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CONFIGURATIONS OF NAGILACTONES C AND D

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In a previous paper (1), the Osaka group described the isolation from Podocarpus Nagi Zori et Moritzi and determination of the planer structures of four nor- and bisnor-diterpenic lactones, nagilactones A, B, C and D. Since the nagilactones A and C, as well as inumakilactones, were also isolated from the seeds and the leaves of P. macrophyllus D. Don. by the Sendai and the Tokyo groups (2), we have collaborated in the determination of the stereochemistry of these compounds, and present here evidence which permits the assignment of structure I and II with absolute configuration for nagilactones C and D, respectively.

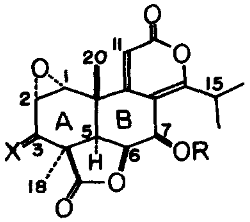
Nagilactone C (I), has two hydroxyl groups as shown by the formation of a 7-acetate (III), and a 3,7-diacetate (IV), while nagilactone D (II) possesses one hydroxyl group and yields a 3-acetate (V) (1). The presence of γ-lactone and a-pyrone groupings in both I and II was detected from UV and IR spectra, the remaining oxygen being assumed to be etheric in both cases. The location of these functional groups was mainly based on the close similarity of the NMR spectra of I, II and nagilactone A and their respective acetates (1).

In establishing the stereochemistry of I and II, the data (2) obtained for inumakilactone A (VI)

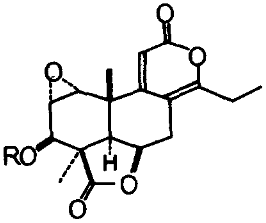
TABLE. NMR Signals of Derivatives of Nagilactones C and D

Compd No.	solv.	Me$_{18}$	Me$_{20}$	Me$_{16}$	Me$_{17}$	H$_1$	H$_2$	H$_3$	H$_5$	H$_6$	H$_7$	H$_{11}$	H$_{14}$	H$_{15}$
I	DMSO	1.33s	1.34s	1.18d (~6.5)	1.21d (~6.8)	3.56d (4.2)	3.3*	4.27m	2.05d (6.5)	4.89dd (6.5, 8.2)	5.27d (8.2)	6.27s	—	3.1~ 3.4*
	Py	1.50s	2.05s	1.26d (6.5)	1.33d (6.5)	3.72d (4.2)	3.5~ 3.7*	4.68d (6.0)	2.07d (8.0)	5.10dd (8.0, 9.0)	5.70d (9.0)	6.69s	—	3.2~ 3.6*
III	CDCl$_3$	1.40s	1.46s	1.24d (6.8)	1.27d (6.8)	3.55d (4.1)	3.44dd (4.1, 5.8)	4.48d (5.8)	2.04d (6.0)	5.04dd (6.0, 9.1)	6.41d (9.1)	6.31s	—	3.00sep. (6.8)
	Py	1.47s	1.80s	1.15d (6.5)	1.19d (6.5)	3.75d (4.2)	3.54dd (4.2, 5.8)	4.66d (5.8)	2.18d (6.5)	5.25dd (6.5, 9.0)	6.75d (9.0)	6.71s	—	3.18sep. (6.5)
IV	DMSO	1.45s	1.16s	1.13d (6.5)	1.23d (~6.5)	3.77d (4.2)	3.52dd (4.2, 6.0)	5.36d (6.0)	2.28d (6.0)	5.16dd (6.0, 8.5)	6.39d (8.5)	6.43s	—	3.03sep. (~7)
	Py	1.58s	1.58s	1.13d (7.0)	1.14d (6.5)	3.83d (4.0)	3.70dd (4.0 6.0)	5.73d (6.0)	2.26d (6.0)	5.28dd (6.0, 9.0)	6.76d (9.0)	6.77s	—	3.17sep. (~7)
II	CDCl$_3$	1.43s	1.26s	1.18t (7.5)	—	3.63d (4.0)	3.48dd (4.0, 6.0)	4.48d (6.0)	1.91d (6.5)	5.0tt (6.5, 7, 10)	3.46dd, 2.80dd (10, 16) (7, 16)	6.35s	—	2.64q (7.5)
V	CDCl$_3$	1.51s	1.22s	1.27t (7.3)	—	3.62d (4.0)	3.51dd (4.0, 5.1)	5.38d (5.1)	1.97d (7.0)	4.91tt (7, 7, 9)	3.45dd, 2.77dd (9, 16) (7, 16)	6.30s	—	2.62q (7.3)
VI	Py	1.40s	1.53s	1.56d (6.5)	—	3.62d (4.0)	3.51dd (4.0, 6.0)	4.65d (6.0)	2.13d (5.5)	5.08s*	5.08s*	6.73s	4.72d (8.5)	4.31m
VII	CDCl$_3$	1.52s	1.13s	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)	4.97dq (4.9, 6.3)
	Py	1.56s	1.31s	1.53d (6.4)	—	3.74d (4.0)	3.62dd (4.0, 6.2)	5.76d (6.2)	2.27d (5.0)	5.13dd (5.0, 1.5)	4.47d (1.5)	6.89s	5.27*	5.27*
VIII	Py	1.43s	1.52s	1.54d (~6)	—	3.64d (4.0)	3.51dd (4.0, 5.5)	4.69d (5.5)	2.16d (5.3)	5.08br.d (5.3)	4.42br.s	6.81s	5.24*	5.2~ 5.4*
IX	CDCl$_3$	1.43s	1.16s	0.96d (6.7)	1.10d (7.5)	2.98d (4.0)	3.37dd (4.0, 6.0)	4.39d (6.0)	1.82d (6.3)	4.77dd (6.3, 8.0)	5.77dm (~8)		3.90dm (~10)	
X	CDCl$_3$	1.41s	0.99s	1.03t (7.0)		2.93d (4.0)	3.35dd (4.0, 6.0)	4.37d (6.0)	1.73d (6.0)	4.87m			4.3m	
XI	Py	1.68s	1.28s	1.12d (7.0)	1.15d (6.5)	3.80d (4.0)	4.15d (4.0)	—	3.01d* (6.5)	5.40dd (6.5, 9.0)	6.76d (9.0)	6.84s	—	3.0~ 3.4*

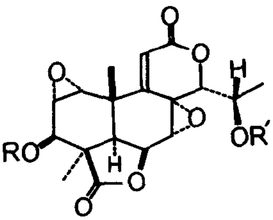
* Signals overlap each other. ** Complicate signal because of virtual coupling.



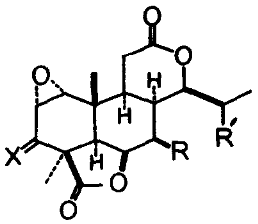
I: X=βOH, αH; R=H
III: X=βOH, αH; R=Ac
IV: X=βOAc, αH; R=Ac
XI: X=O; R=Ac



II: R=H
V: R=Ac



VI: R=R'=H
VII: R=R'=Ac
VIII: R=H, R'=Ac



IX: X=βOH, αH
R=OAc; R'=Me
X: X=βOH, αH; R=R'=H
XII: X=O; R=OAc; R'=Me
XIII: X=O; R=R'=H
XIV: X=βOH, αH
R=OH; R'=Me
XV: X=βOAc, αH
R=OH; R'=Me

derivatives, e.g. inumakilactone A diacetate (VII), can be directly compared; thus, the magnitude of vicinal coupling constants, J_{12}, J_{23} and J_{56}, in the three series (e.g. IV, V and VII) are, as shown in the TABLE, in good agreement with each other, indicating H_1/H_2 cis-, H_2/H_3 trans- and H_5/H_6 cis-configurations. The hydroxyl group at the 3-position and the lactone carbonyl at C_{19} should be cis, because the hydroxyl groups in II and III show an intramolecular hydrogen bonding with the γ-lactone carbonyl groups [ν 3530 and 3534 cm^{-1}, respectively; concentration independent. The carbonyl frequency changes from 1765 and 1767 cm^{-1} (in II and III resp.) to 1785 and 1787 cm^{-1}(in V and IV, resp.)]. Large nuclear Overhauser effect (NOE) observed between 3α-H and 18-methyl group [IV +17%, V +11%] confirmed this assignment. Acetylation of the 3β-hydroxyl group (III→IV and II→V) caused a change in Me_{18} and Me_{20} signals [+0.11 ppm and -0.22 ppm, and +0.10 ppm and -0.23 ppm, respectively, in pyridine (3)] which coincides with the values [+0.13 ppm and -0.21 ppm, respectively] found for the same chemical change (VIII→VII) in inumakilactone A series (4). This indicates the same orientation of C_3-hydroxyl and Me_{20} in the three series.

The molecular model with the suggested configuration indicates that H_1 and H_{11} are in the plane of the α-pyrone moiety and about 2Å apart. This situation was verified in two ways: i) III and II were hydrogenated to give the corresponding tetrahydro compounds IX, m.p. 249-252°, and X, m.p. 267-270°, respectively. In the NMR spectra of IX and X, the signals due to H_1 appear 0.57 and 0.70 ppm higher field than those of III and II, respectively. Apparently, the anisotropy of the α-pyrone is responsible for the large up-field shifts. ii) A large NOE was observed at H_{11} upon the irradiation of H_1 (25% in III and 13% in V) (5).

The absolute configuration of I and II was established to be the same as VI: Jones' oxidation of IX and X yielded the corresponding tetrahydroketones, XII, m.p. 231-234°, ν 1790, 1745, 1725 cm^{-1}, and XIII, m.p. 212-214°, ν 1787, 1742, 1725 cm^{-1}. CD curves of XII and XIII, showing negative Cotton effects with characteristic fine structures, are almost superimposable with that of 3-ketodihydroinumakilactone 15-acetate, m.p. 257-259°. This clearly demonstrates the identity of the absolute configuration of ring A in the three series.

The evidence described above established the configuration of I and II, except that of C_7-hydroxyl group in I. The C_7-OH was assigned to have β-orientation, because i) the J_{67} values are always large (see TABLE) suggesting cis relationship of those hydrogens (6). ii) Acetylation of the hydroxyl group caused the same amount (+0.25 ppm) of up-field shift in Me_{20} signal as does the acetylation of C_3-OH group (7). This indicates that both C_3-OH and C_7-OH are parallel to and nearly equivalent with respect to Me_{20} (8).

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Footnotes and References

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1) Y. Hayashi, S. Takahashi, H. Ona and T. Sakan, Tetrahedron Letters, 2071 (1968).

2) S. Itô, M. Kodama, M. Sunagawa, T. Takahashi, H. Imamura and O. Honda, ibid., 2065 (1968) and the forth coming papers.

3) Positive value denotes down-field shift. Methyl signals in pyridine appear at 1.45 (18Me), 1.53 (20Me), 1.10 ppm (t, J=7.5, 16Me) for II and 1.55 (18Me), 1.30 (20Me), 1.10 ppm (t, J=7.0, 16Me) for V. Two methyl signals were assigned on the basis of a large chemical shift change (-0.30 ppm) in Me_{20} and a small one (+0.03 ppm) in Me_{18} produced by the reduction of α-pyrone group (III→IX, TABLE).

4) Jones' oxidation of III afforded the corresponding 3-ketone XI, m.p. 220° (dec.), ν 1795, 1750, 1732, 1720, 1632, 1654 cm^{-1}. A down-field shift of H_5 signal upon the oxidation of 3β-hydroxyl group was observed in nagilactone C series (III→XI: 2.18→3.01) and inumakilactone A series (2.16→3.03) (2), indicating the identity of configuration of H_5 in two series.

5) 23% of NOE was also observed between the corresponding protons in inumakilactone A diacetate.

6) Cf. J.R. Hanson, Tetrahedron, 22, 1701 (1966), C.R. Bennet and R.C. Cambie, ibid., 23, 927 (1967).

7) This implied that both rings A and B are in boat forms in II.

8) Tetrahydronagilactone C, XIV, m.p. 278-281° (dec.) obtained by the catalytic hydrogenation of I, afforded only the corresponding 3-acetate XV, m.p. 273-275°. This can be explained by the β (axial) orientation of the hydroxyl group, assuming that the hydrogenation occurred from the less-hindered α-side of the molecule and, consequently, δ-isopropyl-δ-lactone moiety well hinders the 7β-hydroxyl group.