Tetrahedron Letters No. 24, pp. 1615-1622, 1963. Pergamon Press Ltd.
Printed in Great Britain.

PIPTOSIDE

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(Received 29 July 1963)

Piptoside, $C_{17}H_{24}O_{12}$, from *Piptocalyx moorei* has been previously characterized as a β-D-glucopyranoside (1). We now present evidence** that piptoside has structure (Ia) in which absolute configurations have so far been assigned only at the methylated carbon atoms in ring L.

Piptoside (Ia), $\nu_{max.}$ 3420, 3230, 1808, 1785, rapidly consumed two equivalents of alkali in aqueous solution; a further slower consumption accompanied by degradation discussed later then occurred. With methyl iodide and silver oxide in formdimethylamide (2) it formed the pentamethyl derivative (Ib), m.p. 123-124°, $[\alpha]_D^{27}$ - 23° (c, 3.3 in $CHCl_3$ or EtOH), $\nu_{max.}$ 1802, 1785. Neither this derivative nor the penta-acetate (Ic), $\nu_{max.}$ 1802, 1755, 1742, showed hydroxyl absorption, and neither

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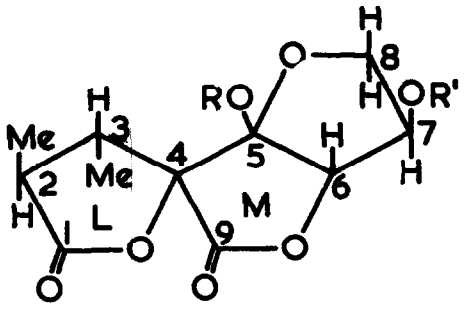
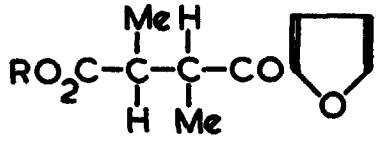
** All new crystalline compounds gave satisfactory analyses. Infrared absorption maxima are in cm^{-1} for Nujol mulls, and assignments not specified are as follows: in the range, 3600-3200 (OH), 1810-1760 (γ-lactone), 1760-1725 (ester), with some overlap in the range 1765-1745. Except as otherwise stated, proton magnetic resonance (p.m.r.) signals are in p.p.m. downfield from a tetramethylsilane reference for deuterochloroform solutions, and J values are in c.p.s.. Relative intensities agree with assignments given.

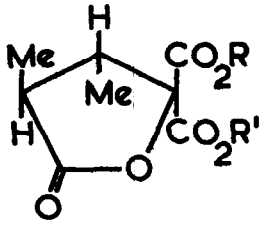


Ia: R = H, R' = GP
Ib: R = Me, R' = TMGP
Ic: R = Ac, R' = TAGP
Id: R = Me, R' = GP
Ie: R = Me, R' = TAGP
If: R = R' = H
Ig: R = R' = Ac
Ih: R = Me, R' = H
Ii: R = Me, R' = Bz

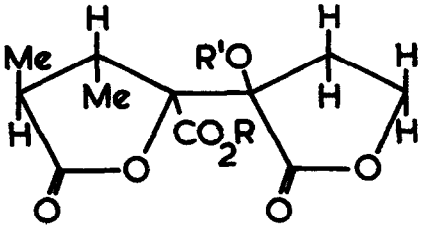
(GP = β-D-glucopyranosyl
TA = 2,3,4,6-tetra-O-acetyl
TM = 2,3,4,6-tetra-O-methyl)



IIa: R = H
IIb: R = Me



IIIa: R = R' = H
IIIb: R = R' = p-$BrC_6H_4COCH_2$
IIIc: R = Et, R' = H
IIId: R = Et, R' = Me



IVa: R = Me, R' = H
IVb: R = Me, R' = Ac
IVc: R = R' = H

parent nor derivatives showed absorption due to free carboxyl or ketone groups or gave any evidence for olefinic unsaturation. Clear features in the p.m.r. spectrum of piptoside (Ia) in deuterium oxide were (i) at highest field near δ1.2, a pair of overlapping doublets, $J \sim 6$ (two $CHC\underline{H}_3$); (ii) at lowest field (δ5.07), a barely-split one-proton signal ($\underline{Y}$; see spectrum of diacetylpiptosidin (Ig) below); and (iii) near δ4.7, a doublet, $J \sim 8$ (axial anomeric H of glucose), which confirms (3) the β-glucopyranoside formulation (1).

Hydrolysis with N-hydrochloric acid at 97° gave D-glucose (1). Extraction of the hydrolysate with chloroform gave (2S,3S)-3-(α-furoyl)-2-methylbutanoic acid (IIa), m.p. 98°, $[\alpha]_D^{16}$ - 2.6° (c, 1.6 in 90% EtOH), $\lambda_{max.}^{EtOH}$ 270, 224 mμ (log ε, 4.16, 3.42), $\nu_{max.}$ 3220, 3120 (furan), 1710 (carboxyl), 1660 (conjugated ketone), 1562 (furan), further characterized as its methyl ester (IIb), m.p. 72°, $\nu_{max.}$ 3140 (furan), 1725 (ester), 1660 (ketone), 1567 (furan), and the red 2,4-dinitrophenylhydrazone of the latter, m.p. 135°, $\lambda_{max.}^{EtOH}$ 380, 262 mμ (log ε, 4.43, 4.24). Ozonolysis of the acid (IIa) gave (-)-2,3-dimethylsuccinic acid of known absolute configuration (4). Subsequent extraction of the hydrolysate with ether gave piptosidin (If), m.p. 185-190°, $[\alpha]_D^{16}$ - 8° (c, 2.0 in H_2O), $\nu_{max.}$ 3500, 3310, 1795, 1765, converted by acetic anhydride and pyridine into diacetylpiptosidin (Ig), m.p. 141°, $[\alpha]_D^{27}$ + 1.2° (c, 2.1 in $CHCl_3$), $\nu_{max.}$ 1810, 1795, 1762, 1750. The p.m.r. spectrum of the latter (Ig) showed the two $CHC\underline{H}_3$ groups as overlapping doublets, $J \sim 6$, near δ1.2, the corresponding methine protons as a multiplet near δ2.5, and the acetate methyl protons as a singlet near δ2.2. The low-field

signals are assigned as follows: quartet B at δ4.23 (exo-H8), quartet A at δ4.65 (endo-H8), doublet Y at δ5.05 (H6), and quartet of doublets X at δ5.37 (endo-H7). Analysis of the ABX system (5) gave $\nu_o\delta_{AB}$ = 25.4, J_{AB} = 10.6, J_{AX} = 6.5, J_{BX} = 4.5; from the doublet splittings, J_{XY} = 0.8. The set of coupling constants is consistent with the above relative stereochemical assignments with AX, BX, and XY dihedral angles near 25°, 135°, and 90°, respectively (6), as may be met approximately in a model by appropriate distortion of the furanose ring from planarity (7), which is accompanied by staggering of the conformation about the C4-C5 bond. The absolute stereochemistry of C4-C7 has not been determined.

Both piptoside (Ia) and piptosidin (If), reacted vigorously with diazomethane in ether-methanol to give monomethyl derivatives which showed no ester absorption in the infrared spectrum. Methylpiptoside (Id), purified by chromatography over cellulose powder in 90% aqueous acetone, was microcrystalline and showed $\nu_{max.}$ 3400, 1810-1790; it was converted by methyl iodide and silver oxide in formdimethylamide (2) into pentamethylpiptoside (Ib), and was further characterized as the tetra-acetyl derivative (Ie), m.p. 190° $[\alpha]_D^{26}$ - 17.6° (c, 3.0 in $CHCl_3$), $\nu_{max.}$ 1797, 1750. Methylpiptosidin (Ih), also produced by the action of 2N hydrogen chloride in boiling methanol on piptoside (Ia), methylpiptoside (Id), or pentamethylpiptoside (Ib), was obtained in two interconvertible forms, both m.p. 155° (undepressed in admixture), $[\alpha]_D^{19}$ - 14° (c, 2.4 in $CHCl_3$), needles, $\nu_{max.}$ 3420, 1797, 1783, or plates, $\nu_{max.}$ 3480, 1802, and further characterized as the benzoyl derivative (Ii), m.p. 165°,

$[\alpha]_D^{27}$ + 10° (c, 3.0 in $CHCl_3$), $\nu_{max.}$ 1805, 1726. Whereas piptoside (Ia) and piptosidin (If) were degraded by alkali, methylpiptoside (Id) and methylpiptosidin (Ih) each consumed 1.9-2.0 equivalents of alkali in water at 75° and was recovered on acidification of the solution after 3 hours, as is expected of the methylfuranosides, (Id) and (Ih).

A solution of piptoside (Ia) in 0.3N sodium hydroxide kept for 6 days at room temperature then acidified gave (-)-2,3-dimethylsuccinic acid (ca. 25%) even when oxygen was rigorously excluded. Glucose was the only reducing compound detected on paper chromatograms of the deionozed aqueous solution. With alkaline hydrogen peroxide, the principal acidic product was 2,3-dimethyl-γ-butyrolactone-4,4-dicarboxylic acid (IIIa), obtained as a hygroscopic syrup but characterized as the di-p-bromophenacyl ester (IIIb), m.p. 174°, and converted by evaporation with ethanol-benzene into the syrupy monoethyl ester (IIIc), showing weak broad bands due to water and carboxyl absorption in the range, 3500-2600, $\nu_{max.}$ 1795, 1745 (carboxyl + ester). We assume the less sterically hindered carboxyl group was that esterified under these conditions. The monoester (IIIc) gave by titration a sodium salt, $\nu_{max.}^{KBr}$ 1777, 1732, 1642 (carboxylate ion), and with ethereal diazomethane the ethyl methyl ester (IIId), m.p. 70-71°, $\nu_{max.}$ 1790, 1762, 1745. Structure (IIId) is defined by the p.m.r. spectrum: two overlapping doublets, $J \sim 6$, near δ1.2 (two $CHC\underline{H}_3$), complex multiplet near δ2.5 (two methine protons), singlet at δ3.8 ($OC\underline{H}_3$), 1:3:3:1 quartet, $J \sim 7$, near δ4.3 ($OC\underline{H}_2CH_3$), and 1:2:1 triplet,

$\underline{J} \sim 7$, near δ1.3 (partly overlapping $CHC\underline{H}_3$ signal) ($CH_2C\underline{H}_3$).

Sodium methoxide in dry methanol at room temperature converted piptoside (Ia) into a mixture of isomers (IVa), with liberation of D-glucose. Methyl α-piptodisinate (α - IVa) (*ca.* 40% yield) had m.p. 149-150°, $[\alpha]_D^{27}$ - 0.4° (*c*, 2.8 in $CHCl_3$), $\nu_{max.}$ 3350, 1775, 1748, 1739, and with cold acetic anhydride and pyridine readily formed the acetyl derivative (α - IVb), m.p. 179°, $[\alpha]_D^{24}$ + 32.4° (*c*, 3.0 in $CHCl_3$), $\nu_{max.}$ 1792, 1772, 1755. Methyl β-piptodisinate (β - IVa) (*ca.* 25% yield) had m.p. 180-182°, $[\alpha]_D^{27}$ - 14.5° (*c*, 2.8 in $CHCl_3$), $\nu_{max.}$ 3450, 1774, 1742, and formed the acetyl derivative (β - IVb), m.p. 144°, $[\alpha]_D^{27}$ - 44° (*c*, 3.0 in $CHCl_3$), $\nu_{max.}$ 1795, 1765, 1740. The isomeric products (IVa) were not interconverted under the conditions of their formation, and each was converted by an excess of sodium hydroxide followed by acidification into the corresponding carboxylic acid (IVc). α-Piptodisinic acid (α - IVc) had m.p. 168°, $\nu_{max.}$ 3370, 2560 (CO_2H), 1784, 1765, 1725 (CO_2H), and its sodium salt $\nu_{max.}$ 3580-3200 (OH + water), 1765, 1630 (carboxylate ion). β-Piptodisinic acid (β - IVc), had m.p. 177°, $\nu_{max.}$ 3430, 2620 (CO_2H), 1770, 1755, 1713 (CO_2H), and its sodium salt $\nu_{max.}$ 3370, 1762, 1627 (carboxylate ion). Neither acid (IVc) gave a colour with ferric chloride, and each regenerated only the corresponding methyl ester (IVa) with ethereal diazomethane. The p.m.r. spectra of the isomers (IVa) and of their acetyl derivatives (IVb) each show the expected features. In particular, integral curves show that each possesses, besides the ester methyl protons (singlet near δ3.9), just two protons attached to oxygenated carbon

(complex multiplet near δ 4.4); these signals were satisfactorily reproduced with limited information obtained by partial analysis as the AB part of ABXY (8). Acetylation causes only minor changes (± 0.07 p.p.m.) in the positions of any signals, which confirms that the acetylatable hydroxyl group in each isomer (IVa) is tertiary.

The products (IVa) may be regarded as saccharinolactones derived from the complicated ketofuranose, piptosidin (If), lactone M being opened by attack of methoxide ion at C9. They are doubtless stereoisomeric at the new asymmetric α-hydroxylactone centre, but configurations have not been assigned. Oxidative cleavage of the C5-C6 bond with alkaline hydrogen peroxide to the acid (IIIa) probably occurs at the diketone intermediate stage (9), and the dimethylsuccinic acid cleaved from piptoside (Ia) by sodium hydroxide corresponds to the formic acid cleaved from simple O-substituted aldoses (9). Similarly, the furan ketoacid (IIa) corresponds to the furfural produced from simple pentoses by action of acid; in the present case, decarboxylation of the potential β-ketoacid system, C5-C4-C9, presumably occurs first.

Theoretically, piptoside (Ia) may be derived by Michael addition of a 5-O-β-D-glucopyranosyl-3-ketoaldonic acid to the isoprenoid, tiglic acid, and this or some variant may represent its biogenesis.

A full account of this work will be submitted to the Australian Journal of Chemistry. We thank Mr. R. Lauzon for most of the infrared spectra, and Dr. H. J. Bernstein, Mrs. G. B. Conway, Mr. R. N. Swindlehurst, and Mrs. A. Westland for various p.m.r. spectra.

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