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STRUCTURES OF NAGILACTONE A, B, C AND D, NOVEL NOR- AND BISNORDITERPENOIDS

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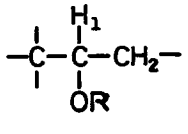
From the leaves and seeds of Podocarpus Nagi, ZOLI. et MORITZI (1), we have isolated three norditerpenoid dilactones, nagilactone A, B and C, and a bisnorditerpenoid dilactone, nagilactone D (TABLE I), and established their structures as I, II, III and IV: The evidence is provided in this paper.

TABLE I.

Compound	Molecular formula	m.p.	$[\alpha]_D$
Nagilactone A (I)	$C_{19}H_{24}O_6$	305° (subl.)	+88.8°
Nagilactone B (II)	$C_{19}H_{24}O_7$	258-261° (dec.)	+92.5°
Nagilactone C (III)	$C_{19}H_{22}O_7$	290° (dec.)	+111°
Nagilactone D (IV)	$C_{18}H_{20}O_6$	265-266° (dec.)	+90°

The IR and UV spectra (2) of nagilactone A (I) disclosed the presence of hydroxyl groups (ν 3460, 3400 cm^{-1}), a γ-lactone (ν 1740 cm^{-1}) and an α-pyrone ring (λmax 300 mμ, ε 5200; $\lambda_{max}^{NaOH-EtOH}$ 370 mμ, ν 1730, 1640, 1560 cm^{-1}) (3). Acetylation of I with acetic anhydride in pyridine gave the 1,7-diacetate (V), $C_{23}H_{28}O_8$, m.p. 312°, $[\alpha]_D^{26}$+28.8°, λmax 300 mμ, ε 5200, ν 1780 cm^{-1}, with no hydroxyl group. Thus all oxygen functions in I are accounted for. NMR signals of I and V are given in TABLE II together with their assignments. The NMDR experiment on V, when coupled with the chemical shift values of hydrogens in V (TABLE II) and the large down-field shifts observed for the signals of H_1 and H_7 upon acetylation (I→V), revealed the arrangements of hydrogens shown in the following partial formulas in V.



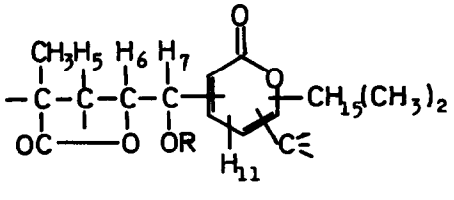


TABLE II.

The NMR Spectra of Nagilactones and its Derivatives (ppm from TMS)[Δ]

Compound	Solvent	Me[a]	Me[b]	Me[c*]	Me[d*]	H-1	H-2	H-3	H-5	H-6	H-7	H-11	H-15
Nagilactone A (I)	DMSO	1.27[s]	1.20[s]	1.16[d] (6)	1.18[d] (6)	3.79[t] (6)	—	—	1.78[d] (6)	4.90[dd] (6)(10)	5.15[d] (10)	6.48[s]	3.21[m] (6)
Nagilactone A diacetate (V)	DMSO	1.30[s]	1.25[s]	1.13[d] (6)	1.16[d] (6)	5.05[m]	—	—	—	5.10[dd] (6)(9)	6.18[d] (9)	5.70[s]	—
Nagilactone B (II)	Pyr.	1.92[s]	1.45[s]	1.27[d] (6)	1.32[d] (6)	4.29[d] (3)	4.29[td] (3)(5)	—	1.90[d] (6.5)	5.20[dd] (6.5)(7.5)	5.65[d] (7.5)	6.95[s]	3.50[m] (6)
Nagilactone B triacetate	Pyr.	1.60[s]	1.45[s]	1.19[d] (6)	1.19[d] (6)	5.70[d] (6)	5.30[m]	—	—	5.40	6.65[d] (9)	6.05[s]	3.10[m] (6)
Nagilactone C (III)	DMSO	1.33[s]	1.34[s]	1.18[d] (~6.5)	1.21[d] (~6.8)	3.56[d] (4.2)	~3.3**	4.27[m]	2.05[d] (6.5)	4.89[dd] (6.5)(8.2)	5.27[d] (8.2)	6.27[s]	—
Nagilactone C diacetate	DMSO	1.16[s]	1.45[s]	1.13[d] (6.5)	1.23[d] (~6.5)	3.77[d] (4.2)	3.52[dd] (4.2)(6)	5.36[d] (6)	2.28[d] (6)	5.16[dd] (6)(8.8)	6.39[d] (8.5)	6.43[s]	—
Nagilactone D (IV)	$CDCl_3$	1.26[s]	1.43[s]	—	1.18[t] (7.5)	3.63[d] (4)	3.48[dd] (4)(6)	4.48[dd] (6)	1.91[d] (6.5)	5.0[tt] (6.5) (7)(10)	α 3.46[dd] (10)(16) β 2.80[dd] (7)(16)	6.35[s]	2.64[m] (7.5)
Nagilactone D monoacetate	$CDCl_3$	1.51[s]	1.22[s]	—	1.27[t] (6.5)	3.62[d] (4)	3.51[dd] (4)(5)	5.38[d] (5)	1.97[d] (7)	4.91[tt] (7)(7) (9)	3.45[dd] (9)(16) 2.77[dd] (7)(16)	6.30[s]	—

Δ Signal multiplicities are abbreviated as s, d, t, m for singlet, doublet, triplet and multiplet, respectively. Coupling constants expressed in cps are listed in parentheses.

* Methyl signals in the isopropyl group always appear as two doublets in these derivatives.

** The signal overlaps with that of water. On addition of acid, it appears at 3.37[dd] with J=4.2 and 5.5 cps, while H_3 becomes doublet (J=5.5) at 4.29 ppm.

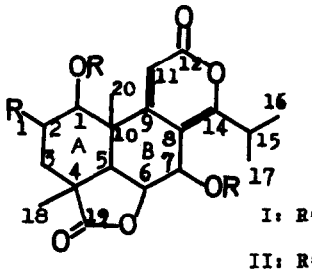
On the catalytic hydrogenation over PtO_2 in acetic acid, I absorbed two moles of hydrogen to give saturated tetrahydronagilactone A (VI), $C_{19}H_{28}O_6$, m.p. 298-300°, $[\alpha]_D^{17}$+31.5°, ν 3520, 3385, 1760, 1730 cm^{-1}, with a δ-lactone and two carbocyclic rings besides a γ-lactone. VI afforded the tetrahydro-1-acetate (VII), $C_{21}H_{30}O_7$, m.p. 274°, $[\alpha]_D^{14}$+25.7° and the tetrahydro-1,7-diacetate (VIII), $C_{23}H_{32}O_8$, m.p. 261-2°, $[\alpha]_D^{20}$+47.5° with Ac_2O in pyridine. VIII was also obtained by acetylation of VII or by hydrogenation of V.

Ozonolysis of V gave isobutyric acid (identified as p-bromophenacyl ester, m.p. 73°) and the dicarboxylic acid (IX) [methyl ester, $C_{19}H_{20}O_{10}$, m.p. 203-5°, $[\alpha]_D^{17}$+72.8°, ν^{Nujol} 1790, 1745 cm^{-1}, δ $ppm^{CDCl_3}_{TMS}$ 1.22 (s, 6H, two methyls), 1.96, 2.12 (both s, $2CH_3COO$), 3.59, 3.79 (both s, $2COOCH_3$), 4.90 (t, 1H, J=6 cps, H_1), 5.17 (d, 1H, J=11.4 cps, H_7), 4.70 (dd, 1H, J=11.4 and 4.8 cps, H_6), 2.99 (d, 1H, J=4.8 cps, H_5)].

As to the position of the substituents on the α-pyrone ring, several different formulas may be considered. From the following reasons, however, we regard the formula I as the most appropriate: Firstly, the chemical shift of the vinyl proton (H_{11}, 5.8-6.0 ppm) is in accord with that of the hydrogen α or γ to the carbonyl group of α-pyrone. Secondly, the sharp singlet nature of H_{11} in NMR spectra of I and V suggests that the adjacent carbon atoms have no hydrogen. Thirdly, two signals in the NMR spectrum of VIII newly appeared at 2.55 ppm (2H, br. dd, J=5 and 11 cps) and 3.80 ppm (dd, 1H, J=4 and 10 cps) as the result of the saturation of α-pyrone to δ-lactone. The former signal is attributed to methylene protons α to the carbonyl group, while the latter, which does not couple with H_7, but with H_{15}, to a δ-proton in the δ-lactone system. Acid hydrolysis of VIII afforded the 7-acetate (X), $C_{21}H_{30}O_7$, m.p. 218-9°, $[\alpha]_D$+8.7°, which is different from the 1-acetate (VII). This indicated that there was some steric hindrance aound 7-OH group, being compatible with the location of isopropyl group at C-14.

The chemical shift of H_{11} (5.70 ppm) in V indicates large up-field displacement compared with those of I and the nagilactone A 7-monoacetate (6.48, 6.78 ppm, respectively); the latter was obtained on mild acid hydrolysis of V as m.p. 237-8°, $C_{21}H_{26}O_7$, λ 300 mμ, ν^{Nujol} 3380, 1770, 1730, 1705, 1620, 1550 cm^{-1}. Therefore, the grouping HO-$\overset{|}{\underset{|}{C}}$-$H_1$ must be located closely to the vinyl hydrogen, rationalizing the location of the hydroxyl group at C-1.

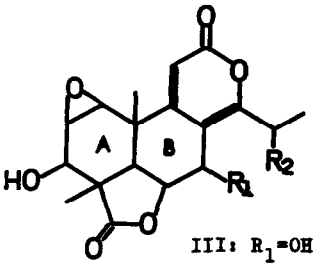
Reduction of V with $NaBH_4$ gave the deoxy compound (XII), $C_{21}H_{26}O_6$, m.p. 196-7°,



I: R=H, R_1=H

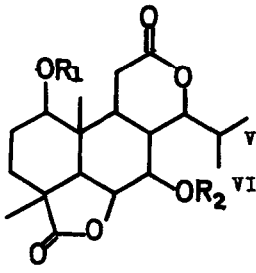
II: R=H, R_1=OH

V: R=Ac, R_1=H



III: R_1=OH, R_2=CH_3

IV: R_1=H, R_2=H

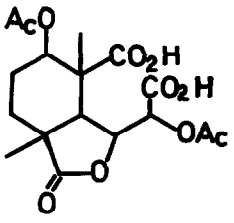


VI: R_1=H, R_2=H

VII: R_1=Ac, R_2=H

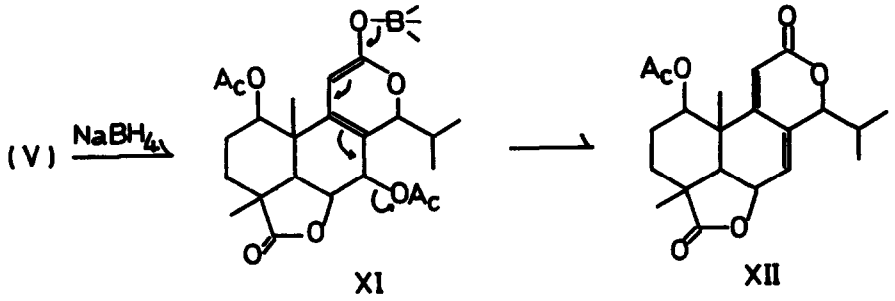
VIII: R_1=Ac, R_2=Ac

X: R_1=H, R_2=Ac



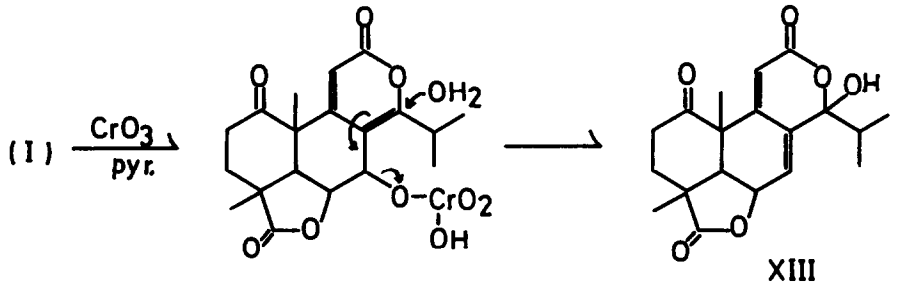
IX

$[\alpha]_D^{22}$-246°, λ 227 sh, 263 mμ, ε 7500, 13000, ν^{Nujol} 1770, 1730, 1710, 1610 cm^{-1}, δ $ppm^{CDCl_3}_{TMS}$ 1.31, 1.35 (two singlet methyls), 0.93, 1.09 (two doublet methyls), 2.21 (s, 3H, $C\underline{H}_3COO$), 5.07 (d, 1H, J=4.8 cps, H_6), 5.11 (t, 1H, J=5 cps, H_1), 5.62 (d, 1H, J=1.8 cps, H_{11}), 6.18 (dd, 1H, J=1.8 and 4.8 cps, H_7), 4.53 (d, 1H, J=9 cps, H_{14}). The proposed structure (XII) is based on the above spectral data and the mechanistic consideration of its formation from V through the intermediate (XI) as follows (4).



XI XII

Oxidation of I with chromic acid in pyridine afforded an acidic substance (XIII), $C_{19}H_{22}O_6$, m.p. 224-5°, the structure of which was assigned on the basis of UV (λ 259 mμ, $\lambda_{max}^{NaOH-EtOH}$ 220, 250 sh mμ) (5), IR (ν^{Nujol} 3340, 1770, 1730, 1720, 1605 cm^{-1}) and NMR spectra [δ ppm_{TMS}^{DMSO} 1.22, 1.43 (two singlet methyls), 0.89, 0.93 (two doublet methyls), 5.45 (t, 1H, J=4.8 cps, H_6), 6.50, 7.35 (two vinyl protons, H_7, H_{11})] and also of the consideration of the following mechanism of the oxidation.



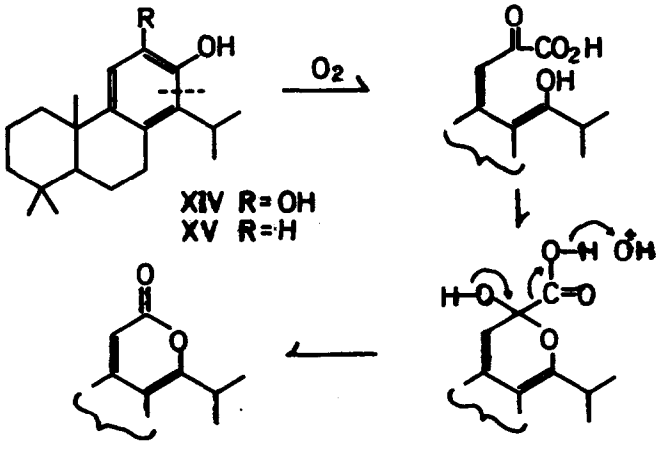
XIII

Nagilactone B (II), giving triacetate, $C_{25}H_{30}O_{10}$, m.p. 254-5°, has UV (λ 300 mμ) and IR spectra (ν 3450, 3250, 1780, 1740, 1640, 1550 cm^{-1}) very similar with those of I, and consumed one mole of HIO_4. Its NMR spectrum (TABLE II) is also very similar to that of I. Thus, the structure (II) was proposed.

Nagilactone C (III), λ 300 mμ, ν^{Nujol} 3400, 1770, 1710, 1640, 1550 cm^{-1} [monoacetate, $C_{21}H_{24}O_8$, m.p. 255°, diacetate, $C_{23}H_{26}O_9$, m.p. 280°] and nagilactone D (IV), λ 305 mμ, ν^{Nujol} 3450, 1780, 1730, 1625, 1550 cm^{-1} [monoacetate, $C_{20}H_{22}O_7$, m.p. 263°] exhibit the similar spectra in IR and UV region to those of I and II. As no ketonic function was recognized, the presence of an ether ring in both compounds was considered in order to account for the number of oxygen in the molecules. In the NMR spectra of III and IV (TABLE II), two proton signals (H_1, H_2) are observed in the range of 3.4-3.8 ppm. They are coupled (J=3-4 cps) with each other and one of them is further coupled (J=5-6 cps) with the carbinyl hydrogen H_3 (established by the NMDR technique). These hydrogens were assigned to the α-epoxy carbinol moiety in the ring A. Of the alternative arrangements of the moiety, the ones depicted were chosen because the acetylation of the hydroxyl group caused essentially no change in chemical shift of H_{11} (TABLE II). Furthermore, the ozonolysis of nagilactone D acetate gave propionic acid (identified as p-bromophenacyl ester, m.p. 58-9°), showing the presence of an ethyl group on the pyrone ring.

The stereochemistry of nagilactones will be discussed later.

It is known that catechols suffer, in vivo, the oxydative cleavage to α-pyrone derivatives following the meta-pyrocatechase type fission (6,7). The hydroxyl derivative (XIV) of totarol (XV), which was isolated from the same plant (1), may be considered as one of the possible biogenetic precursors of nagilactones, and the possible biogenetic pathway is tentatively indicated below.



We wish to express our thanks for Professor Shô Itô, Tohoku University, for his helpful discussions.

References and Footnotes

1) The previous investigations of the components of this plant: a) T. Takahashi, J. Japan Wood Res. Soc., 5, 185 (1959); b) T. Kariyone and T. Sawada, Yakugaku Zasshi, 78, 1010 (1958); T. Sawada, ibid., 78, 1023 (1958).

2) UV and IR spectra were recorded for ethanol solution and KBr disc, respectively, unless otherwise stated.

3) A. I. Scott, Interpretation of the Ultraviolet Spectra of Natural Products, p. 141. Pergamon Press, London (1964); R. N. Jones, C. L. Angell, T. Ito and R. J. D. Smith, Can. J. Chem., 37, 2007 (1959).

4) Cf. E. Schencker, Angev. Chem., 73, 81 (1961).

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7) S. Senoh and T. Sakan, Biological and Chemical Aspects of Oxygenases, ed. by K. Bloch and O. Hayaishi, p. 93. Maruzen Comp. (1966); S. Senoh, S. Imamoto, Y. Maeno, T. Tokuyama, T. Sakan, A. Komamine and S. Hattori, Tetrahedron Letters, 3437 (1964).