Tetrahedron Letters No.48, pp. 4777-4782, 1967. Pergamon Press Ltd. Printed in Great Britain.

# DITERPENES OF THE CASCARILLIN GROUP FROM DODONAEA SPP.

P.R. Jefferies and T.G. Payne

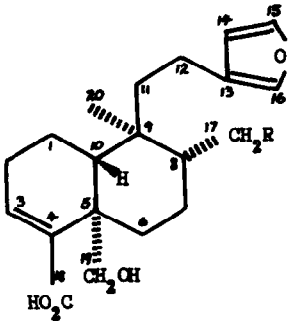
Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia

(Received in UK 30 July 1967)

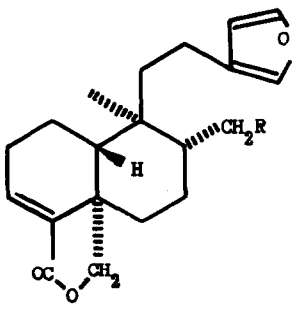
As an extension of our work (1) on Dodonaea spp. we now report diterpenes which possess a rearranged enantio-labdane skeleton of the type exhibited by the cascarillins (2).

The ether extract of D. attenuata A.Cunn. (Sapindaceae) gave the acetoxy-hydroxy-acid I, $C_{22}H_{30}O_6$, m.p. 160-162°, $[\alpha]_D$ -109°, $\lambda_{max}$ 210mμ (ε=10,200) as the major acidic constituent. The NMR spectrum* of I showed signals at 2.65, 2.77, 3.71τ attributed to the two α and one β proton of a β-substituted furan ring. A triplet at 3.26τ (1H; J,3c/s) was assigned to a β-vinyl proton in an αβ-unsaturated carbonyl grouping having a methylene group adjacent to the vinyl hydrogen. Singlets at 9.18(3H), 7.97(3H) were assigned to a tertiary methyl and acetate group respectively.

Saponification or $LiBH_4$ reduction of the natural acid I gave a dihydroxy-acid II, m.p. 174-176°, $[\alpha]_D$ -107°, which when heated with N,N'-dicyclohexylcarbodiimide (3) in pyridine,




I. R = OAc
II. R = OH
III. R = H




IV. R = OH
V. R = OAc
VI. R = H

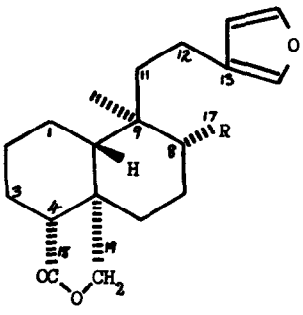
* NMR spectra were recorded using a Varian A60 spectrometer. Spectra were run in $CDCl_3$ or $CHCl_3$ as solvent and chemical shifts recorded on the τ-scale relative to T.M.S. Coupling constants were derived from first order analysis.

lactonized to give the hydroxy-lactone IV, m.p. 180-181°, $[\alpha]_D$ -154°. Similar treatment of the natural acid I or acetylation of IV with acetic anhydride gave the acetoxy-lactone V, m.p. 97-98°, $[\alpha]_D$ -137°, establishing chemically that the ester grouping in I was an acetate. The I R spectrum of V in $CS_2$ solution showed $\nu_{max}$ 1775 and 1740 $cm^{-1}$ due to the αβ-unsaturated-γ-lactone and acetate groups but lacked hydroxyl absorption.

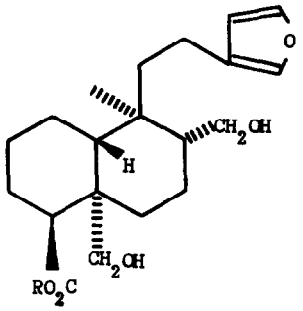
Reduction of I with sodium in ethanol saturated the $\Delta^3$ olefinic linkage and gave a 3:2 mixture of the hydroxy lactone VII, m.p. 151-153°, $[\alpha]_D$ -28°, $\nu_{max}$ 3625 (-OH), 1785 $cm^{-1}$ (γ-lactone), and the dihydroxy acid XIII, m.p. 169-170°, $[\alpha]_D$ -3°. These two products were formulated as epimers at C-4 since methylation of XIII gave the methyl ester XIV, m.p. 62-64°, $[\alpha]_D$ +6°, which gave the lactone VII after treatment with NaOMe in MeOH and saponification. The NMR spectrum of VII showed the C-19 protons as an AB system $\tau_A$,5.69; $\tau_B$,5.75 (J=10c/s) which indicated that this methylene group was attached to a fully substituted carbon atom. The C-17 protons appeared as the AB portion of an ABX system ( $\tau_A$,6.17; $\tau_B$,6.68; $J_{AB}$=10.5, $J_{AX}$=2.5, $J_{BX}$= 7c/s) which indicated that the adjacent carbon atom bears one proton. The assignment was confirmed by oxidation of VII with $CrO_3$ in pyridine to give the lactone-acid XII, m.p. 194-204°, $[\alpha]_D$ -32°, and the aldehyde VIII, m.p. 132-133°, $[\alpha]_D$ -16°, for which the NMR spectrum showed a doublet at 0.28τ (J= 3c/s) due to the aldehyde proton and signals due to the C-19 protons as an AB system ( $\tau_A$,6.64; $\tau_B$,6.70; $J_{AB}$=10c/s).

The relative position of the acetoxymethyl group and the β-substituted furan ring in I was established as follows. Acetylation of the hydroxy-lactone VII gave the acetate IX, m.p. 97-98°, $[\alpha]_D$ -24°, which when oxidized with ozone followed by the Jones reagent (4) gave the tris-nor-acetoxy-acid XV, m.p. 116-117°, $[\alpha]_D$ -23°. Saponification of XV gave the hydroxy-acid XVI, m.p. 175-176°, $[\alpha]_D$ -18°, which was oxidized with the Jones reagent (4) to the corresponding diacid, heated with acetic anhydride and then at 280° to give the keto-lactone XIX, m.p. 151-153° and 157-159°, $[\alpha]_D$ +128°, $\nu_{max}$ 1785, 1740, 1413 $cm^{-1}$ ( γ-lactone, cyclopentanone) (5). The formation of a cyclopentanone indicates that there are four carbon atoms linking the furan and acetoxymethyl functions in I.

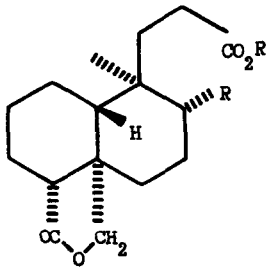
Treatment of the lactone-aldehyde VIII with boiling $Ac_2O$/NaOAc followed by ozonolysis and Jones oxidation (4) of the resulting enol-acetate gave the lactone-keto-acid XX, m.p. 158-159°, $[\alpha]_D$ +20°. Methylation gave XXI, m.p. 85-86°, $[\alpha]_D$ +41°, which showed IR absorption at 1785, 1735, 1710 $cm^{-1}$ attributed to γ-lactone, ester and cyclohexanone groupings respectively (5). Bromination and dehydrobromination of XXI gave the conjugated ketone XXII, m.p. 115-117°, $\lambda_{max}$ 225mμ (ε=7000), $\nu_{max}$ 1785, 1740, 1675 $cm^{-1}$. The NMR spectrum of XXII showed the two olefinic protons as an AB quartet



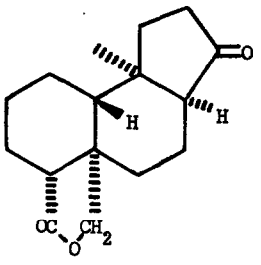
VII. R = $CH_2OH$
VIII. R = CHO
IX. R = $CH_2OAc$
X. R = $CH_2Cl$
XI. R = $CH_3$
XII. R = $CO_2H$



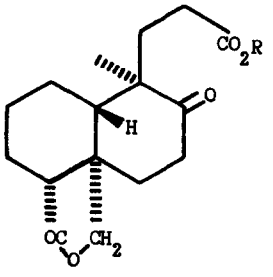
XIII. R = H
XIV. R = $CH_3$



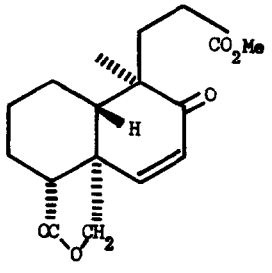
XV. R = $CH_2OAc$ R′ = H
XVI. R = $CH_2OH$ R′ = H
XVII. R = $CH_3$ R′ = H
XVIII. R = $CH_3$ R′ = $CH_3$



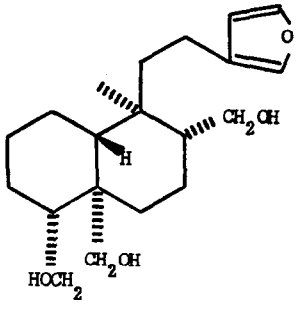
XIX.



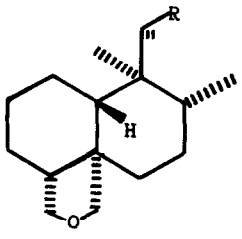
XX. R = H
XXI. R = $CH_3$



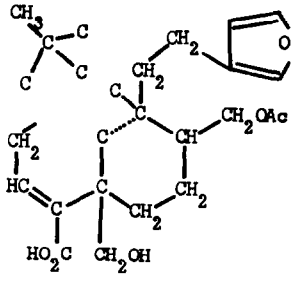
XXII



XXVII.



XXIII. R = $CH_2CO_2H$
XXIV. R = $CH_2C(OH)Ph_2$
XXV. R = $CH{=}C(Ph)_2$



XXVI.

$\tau_A$ 3.09, $\tau_B$ 3.95 ($J_{AB}$= 10c/s) indicating a cis-disubstituted olefinic linkage. Treatment of XXII with NaOH liberated formaldehyde presumably by a retro-aldol fission of the C-5 substituent since the keto-lactone XXI did not react in this manner. This indicates the relationship between the lactone and conjugated ketone functions in XXII and hence the number and nature of the carbon atoms linking the hydroxymethyl and acetoxymethyl groups in I.

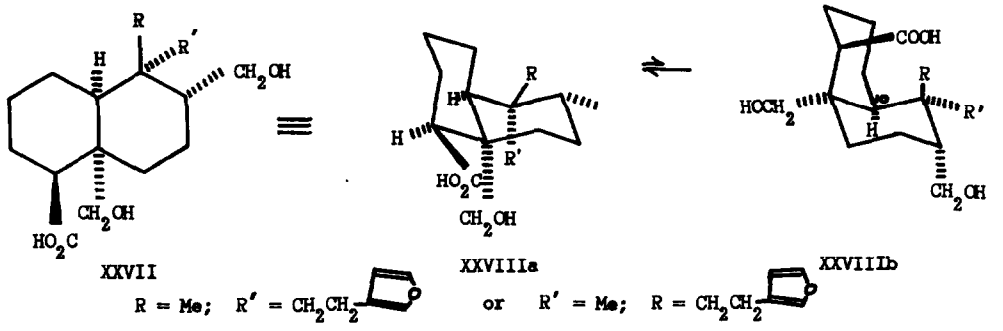
Evidence for the side chain in I followed from a Barbier-Wieland type degradation of a suitably protected tris-nor-acid XXIII. Thus the lactone VII with $POCl_3$ in pyridine gave the chloro-lactone X, m.p. 139-140°, $[\alpha]_D$ -24°, which was saponified with NaOH in a n-butanol and then reduced, by the addition of sodium, to the lactone XI, m.p. 96-97°, $[\alpha]_D$ -13°. Oxidation of XI with ozone followed by the Jones reagent (4) gave the acid XVII, m.p. 156-158°, $[\alpha]_D$ -7°, which was reduced with $LiBH_4$ and the resulting dihydroxy-acid dehydrated with toluene-p-sulphonic acid in benzene to the ether XXIII, m.p. 129-131°, $[\alpha]_D$ +6°. Methylation of XXIII and treatment with phenylmagnesium bromide in ether gave the diphenylcarbinol XXIV, m.p. 181-182°, $[\alpha]_D$ +0°. Dehydration gave XXV, m.p. 103-104°, $[\alpha]_D$ +49°, the NMR spectrum of which showed the vinyl proton as a triplet at 2.24$\tau$ (J=7.5c/s) and 2 proton doublet at 8.82$\tau$ (J=7.5c/s), signals expected for the protons at C-11 and C-12 in XXV which should only couple with each other. Partial structure XXVI summarizes evidence accumulated to this point for the constitution of the natural acid I. Evidence for the decalin ring system was obtained by dehydrogenation of the lactone XI with selenium which gave 1,2-dimethylnapthalene (21%) isolated as the trinitrobenzene adduct. This result together with the evidence summarised in partial structure XXVI requires that natural acid have the constitution I.

Stereochemistry

The carboxyl group in the lactone VII must be equatorial since treatment of the dihydroxy-methyl-ester XIV with NaOMe/MeOH followed by saponification gave mainly the hydroxy lactone VII.

The failure of the dihydroxy-acid XIII to lactonize, even under the forcing conditions of N,N'-dicyclohexylcarbodiimide catalysis is expected if the $-CH_2OH$ and $-CO_2H$ groups have a trans diaxial arrangement. Analogous systems (6) with hydroxymethyl and carboxyl groups on adjacent carbon atoms lactonize spontaneously where the groups have a trans-diequatorial or cis arrangement. The failure of XIII to lactonize also requires a trans A/B ring junction. Where the rings are cis-fused lactonization can be expected for any conformation with the C-4 and C-5 substituents cis. For trans groups conformation XXVIIIa, which should lactonize, is the most stable. Although XXVIIIb would not form a lactone, the carboxyl and C-10 substituent impose strain comparable to 1,3 diaxial

$-CO_2H$ and t-butyl groups and is unfavourable with respect to XXVIIIa. Hence the failure of XIII to lactonize is interpreted in terms of a trans A/B ring



XXVII XXVIIIa XXVIIIb

R = Me; R′ = $CH_2CH_2$–⟨furan⟩ or R′ = Me; R = $CH_2CH_2$–⟨furan⟩

junction and trans-diaxial $-COOH$ and $-CH_2OH$ groups.

A parallel argument is based on the infrared spectrum of the dihydroxy-methyl ester XIV which shows a single intense absorption band at 3640 $cm^{-1}$ ($CCl_4$) due to the two non-bonded primary hydroxyl groups, and carbonyl absorptions at 1730 $cm^{-1}$. The absence of intramolecular hydrogen bonding between the C-19 hydroxyl and the ester carbonyl indicates that they are held remote from each other.

The stereochemistry at C-9 was assigned by an examination of solvent effects (7,8) on the chemical shift of the methyl group in the keto-lactone-ester XXI. A 0.52 ppm. upfield shift of the C(9) methyl group in XXI was observed on changing solvent from $CHCl_3$ to benzene, a value which compares with 0.36 ppm. for the ester XVIII. The difference in these values, 0.16$\tau$, which may be attributed to the effect of the C-8 function, is in reasonable agreement with those for axial methyl groups adjacent to a ketone (8).

To establish the configuration at C-8, the methyl ester of XII was heated with NaOMe/MeOH for 2 days then reduced with $LiAlH_4$ to the triol XXVII, m.p. 183-185°, $[\alpha]_D$ -31°, identical to material obtained from a similar reduction of the lactone-alcohol VII. Hence the acetoxymethyl group in I is considered to have the more stable equatorial position.

The mode of formation of the cyclopentanone XIX would require it to have the more stable cis ring junction (9) regardless of the initial stereochemistry at C-8. The rotary dispersion curve of this compound shows a strong, positive Cotton effect ($[\Phi]_{312}$ +6640°(peak); $[\Phi]_{277}$ -4750° (trough) ) which corresponds closely with that of 23,24-bisnor-A(4)-nor-5β(H)-lupan-3-one (10) establishing the absolute configuration of XIX and the natural acid I.

Hautriwaic Acid:- The lactone VI, $C_{20}H_{26}O_3$, m.p. 119-120°, $[\alpha]_D$ -156° was obtained from a

methylated acidic extract of D. attenuata A. Cunn. var. linearis Benth. after chromatography on alumina. Saponification gave the hydroxy-acid III, m.p. 183-184°, $[\alpha]_D$ -105°. The physical constants of III and the lactone VI suggest that these compounds are identical with hautriwaic acid (ex. Dodonaea viscosa L.) (11) and its lactone respectively. Reduction of the hydroxy-acid III with Na/EtOH gave the lactone XI identical with material prepared from I establishing the structure and stereochemistry of lactone VI and acid III.

## REFERENCES


1. R.M. Dawson, M.W. Jarvis, P.R. Jefferies, T.G. Payne and R.S. Rosich, Aust. J. Chem. 19, 2133 (1966).
2. T.G. Halsall, A.W. Oxford, and W. Rigby, Chem. Comm. 218 (1965) and references therein.
3. R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey and R.W. Kiestead, Tetrahedron 2, 1 (1958).
4. R.G. Curtis, I. Heilbron, E.R.H. Jones, and G.F. Woods, J. Chem. Soc. 457 (1953).
5. K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day Inc., San Francisco (1962).
6. H.H. Appel, J.D. Connelly, K.H. Overton and R.P.M. Bond, J. Chem. Soc. 4685 (1960).
7. M. Fetizon and J.C. Gramain, Bull. Soc. Chim. Fr. 3444(1966).
8. D.H. Williams and N.S. Bhacca, Tetrahedron 21, 2021 (1965).
9. L. Ruzicka, V. Prelog and P. Meister, Helv. Chim. Acta 28, 1651 (1945).
10. N.L. Allinger, R.B. Hermann and C. Djerassi, J. Org. Chem. 25, 922 (1960).
11. Munio Kotake and Kei-ichi Kuwata, J. Chem. Soc. Japan 57, 837 (1936).

12. We thank Dr A.V. Robertson of the University of Sydney for the ORD measurements, and General Motors Holden for a postgraduate award (T.G.P.). This work was supported by Grant No. CA07810-01 from the National Cancer Institute.