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TAXININE

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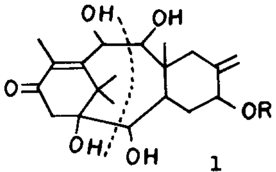
Several structural studies have already been reported[1-5] on taxine and taxinine(desdimethylaminotaxine) isolated from the leaves of the yew, Taxus baccata L. subsp. cuspidata Pilg. et Zucc. On the other hand, O-cinnamoyltaxicin-I,-II*and-III have been isolated from the European yew, Taxus baccata L.[6]and recently[7], two alternatives structures, 1 and 2 have been forwarded by Lythgoe and co-workers; their evidence is based on the periodate cleavage of the molecule into two halves.



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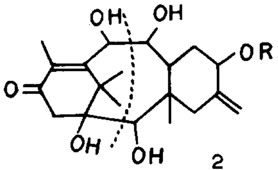

2

R : $-COCH=CH-C_6H_5$

The evidence cited in this and the following communication on the Japanese taxinine allows one to establish its structure as 3.

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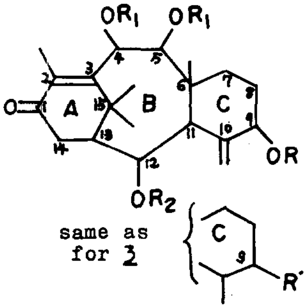
* As stated in reference 7, "taxinine" is probably O-cinnamoyltaxicin-II triacetate.



3 R_1= R_2= Ac, R= cinnamoyl
4 R_1= R_2= Ac, R= dihydrocinnamoyl
7 R_1= H, R_2= Ac, R= cinnamoyl

5 R'= dihydrocinnamate
6 R'= H

Taxinine, $C_{35}H_{42}O_9$, m.p. 264-5°, M.W. 606.7, found, 611+10 (X-ray)*, 602 (ultracetrifuge sedimentation equilibrium)**, has the following spectroscopic properties: $\nu_{cm^{-1}}^{KBr}$ 1745 (acetates) 1720, 1644 (cinnamate), 1674 (ketone), 911 ($C=CH_2$); λ_{max}^{MeOH} 218 223, 280 mμ (log ε 4.28, 4.22, 4.45); $\delta_{ppm}^{CDCl_3}$*** 0.95, 1.18, 1.79, 2.30 (all singlets, tertiary methyls), 2.06, 2.06, 2.08 (acetates), 1.6-3.2 (overlapping peaks assigned to C_7-, C_8-, C_{14}-methylenes and C_{13}-methine), 3.44 (dif.d., J=7 cps, C_{11}-H) 4.88 (1H dif.s., $=CH_2$), 5.37 (2H dif.s., $=CH_2$ and C_9-H), 5.88 (q., J=7 and 2 cps, C_{12}-H), 5.90 and 6.06 (AB type q., J=10 cps C_4- and C_5-H), 6.3-7.8 (trans-cinnamate protons). Hydrogenation of taxinine in acetone over Pd/C afforded besides the dihydro- and tetrahydro-derivatives, **4**, m.p. 246-7° and **5**, m.p. 279°,

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* Kindly measured by Dr. T.Kanzawa, Takeda Chemical Industries

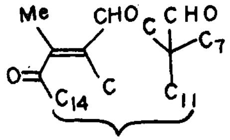
** Kindly measured by Dr. N.Iso, Department of Chemistry, Tokyo Kyoiku University.

*** Assignments are based on nuclear magnetic double resonance (NMDR) data given in the succeeding communication.

Abbreviations: dif., diffuse; s., singlet; d., doublet; q., quartet.

$\delta_{ppm}^{CDCl_3}$ 0.69 (d., J=7 cps, C_8-Me), a small amount of dihydrocinnamic acid and the hydrogenolysed product 6, m.p. 196-7°. Formation of the last two compounds indicated the presence of an allylic cinnamoyl group. Further, the hydrogenolysis product 6 contains an unsaturated ketone, $\nu_{cm^{-1}}^{CHCl_3}$ 1680 and 1661 (shoulder), but the λ_{max}^{MeOH} at 272 mμ (log ε 3.78) suggested that the group was present in an unusual environment.

Methanolysis of taxinine with sodium methoxide[8] gave dideacetyltaxinine 7, $C_{31}H_{38}O_7$, m.p. 216°, which gave taxinine upon reacetylation, and an acetonide, $C_{34}H_{42}O_7$, m.p. 192-3°, when treated with Me_2CO-$HClO_4$[9]. Methanolysis of tetrahydrotaxinine 5 followed by periodate oxidation afforded the dialdehyde 8, $\delta_{ppm}^{CDCl_3}$ 9.37 (s) and 10.25 (s), the λ_{max}^{MeOH} at 210 and 259 mμ corresponding to that of an enedione. Reduction of tetrahydrotaxinine 5 with Zn-AcOH under reflux led to deacetoxytetrahydroisotaxinine 9, $C_{33}H_{44}O_7 \cdot CH_3OH$, m.p. 78°, λ_{end}^{MeOH} 208 (log ε 4.03), $\nu_{cm^{-1}}^{CHCl_3}$ 1738 (esters), 1708 (ketone), $\delta_{ppm}^{CDCl_3}$ 1.78 (d., J=9.4 cps, C_2-Me), 5.09, 5.66 (AB type q., J=11.4 cps). The evidence cited in this paragraph suggests part structure 10.



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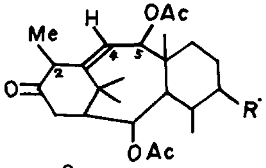

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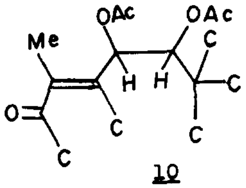
R' = dihydrocinnamate



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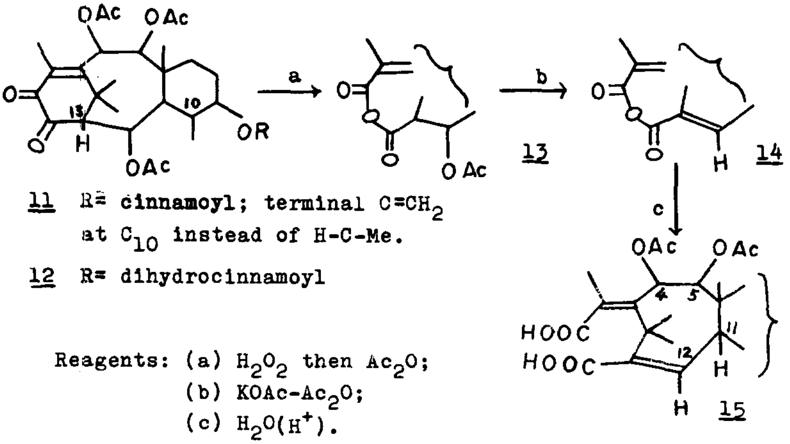
Selenium dioxide oxidation of taxinine 3 gave the non-enolizable α-diketone, oxotaxinine 11, $C_{35}H_{40}O_{10}\cdot\frac{1}{2}C_2H_5OH\cdot\frac{1}{2}H_2O$, m.p. 220°(dec.), λ_{max}^{MeOH} 218 and 284 mμ (log ε 4.30 and 4.37); $\nu_{cm^{-1}}^{CHCl_3}$ 1715 and 1698 (α-diketone); $\delta_{ppm}^{CDCl_3}$, a clear one-proton doublet at 2.88 (J=3.0 cps) due to C_{13}-H. Tetrahydrotaxinine 5 similarly gave the corresponding oxo-derivative 12, $C_{35}H_{44}O_{10}\frac{1}{2}C_2H_5OH\cdot\frac{1}{2}H_2O$, m.p. 279-280°. The reaction sequence outlined below finally yielded the dicarboxylic acid 15, m.p. 243-4°, λ_{end}^{MeOH} 209 mμ (log ε 4.26). Since in acid 15 the C_4-C_5 α-diacetoxy group is retained (NMR: AB type quartet at 5.03 and 6.02, J=13 cps, in acetone), formation of the α,β-unsaturated acid involves β-elimination of the third acetoxyl group; furthermore, a one-proton doublet at 6.77 ppm (J=1.3 cps, C_{12}-H in acetone) indicates the presence of an additional adjacent proton, C_{11}-H. Thus, 10 can be extended to 16.



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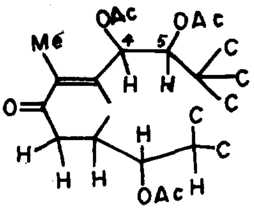
15

11 R= cinnamoyl; terminal $C=CH_2$ at C_{10} instead of H-C-Me.

12 R= dihydrocinnamoyl

Reagents: (a) H_2O_2 then Ac_2O;
(b) KOAc-Ac_2O;
(c) $H_2O(H^+)$.



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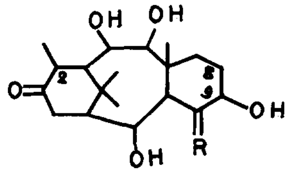
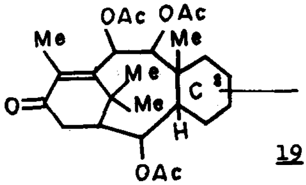


17 R= CH_2

18 R= O

When taxinine 3 was reduced with $LiAlH_4$ in boiling tetrahydrofuran, an unusual 1,4-reduction[10] occurred to give taxinol[5] 17, m.p. 254-5°, $\nu_{cm^{-1}}^{KBr}$ 1685, $\delta_{ppm}^{pyridine}$ 1.29 (d., J=6.6 cps, C_2-Me), the ozonolysis of which afforded formaldehyde and noroxotaxinol 18, m.p. 216-7°, $\nu_{cm^{-1}}^{KBr}$ 1707. Consideration of the fact that the taxinine NMR exhibits three methyl singlets in addition to the olefinic methyl leads to expression 19.

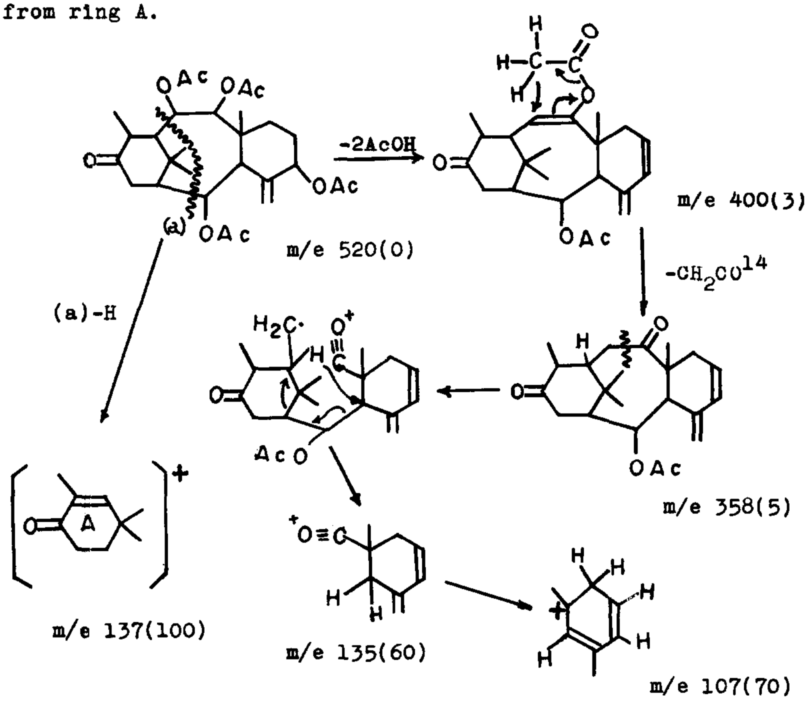


$=CH_2$ and $-OCOCH=CH\cdot C_6H_5$ attached to adjacent positions in ring C

19

Nuclear magnetic double resonance experiments[11] revealed that the C_{11}-H doublet is long-range coupled to one of the terminal methylene protons (4.88 ppm in taxinine), and that the proton alpha to the cinnamate group is weakly coupled to an adjacent methylene group (C_8-methylene). This establishes the structure of taxinine as 3, which is corroborated by NMR[11] and mass spectroscopic results. The strained bicyclic A/B system is responsible for the red shift[12] in the UV absorption of the C_1-ketone in taxinine derivatives and the low $\nu_{C=O}$[13] of taxinol derivatives.

The mass spectra of taxinol and derivatives*, which were characterized by a conspicuous peak at m/e 137 arising from a ring A fragment provided further support for the derived structure. In tetraacetylnoroxotaxinol, where the C=CH$_2$ is replaced by C=O, the peaks shown below for tetraacetyltaxinol are shifted two mass units higher; thus the m/e 135 peak is also shifted to 137 and overlaps the m/e 137 peak originating from ring A.



Figures in ( ) denote % intensity relative to base peak.

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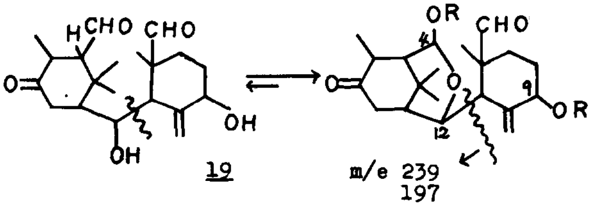
* The low volatility of taxinine derivatives made them unsuitable for mass spectroscopic measurements.

Finally, periodate oxidation of taxinol 17 gave rise to secotaxinol, m.p. 109-110°, an equilibrium mixture in $CDCl_3$ (12.5 % solution) of 19 (25 %) and 20 (75 %) as indicated by the relative intensities of aldehydic protons at δ 9.33 ppm (singlet) and 9.75 ppm (doublet, J=4.3 cps). Acetylation of secotaxinol(19⇌20) resulted in the hemiacetal diacetate 21, m.p. 108-9°, $\delta^{CDCl_3}_{ppm}$ 3.89 (q., J=2.5 and 7.5 cps, C_{12}-H), 4.86 and 5.10 ($C=CH_2$), 5.61 (q., J=6 and 12 cps, C_9-H), 6.17 (d., J=6 cps, C_4-H) and 9.24 (s., -CHO). The high mass region of the mass spectra of secotaxinol 20 (or 19) and its diacetate 21 was revealing in that rather strong peaks were observed at m/e 197 in the former, and at 239 and 197 (= m/e 239 minus $-CH_2CO$) in the latter; these peaks confirm the C_4-C_5 seco structures assigned to these compounds.



19

20 R= H

21 R= Ac

Professor S.Uyeo and co-workers, Kyoto University, have arrived at the same conclusion regarding the structure of taxinine[15].

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