

HETERODENDRIN IN ACACIA SPP.

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Heterodendrin (1), the glucoside of (S)-2-hydroxy-3-methylbutanenitrile, belongs to a rapidly expanding family of natural products, also including proacacipetalin (2) and congeners (3,4), 3-hydroxyheterodendrin (5), cardiospermin and its esters (6,7), as well as cyanogenic lipids (8) and their allylically rearranged descendants (9). The botanical distribution of heterodendrin appears to be relatively broad, the glucoside being reported from the Sapindaceae (1), Rosaceae (6), Poaceae (10), and a single species of the genus *Acacia* (Leguminosae) (11). Following our earlier study of proacacipetalin (2,12), we report now the isolation of heterodendrin from leaves of *Acacia hebeclada* DC. and *Acacia giraffae* Willd.

Synthesis of heterodendrin was attempted by the Koenigs-Knorr condensation of α -acetobromoglucose with 2-hydroxy-3-methylbutanenitrile. In spite of numerous variations of the reaction conditions, the yield of the tetraacetates of heterodendrin and its epimer epiheterodendrin (13) was low. Thus, the evidence accumulates that the cyanohydrin approach (14-17) to synthesis of natural cyanohydrin glycosides, albeit more straightforward, is generally less efficient compared to the classical synthetic approach of Emil Fischer (18-20). Heterodendrin tetraacetate was also obtained by catalytic hydrogenation of proacacipetalin tetraacetate. The difference between the molecular rotations of heterodendrin tetraacetate and epiheterodendrin tetraacetate was $\Delta[M]_D = 243^\circ$.

The present report indicates that the co-occurrence of heterodendrin and proacacipetalin in *Acacia* may be quite general. Feeding experiments suggest

that proacacipetalin is biosynthesized from L-leucine (21), although the hypothesis that proacacipetalin is formed by way of heterodendrin and its 3-hydroxylated derivative (5) has yet to be verified.

EXPERIMENTAL

ISOLATION OF GLUCOSIDES.—The plant material was collected near Pretoria by Dr. P.J. Robertse, Department of General Botany, University of Pretoria, and obtained through the kindness of Dr. F. Narthey, Institute of Plant Physiology, University of Copenhagen, where voucher specimens are preserved. Air-dried, pulverized leaves of *A. hebeclada* (90 g) or *A. giraffae* (95 g) were dropped in small portions into 2 liters of boiling 80% EtOH over a period of 10 min in order to deactivate hydrolytic enzymes, the extract filtered, and the plant material reextracted with 1 liter of the same boiling solvent. The combined extracts were evaporated and fractionated on a 70×4 cm silica gel column with EtOAc-MeOH (5:1). The cyanogenic (22) fractions were rechromatographed on a 80×2 cm silica gel column eluted with EtOAc-MeOH-H₂O (93:5:2) to give 0.6 g (*A. hebeclada*) or 0.3 g (*A. giraffae*) of a mixture of proacacipetalin and heterodendrin in a ratio of 9:1 and 6:1, respectively (270 MHz ¹H nmr). The mixtures were resolved by hplc on a 25×1.6 cm Lichrosorb RP-18 (10 μ m) column, with H₂O-MeOH (85:15) (4 ml/min, refractive index detection). The glucosides were identified by ¹H- and ¹³C-nmr spectroscopy (2,13,23).

SYNTHESIS OF TETRAACETATES OF HETERODENDRIN AND EPIHETERODENDRIN.—A mixture of 0.86 g (10 mmol) of 2-hydroxy-3-methylbutanenitrile (prepared by mixing isobutyraldehyde with aqueous KCN, acidification with H₂SO₄, extraction with Et₂O and distillation), 4.5 g (11 mmol) of α -acetobromoglucose, 2.8 g (11 mmol) of Hg(CN)₂, and 12 ml of freshly redistilled MeNO₂ was stirred overnight at room temperature. The mixture was evaporated, taken up to Et₂O, filtered, and chromatographed on a 80×2 cm silica gel column with Et₂O. The least polar fractions were rechromatographed in the same system to give, in order of elution, 60 mg of heterodendrin acetate and 65 mg of epiheterodendrin acetate (total yield 3%). Numerous variations of the reaction condi-

tions (various solvents, use of AgCN, AgBF₄, AgClO₄, Ti₂CO₃, Hg(CN)₂/HgBr₂) did not lead to any significant improvement of the yield, as judged from ¹H-nmr spectra of the crude reaction products.

Heterodendrin tetraacetate.—Mp 106-107° [lit. (24) mp 106-108°]; [α]_D²⁵ = -45° (c=0.5, MeOH) [lit. (24) -37°]; ¹H nmr (270 MHz, CDCl₃) 1.04 and 1.05 (CH₃, each d, ³J=7 Hz), 2.01, 2.04, 2.07, and 2.10 (CH₃CO), 3.76 (H5'), 4.18 and 4.26 (H6'A and H6'B, ²J_{AB} = -12.5 Hz, ³J_{AX} = 2.5 Hz, ³J_{BX} = 4.5 Hz), 4.43 (H2, d, ³J = 5.5 Hz), 4.76 (H1', d, ³J = 7.8 Hz), 5.04, 5.10, and 5.25 (H2', H3', H4'); ¹³C nmr (125.7 MHz, CDCl₃) 17.12 and 17.70 (CH₃), 31.60 (C3), 61.63 (C6'), 68.20 (C4'), 70.69, 71.86, 72.32, and 72.46 (C2, C2', C3' and C5'), 98.55 (C1'), 116.37 (C1), acetate groups 20.57 (three), 20.71, 169.37, 169.45, 170.10, 170.58.

Epibeterodendrin tetraacetate.—Mp 139-140° [lit. (13) mp 144°]; [α]_D²⁵ = +11.5° (c=0.5, MeOH); ¹H nmr (270 MHz, CDCl₃) 1.04 and 1.06 (CH₃, each d, ³J = 7 Hz), 2.01, 2.03, 2.03, and 2.10 (CH₃CO), 3.78 (H5'), 4.06 (H2, d, ³J = 6 Hz), 4.15 and 4.32 (H6'A and H6'B, ²J_{AB} = -12.5 Hz, ³J_{AX} = 2.5 Hz, ³J_{BX} = 5.5 Hz), 4.64 (H1', d, ³J = 7.8 Hz), 5.05, 5.09, and 5.21 (H2', H3', H4'); ¹³C nmr (125.7 MHz, CDCl₃) 17.54 and 17.63 (CH₃), 32.31 (C3), 61.87 (C6'), 68.33 (C4'), 71.19, 72.32, and 72.56 (C2', C3' and C5'), 74.32 (C2), 101.58 (C1'), 116.96 (C1), acetate groups 20.54, 20.57 (two), 20.71, 169.00, 169.36, 170.27, 170.76.

HYDROGENATION OF PROACACIPETALIN TETRAACETATE.—The acetate (100 mg) (2) was hydrogenated on Pd/BaSO₄ in dioxane at ambient pressure and temperature to give, after purification by chromatography (silica gel, Et₂O), 60 mg (60%) of heterodendrin tetraacetate, identical in all respects with synthetic material.

ACKNOWLEDGMENTS

Nmr equipment (Bruker HX 270 and AM 500) used in this work was purchased by the Danish Natural Science Research Council and the Carlsberg Foundation.

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Received 26 March 1986