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STEREOCHEMISTRY OF NAGILACTONE A AND B

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The stereochemistry of nagilactone A and B was established by the spectral analyses and the X-ray method. The absolute configurations of both substances were also proposed.

The structures of four nagilactones, A, B, C, and D, isolated from Podocarpus nagi Zoll. et Moritzi, have been proposed previously$^{1)}$ and the stereochemistry of nagilactone C and D has already been discussed$^{2)}$. Recently, much attention has been drawn to the biologically active constituents in various Podocarpus species, and a number of nor- and bisnor-diterpenoid dilactones, having very similar carbon framework, have been isolated$^{3)}$. The structures of the compounds in this field have been deduced from the spectroscopic evidences. In this communication, we wish to present the determination of the stereochemistry of nagilactone A and B by means of the conventional spectral analyses and the X-ray method.

The values of the nmr parameters (Table I), $J_{5,6}$ and $J_{6,7}$ of nagilactone A (I) and its derivatives, II and III, were reasonable for the orientations: trans-A/B juncture and cis-relationships of H_5/H_6 and H_6/H_7, as reported for nagilactone C which had the similar J values between the corresponding protons. The observed difficulty towards acid hydrolysis of 7-acetoxyl group in the diacetate to afford I-7-monoacetate (III)$^{1)}$ was also compatible with the structure II for nagilactone A diacetate, in which 7β-acetoxyl group must be hindered by 10-methyl and the γ-lactone groups. The large diamagnetic displacement of H_{11} signal, from 6.48 ppm in I (6.78 ppm in III) to 5.70 ppm in II, by acetylation of the hydroxyl group on ring A indicated that the proton was located in close proximity of the hydroxyl group, to which 1β orientation was assigned. Therefore, the relative configuration of nagilactone A was given in the structure I. This assignment was confirmed unambiguously by the X-ray study on the diacetate (II) in the following procedure.

The crystals, $C_{23}H_{28}O_8$, are orthorhombic, space group $P2_12_12_1$; $\underline{a}$ = 10.43 (1), $\underline{b}$ = 15.45(1), $\underline{c}$ = 13.65(1) Å ; D_x = 1.32 g·cm^{-3}(z=4). Weissenberg intensity data were collected by means of Cu Kα radiation for eleven layers on the $\underline{a}$ axis and four layers on the $\underline{b}$ axis. The independent 2581 reflections were observed and no corrections were made for absorption and extinction.

The structure was solved by use of the symbolic addition procedure[4,5]. Three phases were assigned to define the origin and the fourth phase was assigned to specify the enantiomorph: 0 10 5 (0), 0 3 6 ($\pi/2$), 9 2 0 ($\pi/2$), 2 0 9 ($\pi/2$). Phases for three additional reflections were designated by symbols: 4 1 10 (A), 4 1 11 (B), 1 14 0 (C). In the course of applying the Σ_2 formula to obtain 62 new phases, it became apparent that $B = \pi/2$, $C = -\pi/2$ or $B = -\pi/2$, $C = \pi/2$. No valuable information was obtained for the symbol A. In order to apply the tangent formula[6], numerical phases from 0 to 2π in steps of $\pi/4$ were assigned to the symbol A. Each of the sixteen combinations of initial phases was used as input into the tangent formula. An E map was calculated by use of 439 reflections with the phases in the most consistent set ($R = 0.25$[4]). The positions of all the atoms except C_{16} and C_{17} of the isopropyl group were easily located and further confirmed by a least-squares refinement. The two remaining carbon atoms were found by a difference Fourier synthesis. When anisotropic thermal vibrations were applied to all of the non-hydrogen atoms, the conventional R factor was reduced to 0.11.

The molecular structure of nagilactone A diacetate is shown in Figure I. The ring A has a distorted chair conformation with deviations from the least-squares plane ranging from 0.11 to 0.43 Å. The ring C (α-pyrone ring) is nearly planar within 0.05 Å, and bond lengths, C_8-C_9 = 1.45 Å and C_{11}-C_{12} = 1.43 Å, show that the considerable delocalization occurs in this ring. C_{10}, C_{15} and O_{27} attached to this ring lie approximately on this plane, although their deviations from the plane are 0.08, 0.11 and 0.15 Å, respectively, and may be significant. However, C_7 deviates by 0.25 Å towards the same side of the plane as O_{27}. In the ring B, C_7, C_8, C_9 and C_{10} are coplanar within 0.05 Å with C_5 and C_6 deviating by 1.08 and 0.71Å, respectively, towards the same direction from this plane. The γ-lactone system is approximately planar with C_5 by 0.62 Å out of the plane. A difference of 0.07 Å between the bond lengths of C_6-O_{26} = 1.46 Å and C_{19}-O_{26} = 1.39 Å may be due to the contribution of the resonance to this system as pointed out by other reports[7,8].

Oxidation (CrO_3 in pyridine) of tetrahydronagilactone A 7-monoacetate (VII), prepared from tetrahydro-diacetate (VI)[1], gave tetrahydro-1-oxo-7-acetate (VIII), $C_{21}H_{28}O_7$, mp 310-315°(dec), ν_{max}^{Nujol} 1780, 1760, 1730 cm^{-1}, $[\theta]_{297}$ -4800. The magnitude of the coupling constants, $J_{7,8}$(2 Hz), $J_{8,9}$(12 Hz), and $J_{8,14}$(2.5 Hz), of the latter allowed us to infer the cis-relationships of H_7/H_8, H_8/H_9 and H_8/H_{14}. On this basis, the negative Cotton effect was in consistent with the absolute configuration represented in VIII for the tetrahydro 1-oxo-7-acetate, and therefore I for nagilactone A.

Nagilactone B (IV) exhibited the similar behaviors to nagilactone A in its nmr spectrum: the chemical shifts of the corresponding protons and the large up-field displacement (0.90 ppm) of H_{11} signal on the transformation from IV to the triacetate (V). The location of the third secondary hydroxyl group in IV was shown to be 2β-position by the following facts: (1) consumption of one equivalent of periodate, (2) facile formation of an acetonide, $C_{22}H_{28}O_7$, mp 240°, ν_{max}^{Nujol} 3450, 1785, 1720, 1620, 1545 cm^{-1}, (3) magnitide of $J_{1,2}$ was 3 Hz in IV and 6 Hz in V. The same sign of the Cotton effects of II and V9) suggested the absolute structure IV for nagilactone B.

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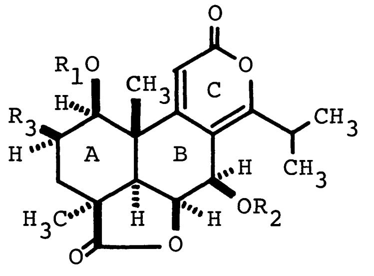
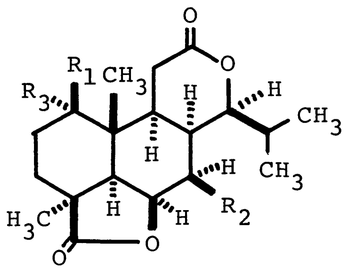


I $R_1 = R_2 = R_3 = H$
II $R_1 = R_2 = Ac$, $R_3 = H$
III $R_1 = R_3 = H$, $R_2 = Ac$
IV $R_1 = R_2 = H$, $R_3 = OH$
V $R_1 = R_2 = Ac$, $R_3 = OAc$



VI $R_1 = R_2 = OAc$, $R_3 = H$
VII $R_1 = OH$, $R_2 = OAc$, $R_3 = H$
VIII $R_1, R_3 = O$, $R_2 = OAc$

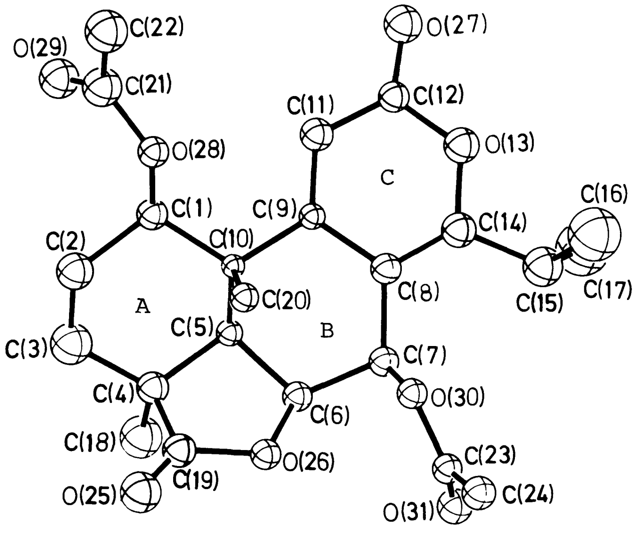


Figure I. The molecular structure of nagilactone A diacetate.

Table I. The nmr spectra of nagilactone A and B, and their derivatives represented in δ ppm (J Hz).

Compd	Solvent	H-1	H-2	H-5	H-6	H-7	H-11	H-14
I	DMSO	3.79br.t	---	1.78d (6)	4.90dd (6,10)	5.10d (10)	6.48s	---
II	DMSO	5.05m	---	---	5.10dd (6,9)	6.18d (9)	5.70s*	---
III	$CDCl_3$	3.96br.t	---	1.78d (5.5)	5.02dd (5.5,9.5)	6.26d (9.5)	6.78s	---
VI	$CDCl_3$	4.63br.t	---	1.75d (6)	4.72dd (6,8.5)	5.77dd (3,8.5)	---	3.77dd (2.5,10)
VIII**	$CDCl_3$	---	---	1.98d (7.5)	4.77t (7.5,7.5)	5.80dd (2,7.5)	---	3.85dd (2.5,10.5)
IV	Py	4.29d (3)	4.29td (3,5)	1.90d (6.5)	5.20dd (6.5,7.5)	5.65d (7.5)	6.95s	---
V	Py	5.70d (6)	5.30m	---	5.40	6.65d (9)	6.05s	---

* 5.83s in $CDCl_3$. ** The signals due to H-8 and H-9 were observed as a broad doublet and a broad triplet, respectively, in the presence of 0.8M-$Eu(DPM)_3$ at 55° ($J_{8,9}$ = 12 Hz).

Footnotes and References

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9. $[\phi]^{320}_{max} - [\phi]^{275}_{min} = +4280$ in II, and +3850 in V.

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