, and on mild hydrolysis with 5%-HCl, glucose (identified by paper chromatography) and the hydrochloride IX, $C_{18}H_{21}O_8Cl$, m.p. 254-255°, which was identical with the compound obtained from inumakilactoneA (V) by the same reaction. These chemical evidences and detailed n.m.r. analyses (see TABLE) revealed that VII was a glucoside of V. The location of the glucosidyl residue was deduced also from the n.m.r. spectral analysis. Although the spectrum of VIII is very similar to that of inumakilactone A diacetate (VI), major difference is seen in the chemical shifts of H_{15}, Me_{16} and H_7 (TABLE), in addition to the signals of glucose group, suggesting glucosidyl at C_{15}. The large coupling



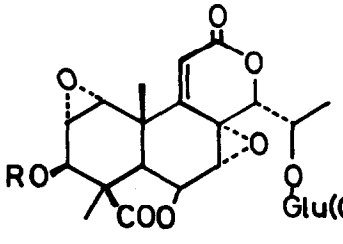
I R=H
II R=Ac



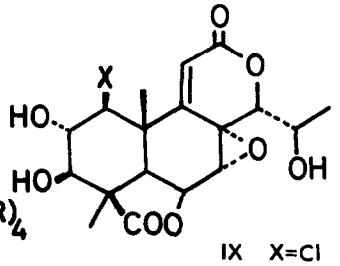
III R=H
IV R=Ac



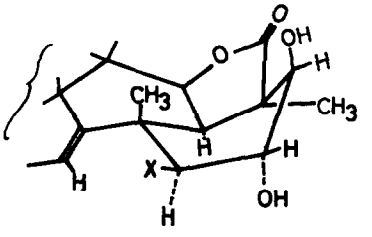
V R=H
VI R=Ac



VII R=H
VIII R=Ac



IX X=Cl
X X=Br
XI X=OH



A

TABLE. N.m.r. Spectra of Pertinent Inumakilactones and their Derivatives*1

Comp.	II	IV	V	VII	VI	VIII	IX	X	XI
Solv.	$CDCl_3$	$CDCl_3$	Py	Py	$CDCl_3$	$CDCl_3$	Py	Py	Py
Me_{18}	1.45	1.45	1.53	1.50	1.52	1.53	1.60	1.66	1.63
Me_{20}	1.30	1.33	1.40	1.35	1.13	1.15	1.95	2.04	1.92
Me_{16} (Me_{17})	1.25d (8.0)	1.21d (7.0) 1.24d (7.0)	1.56d (6.5)	1.57d (6.0)	1.41d (6.3)	1.33d (6.0)	1.53d (6.0)	1.57d (6.0)	1.59d (6.5)
H_1	5.05m	5.10m	3.62d (4.0)	3.62d (4.0)	3.48*2	3.46*2	4.95d (3.0)	5.03d (2.5)	4.65br*2
H_2	*3	*3	3.51dd (4.0,6.0)	3.52dd (4.0,6.0)	3.45*2	3.44*2	4.67dd (5.0, 3.0)	4.75br	4.65br*2
H_3	*3	*3	4.65d (6.0)	4.65d (6.0)	5.46m	5.45m	4.31d (5.0)	4.40br	4.40br
H_5	1.87d (5.0)	1.89d (6.0)	2.13d (5.5)	2.10d (5.0)	2.07d (4.8)	2.00d (5.0)	2.73d (4.5)	2.70d (4.5)	2.83d (4.5)
H_6	5.05m	5.05dd (9.2,6.0)	5.08*2	*4	4.86dd (4.8,1.3)	4.85dd (5.0,1.0)	5.33dd (4.5,1.5)	5.32dd (4.5,1.5)	5.31dd (4.5,1.5)
H_7	6.25d (10.0)	6.35d (9.2)	5.08*2	*4	3.99d (1.3)	4.74d (1.0)	5.15d (1.5)	5.16d (1.5)	5.16d (1.5)
H_{11}	5.90	5.83	6.73	6.70	6.40	6.35	6.52	6.60	6.75
H_{14}	——	——	4.72d (8.5)	4.52d (10.0)	4.78d (4.9)	4.40d (8.0)	4.73d (8.5)	4.73d (8.5)	4.74d (8.5)
H_{15}	3.22m	2.97sept (7.0)	4.13m	*3	4.97d,q (4.9,6.3)	4.06d,q (8.0,6.0)	4.35d,q (8.5,6.0)	4.40br	4.40br
H_{17}	4.15m	——	——	——	——	——	——	——	——
CH_3CO	2.00 2.16 2.20	2.12 2.14			2.06 2.12	2.00, 2.02 2.03, 2.10 2.15			

*1 Expressed in ppm from TMS. Numbers without signal multiplicity (d, t, m, etc.) are singlets. Numbers in parentheses denote coupling constants.

*2 Chemical shifts are approximate because of overlapping.

*3 Unassignable.

*4 The signal overlaps with that of water.

constant (J=8, at 4.64 ppm in $CDCl_3$) of H_1 of glucose residue of VIII discloses the axial nature of the anomeric hydrogen. Thus, VII was concluded as inumakilactone A 15β-glucoside. VII was shown to be a potent inhibitor of the expansion and division of plant cells (9).

The structure of IX mentioned above was determined on the comparisons of its n.m.r. data with the corresponding derivatives X and XI, prepared from V by HBr and 1N-H_2SO_4 treatments, respectively. As seen in TABLE, the chemical shift of H_{11} as well as of Me_{20} in these compounds vary significantly; the fact only explicable by the presence of halogen atoms at C_1, hence the assignment of H_1. Since the original configurations in V should be retained at C_2 and C_3, H_2 and H_3 should be trans (H_2=β, H_3=α). While the magnitude of $J_{2,3}$(=5 Hz) is only interpretable by the ring A of a twisted boat conformation, that of $J_{1,2}$(=2.5-3 Hz) reveals H_1 to be α (axial)-orientation when a trans opening of an epoxide is taken into consideration. Thus the n.m.r. data can be reconciled when the compounds IX and X have 1β-halo-2α,3β-dihydroxy structure with the ring A in a twisted boat conformation as shown in A (10).

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7) The compound previously designated as inumakilactone D (S. Itô and M. Kodama, Kagaku no Ryoiki, Special Publication, 86, Nankodo, 1968) is identical with ponalactone (5).

8) Private communication from Dr. Y. Hayashi, Osaka City University.

9) The biological activity test was carried out by courtesy of Dr. M.N. Galbraith at the Division of Applied Chemistry, C.S.I.R.O. to whom our sincere thanks are due. For method, see (3a) and (6).

10) Inumakilactone C (2) also undergoes the epoxide ring cleavage with acids. N.m.r. analysis revealed the same part structure A in the products. M. Sunagawa, M.Sc. Thesis, Tohoku University, 1968.