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STRUCTURE OF INUMAKILACTONE A, A BISNORDITERPENOID

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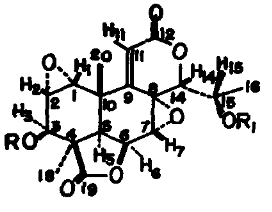
Inumakilactone A is a bitter principle first isolated (1,2) by one of us (T. T.) from the wood of Podocarpus macrophyllus D. Don (Japanese name: Inumaki) together with the other constituents (3). We have isolated the same compound as the major constituent of seeds of the same plant together with nagilactone C (4) and a few other related compounds, and now wish to provide here the evidence which permits the assignment of the novel bisnorditerpenoid dilactone structure I for this compound.

Constitution Inumakilactone (I) (5) [$C_{18}H_{20}O_8$, m.p. 251-3° (dec.), $[\alpha]_D \pm 0°$, λmax 220 mμ (ε 11000), ν 3460, 1760, 1705, 1640 cm^{-1}] afforded the diacetate (II) (2) [m.p. 263-4° (dec.), ν 1772, 1750-1700 cm^{-1}, no OH absorption, $[\alpha]_D$ +34.7°, $[\theta]_{263}$ -17200] by acetylation with Ac_2O-NaOAc, and, on catalytic hydrogenation (PtO_2), yielded the dihydro derivative (III) (2) [m.p. 260-5°, ν 3460, 1760, 1740 cm^{-1}]. The spectral properties of these compounds confirmed the presence of two hydroxyl groups and a γ-lactone and an α,β-unsaturated-δ-lactone; the remaining two oxygen atoms were attributed to ether linkages.

The NMR spectrum of II (TABLE I), in conjunction with the NMDR experiments (FIG. I) (6), disclosed the arrangement of the hydrogens on C_1-C_2-C_3, C_5-C_6-C_7, C_{14}-C_{15}-C_{16} and C_{11}. The position of the acetoxyl groups at C_3 and C_{15} in II was suggested by the large acetylation shift of H_3 (1.11 ppm) and H_{15} (0.96 ppm) compared to the other hydrogens (TABLE I) and confirmed by the following experiments: The 15-acetate (IV) [m.p. 256-8° (dec.), ν 3510, 1768, 1735, 1715, 1644 cm^{-1}] obtained by mild acetylation of I was oxidized with Jones' reagent to afford the 3-ketone (V) [m.p. 270° (dec.), ν 1797, 1745 sh, 1732, 1650 cm^{-1}] which clearly showed NMR signals due to H_1 and H_2 as a pair of doublets (TABLE I). On the other hand, similar oxidation of the 3-acetate (VI) [m.p. 294-7° (dec.), ν 1757, 1736 sh, 1724, 1640 cm^{-1}] obtained by the mild acid hydrolysis of II, yielded the 15-ketone (VII) [m.p. 215-8° (dec.), ν 1780, 1742, 1722, 1642 cm^{-1}] which exhibited three singlet methyl signals and a singlet due to H_{14} in its NMR spectrum. These experiments also revealed that C_6 and C_{14} are connected with the lactonic oxygens.

Catalytic hydrogenation of II afforded the corresponding dihydro derivative (VIII) [m.p. 247-8° (dec.), ν 1778, 1746 cm^{-1}]. In the NMR spectrum of VIII in $CDCl_3$-benzene,

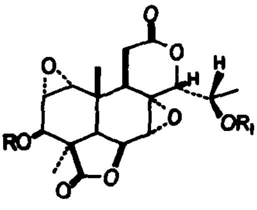


I: R=R$_1$=H

II: R=R$_1$=Ac

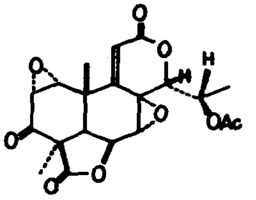
IV: R=H, R$_1$=Ac

VI: R=Ac, R$_1$=H

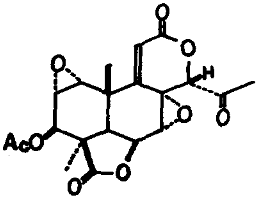


III: R=R$_1$=H

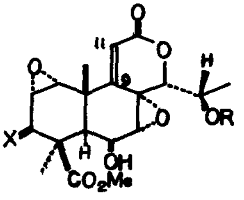
VIII: R=R$_1$=Ac



V



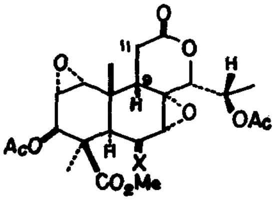
VII



IX: X=βOH, αH, R=H

X: X=βOAc, αH, R=Ac

XIII: X=O, R=Ac



XI: X=βOH, αH

XII: X=O

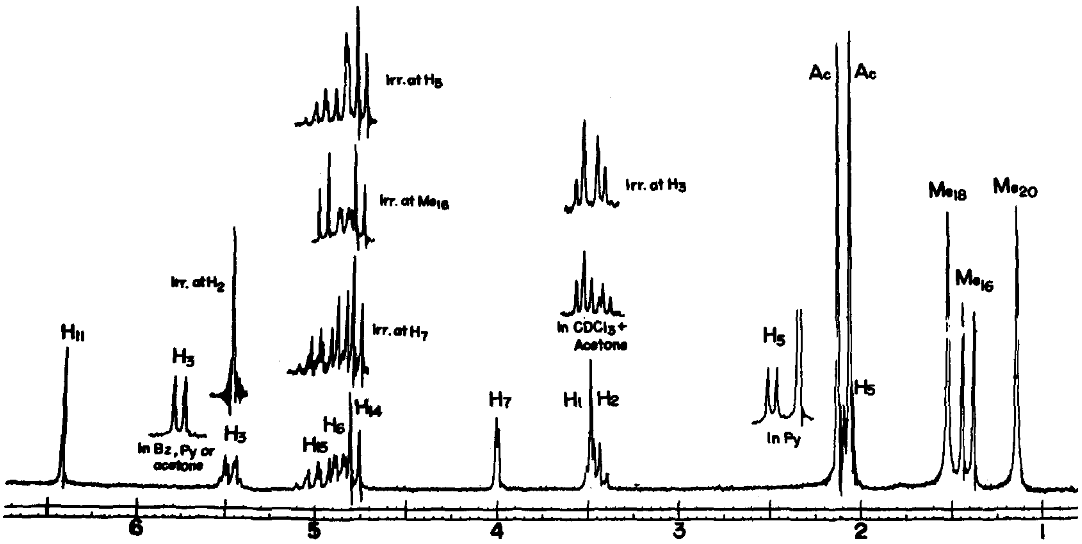


FIG. I. NMR and NMDR Spectra of Inumakilactone A diacetate (II) (100 MHz, CDCl$_3$)

a new proton (H_9) appeared as a doublet of doublets (δ 1.72, J=12.2, 6.2 Hz) coupled only with the C_{11}-methylene (δ 2.34, J=14.8, 12.2 Hz and δ 2.60, J=14.8, 6.2 Hz) indicating both C_8 and C_{10} are quaternary. Since the multiplicity of the H_{14} signal revealed that C_{14} was connected with a quaternary carbon (NMR of II and VII), C_{14} is incorporated in the α,β-unsaturated-δ-lactone part; hence C_6 forms a part of the γ-lactone (7). The chemical shifts and coupling constants of H_1 and H_2 suggested the presence of 1,2-epoxide at C_1 and C_2.

The number of atoms in the part structures established so far in I amounts to $C_{15}H_{20}O_8$ out of the molecular formula, $C_{18}H_{20}O_8$. Since no indication of the presence of a further double bond in I was observed, the presence of three quaternary carbons, one more oxide linkage and two carbocyclic rings are concluded. The two carbocyclic rings must be constructed in such a way to fulfill the following requirements: The chemical shift difference (0.54 ppm) of H_1 in II and VIII means that H_1 must be situated close to and in the same plane as the double bond. Moreover, Me_{20}, H_5, H_7 and H_{14} should be in the proximity of the double bond because they also are subjected to the paramagnetic effect (0.2 ppm or more) of the double bond (NMR of II and VIII). Large up-field shifts (0.64 and 0.81 ppm) of H_7 were observed upon acetylation (VI→II) and oxidation (VI→VII), respectively, of the C_{15}-hydroxyl group indicating the two groups to be in close proximity. The only arrangement of the partial structure which satisfy all of the foregoing evidence is I. The presence of a C_7, C_8-oxide is consistent with the position of the first extremum in the ORD of the keto ester XII described below (8).

Configuration The absolute configuration of the C_7, C_8-epoxide ring was deduced from the Cotton effect in the ORD of the keto ester XII: When I was submitted to alkaline (Na_2CO_3) methanolysis, the γ-lactone opened preferentially to give the trihydroxy ester (IX) [m.p. 259-260° (dec.)], acetylation of which yielded the hydroxy-diacetoxy ester (X) [amorphous, ν^{CHCl_3} 3320, 1733 cm^{-1}]. Catalytic (PtO_2) hydrogenation of X to the dihydro hydroxy ester (XI) [m.p. 265-7°, ν 3390, 1766, 1733, 1689 cm^{-1}] followed by chromic acid oxidation afforded the keto ester (XII) [m.p. 257-9° (dec.), ν 1750-1728 cm^{-1}]. XII displayed a negative Cotton effect ($[\Phi]_{330}^{trough}$ -1180, $[\Phi]_{275}^{peak}$ + 3060) showing the epoxide to have an α-configuration (10). Similar alkaline methanolysis of V yielded, after acetylation, the hydroxy keto ester (XIII) [m.p. 229-230° (dec.), ν 3360, 1735, 1713 cm^{-1}].

As shown in TABLE I, all inumakilactone derivatives with a γ-lactone function have J_{56} equal to 4.6-5.5 Hz, which is in accord with the values (5.5-8 Hz) for cis hydrogens in diterpene lactones of known configuration (trans hydrogens show J=11-13 Hz) (11). In these derivatives J_{67} remains less than 1.5 Hz. The dihedral angle obtained from the molecular model with H_5/H_6 cis suggests $J_{calc.}$=3-4 Hz if H_6/H_7 is cis and $J_{calc.}$=0.7-1.0 Hz if the two hydrogens are trans, the latter figures being in accord with the observed J_{67}. Thus, the configuration of H_5 and H_6 is α. Consequently, the γ-lactone function has β-configuration.

The β-orientation of Me_{20} was established in the following ways: Scale models con-

TABLE I. NMR Signals of Inumakilactone A Derivatives**

Compd No.	Solv.	Me$_{18}$	Me$_{20}$	Me$_{16}$	H$_1$	H$_2$	H$_3$	H$_5$	H$_6$	H$_7$	H$_{11}$	H$_{14}$	H$_{15}$	Ac	MeOCO
I	Py	1.53	1.40	1.56d (6.5)	3.62d (4.0)	3.51dd (4.0,6.0)	4.65d (6.0)	2.13d (5.5)	5.08*	5.08*	6.73s	4.72d (8.5)	4.31m		
II	Py	1.56	1.31	1.53d (6.4)	3.74d (4.0)	3.62dd (6.2,4.0)	5.76d (6.2)	2.27d (5.0)	5.13dd (5.0,1.5)	4.47d (1.5)	6.89s	5.27*	5.27*	1.97 2.12	
	CDCl$_3$	1.52	1.13	1.41d (6.3)	3.48*	3.45*	5.46m	~2.07*	4.86dd (4.8,1.3)	3.99d (1.3)	6.40s	4.78d (4.9)	4.97d,q (4.9,6.3)	2.06 2.12	
IV	CDCl$_3$	1.46	1.23	1.43d (6.2)	3.4-3.6*	3.4-3.6*	4.4-4.6m	~2.02*	~4.93*	4.00 b,s	6.41s	4.75d (5.5)	4.9-5.1*	2.11	
V	CDCl$_3$	1.56	1.00	1.43d (6.2)	3.77d (4.0)	3.68d (4.0)	—	2.66d (5.0)	4.86*	4.03d (~1)	6.45s	4.77d (5.0)	4.8-5.0*	2.08	
	Py	1.66	1.09	1.54d (6.5)	3.77d (4.1)	4.07d (4.1)	—	3.03d (5.0)	5.27dd (5.0,1.5)	4.55d (1.5)	6.96s	~5.35*	~5.3*	2.00	
VI	Py	1.57	1.34	1.58d (6.0)	3.5-3.8*	3.5-3.8*	5.75d (6.0)	2.28d (4.6)	~5.14*	5.11s	6.81s	4.76d (8.5)	4.1-4.5*	2.14	
VII	CDCl$_3$	1.52	1.16	2.40s	3.48*	3.3-3.5*	5.45m	2.04 (5.0)	4.79dd (5.0,1.5)	4.01d (1.5)	6.44s	4.98s	—	2.14	
	Py	1.55	1.29	2.39s	3.77d (4.2)	3.5-3.7*	5.76d (6.2)	2.29d (5.0)	5.12dd (5.0,1.3)	4.30d (1.3)	***	5.53s	—	2.12	
VIII	CDCl$_3$	1.50	0.92	1.38d (6.5)	2.94d (3.9)	3.34dd (6.0,3.9)	5.38d (6.0)	1.85d (5.3)	4.76d (5.3)	3.74s	2.68dd (15.5,11.5) 2.88dd (15.5,7.2)	4.51d (3.5)	4.86d,q (6.5,3.5)	2.04 2.11	
IX	Py	1.79	1.52	1.60d (6.2)	3.6-3.85*	3.6-3.85*	4.94d (2.1)	~1.80*	~4.75*	3.92 b,s	6.64s	4.81d (8.0)	4.2-4.6*		3.69
X	CDCl$_3$	1.28	1.56	1.39d (6.0)	3.41s	3.41s	5.01s	~2.1*	4.48dd (2.5)	3.73d (~2.5)	6.20s	4.76d (4.0)	4.8-5.1*	2.07 2.18	3.79
XI	CDCl$_3$	1.29	1.29	1.37d (6.2)	2.92d (4.0)	3.27d (4.0)	5.00s	***	4.41t (~2)	3.53d (2.1)	2.3-2.9*	4.55d (2.8)	4.86d,q (6.2,2.8)	2.04 2.18	3.78
XII	CDCl$_3$	1.39	1.26	1.36d (6.0)	3.04d (4.0)	3.27dd (4.0,~1)	5.04d (1.0)	2.85s	—	3.51s	2.6-2.9*	4.58d (2.7)	4.73d,q (6.0,2.7)	2.04 2.15	3.68
XIII	CDCl$_3$	1.39	1.73	1.40d	3.51d (3.6)	~3.8*	—	***	4.49b,t (~2)	~3.8*	6.28s	4.80d (4.0)	4.8-5.2*	2.10	3.81

* Chemical shifts are approximate because of serious overlapping. ** Multiplicity of the signals is abbreviated to s, d, dd, t, q, m and b for singlet, doublet, double doublet, triplet, quartet, multiplet and broad. *** Means the signal hidden under the other signals.

structed with a β-orientation of the γ-lactone grouping require the methyl group to be β-axial in order for H_1 to be situated in the plane of the $\Delta^{9,11}$ double bond. This is in accord with the resistance of the 6β-hydroxyl group to acetylation (IX→X, V→XIII), the up-field shift of the Me_{20} signal upon the oxidation of the 6β-hydroxyl group (XI→XII) and the inhibition of ketal formation from XII as was observed by the lack of change in its ORD curve on the addition of acid (12). The large down-field shift of Me_{20} (TABLE I) observed on the cleavage of the γ-lactone (e.g. II→X, V→XIII) can be explained by the anisotropic effect of the γ-lactone ring replaced by that of an ester grouping (which may be freely rotating) and by the creation of a new 1,3-diaxial interaction between the methyl group and 6β-hydroxyl group which was masked as modified acetate in II (13).

The orientation of the oxygen functions on the A-ring was established as follows: Observation of intramolecular hydrogen bonding between the 3-hydroxyl and the γ-lactone carbonyl groups [IV, $\nu_{OH}^{CHCl_3}$ 3534 cm^{-1} (concentration independent), $\nu_{C=O}^{CHCl_3}$ 1740 cm^{-1}, II, $\nu_{C=O}^{CHCl_3}$ 1793 cm^{-1}] and a large nuclear Overhauser effect (14) between Me_{18} and H_3 (17% increase of area) means that H_3 is α-oriented. The axial nature of the 3β-hydroxyl, suggested by the above-mentioned intramolecular hydrogen bonding was supported by the fact that up-field shifts of the Me_{20} signal upon acetylation (IV→II) and oxidation (IV→V) were observed in the derivatives with a γ-lactone, in contrast to the down-field shifts observed by corresponding chemical modifications of the 3β hydroxy-5α steroids (13). The coupling constant J_{23} in the NMR spectra of all compounds with the γ-lactone falls in the range of 6±1 Hz. This large value is markedly decreased to 0~1.0 Hz when the γ-lactone is cleaved (TABLE I). This change can be reconciled only when these lactones have 3β-axial-hydroxy-1,2-α-epoxide structures with the ring A in a twisted boat conformation which changes to a half-chair conformation when the lactone is opened; inspection of models shows that the dihedral angle between H_2 and H_3 changes from ca. 40° to 85° during the conversion of ring A from a twisted boat to a half-chair.

Finally, the stereochemistry at C_{14} and C_{15} was elucidated as follows: α-Orientation of the side chain, suggested by the close proximity of H_7 and the C_{15}-hydroxyl group as described earlier, received further support from the negative Cotton effect (vide supra) of the enelactone chromophore in II, assuming that the side chain has an equatorial orientation (15). The S-configuration for C_{15} was established by the application of the benzoate rule [$[M]_D$+99° for VI and $[M]_D$+226° for its benzoate, m.p. 292-4° (dec.)] (16) and Horeau's asymmetric synthesis (17).

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5) Correct analytical figures were obtained for all compounds described in this paper. UV and IR spectra were refered to methanol solution, and KBr disk, respectively, unless otherwise stated. All $[\alpha]_D$s were measured in pyridine and CD and ORD in methanol.

6) All NMR data are listed in TABLE I. Measurement was carried out at 60 and/or 100 MHz.

7) Of the two possible γ-lactone part-structures, the one involving C_7 in a part of the lactone was discarded because this structure is inconsistent with many evidences described below.

8) The bathochromic effect of a 2-axial hydroxyl or acetoxyl group on the first extremum of the $n\rightarrow\pi^*$ transition in ORD of ketones is well known (9); the similar effect of epoxy ring has been observed (10).

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