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PLANTS AS A SOURCE OF CHIRAL CYCLOPENTENES: TARAKTOPHYLLIN AND EPIVOLKENIN, NEW CYCLOPENTENOID CYANOHYDRIN GLUCOSIDES FROM FLACOURTIACEAE[1]

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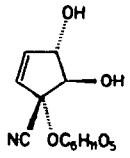
Abstract: Naturally occurring cyclopentenoid cyanohydrin glucosides are hydrolyzed enzymatically to chiral, hydroxylated 2-cyclopentene-1-ones, of potential interest as synthetic intermediates. Two novel cyclopentenoid cyanohydrin glucosides, taraktophyllin and epivolkenin [respectively (1R,4S)- and (1S,4R)-1-(β-D-glucopyranosyloxy)-4-hydroxy-2-cyclopentene-1-carbonitrile] were isolated from Taraktogenos heterophylla and Hydnocarpus anthelmintica (Flacourtiaceae), the structures being assigned on the basis of spectroscopic and optical rotation (the Brewster rules) data.

Chiral derivatives of cyclopentene are of interest as starting materials for synthesis af many classes of bioactive natural products,[5] for example the antibiotics pentenomycins[6] and other mould metabolites[6b,7,8] and, notably, the prostaglandins.[9] In particular, routes to optically active 4-hydroxy-2-cyclopentene-1-ones have been the subject of many synthetic endeavours,[5,10-14] often employing enzymes as chiral inducers. We wish to point out that optically pure hydroxycyclopentenones are obtainable by enzymatic hydrolysis of natural cyclopentenoid cyanohydrin glucosides,[3,4] which occur in a pantropical cluster of plant families consisting of Flacourtiaceae,[15] Passifloraceae,[16] Turneraceae, Malesherbiaceae[18] and Achariaceae.[19] Some of these plants are commercially exploited for their seed oils,[20] others (Passiflora) are common ornamental plants. The contents of cyclopentenoid glucosides in fresh tissues vary from traces to 0.5-1%,[2-4,16,21] in extreme cases reaching 7%.[22] A typical representative of the group is gynocardin (1),[22] a derivative of (2) which is a potential intermediate for synthesis of (+)-terrein.[7a] Perhaps even more common are tetraphyllin B (3) and volkenin (4),[3,4] hydrolyzable to the useful[5] cyclopentenones (5) and (6).[3,4]



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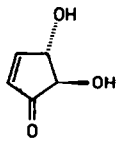

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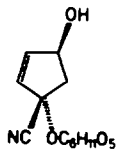

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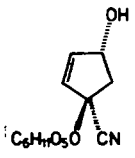

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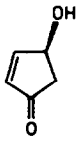

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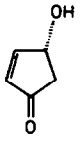

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$C_6H_{11}O_5$ = β-D-glucopyranosyl

Table 1. ^{1}H NMR Spectra of Taraktophyllin and Epivolkenin and their Derivatives.[a]

	H-2,H-3[b]	H-4[c]	H-5	H-1'[d]	H2'	H3'	H4'	H5'	H6'
Taraktophyllin (7)	6.13 and 6.23	4.81	2.22 and 3.04[e]	4.67	3.22[f]	g	g	g	3.67 and 3.87[h]
Epivolkenin (8)	6.14 and 6.27	4.81	2.25 and 3.02[e]	4.62	3.22[f]	g	g	g	3.68 and 3.86[h]
Taraktophyllin pentaacetate[i]	6.13 and 6.23	5.63	2.19 and 3.17[j]	4.97	5.04[kl]	5.25[k]	5.05[kl]	3.81	4.20 and 4.23[m]
Epivolkenin pentaacetate[n]	6.05 and 6.29	5.65	2.37 and 3.06[j]	4.91	5.03[kl]	5.24[k]	5.04[kl]	3.79	4.17 and 4.22[m]
Penta-O-trimethylsilyltaraktophyllin	6.03 and 6.18	4.83	2.16 and 3.03[o]	4.65	p	p	p	p	3.62 and 3.79[r]
Penta-O-trimethylsilylepivolkenin	5.96 and 6.11	4.82	2.24 and 3.01[o]	4.57	p	p	p	p	3.64 and 3.76[r]

[a] 250 or 500 MHz spectra in methanol-d_4 (free glucosides) or chloroform-d (the derivatives). [b] J_{AB} 5.5 Hz, J_{AX} 1.5 Hz (1.2 Hz for the acetates), J_{BX} 2.0 Hz. [c] Complex pattern. [d] $J_{1,2}$ 7.7 Hz for the glucosides, 7.9 Hz for the acetates, 7.3 Hz for the TMS-ethers. [e] J_{AB} -14.5 Hz, J_{AX} 4.8 Hz, J_{BX} 7.2 Hz. [f] $J_{1,2}$ 7.7 Hz, $J_{2,3}$ ca. 9 Hz. [g] Complex pattern at 3.30-3.40. [h] J_{AB} -12.0 Hz, J_{AX} 5.5 Hz, J_{BX} 2.0 Hz. [i] Acetyl groups at δ 2.01, 2.04, 2.06 (two) and 2.09. [j] J_{AB} -15.0 Hz, J_{AX} 4.5 Hz, J_{BX} 7.2 Hz. [k] Assigned by comparison with deidaclin and tetraphyllin A (ref. 2). [l] The assignment may be reversed. [m] J_{AB} -12.3 Hz, J_{AX} 2.5 Hz, J_{BX} 5.5 Hz. [n] Acetate groups at δ 2.01, 2.04, 2.05, 2.07 and 2.10. [o] J_{AB} -14.0 Hz, J_{AX} 5.8 Hz, J_{BX} 6.9 Hz. [p] Complex pattern at 3.25-3.45. [r] J_{AB} -11.0 Hz, J_{AX} 5.5 Hz, J_{BX} 2.2 Hz.

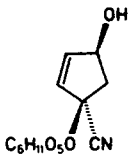
Table 2. ^{13}C NMR Spectra of Taraktophyllin and Epivolkenin and their Derivatives.[a]

	C-1	C-2,C-3	C-4	C-5	CN	C-1'	Remaining glucose carbons
Taraktophyllin (7)	82.8	133.2,142.6	74.4	48.2	120.4	101.7	62.9,71.6,75.0,78.2,78.4
Epivolkenin (8)	82.3	132.1,143.3	75.0	>48.2[b]	120.6	101.2	62.9,71.7,75.0,78.2,78.4
Taraktophyllin pentaacetate[c]	81.1	133.9,137.2	74.8	44.1	117.2	98.1	61.9,68.3,70.9,72.4,72.7
Epivolkenin pentaacetate[c]	80.8	132.8,138.0	75.7	44.6	117.5	98.0	61.9,68.3,71.0,72.5,72.7
Penta-O-trimethylsilyltaraktophyllin	80.9	132.4,140.3	73.1	47.7	118.5	100.8	62.2,71.6,75.3,77.4,78.4
Penta-O-trimethylsilylepivolkenin	80.3	130.4,141.5	74.0	49.3	118.6	99.9	62.0,71.5,75.0,77.5,78.3

[a] 62.9 or 125.7 MHz spectra in methanol-d_4 (free glucosides) or chloroform-d (the derivatives). [b] The resonance is obscured by the solvent resonance; in deuterium oxide this carbon appears at δ 46.5 (remaining resonances in this solvent δ 61.1,70.0,73.4,73.8,76.1,81.5,99.7,120.0,130.7 and 142.8). [c] Acetyl groups at δ 20.6 (three), 20.7,20.9,169.2,169.4,170.1,170.3 (epivolkenin acetate) or 170.4 (taraktophyllin acetate), 170.6.

In this paper we report on isolation of two new cyclopentenoid cyanohydrin glucosides (7) and (8). Together with (3) and (4) they comprise all the stereoisomers of 1-(β-D-glucopyranosyloxy)-4-hydroxy-2-cyclopentene-1-carbonitrile; the cyclopentenoid moieties of (7) and (8) represent enantiomeric forms of the carbon framework of the Hantzsch acid, a synthetically useful ring-contraction product of phenol.[8,13]

Hydnocarpus anthelmintica Pierre ex Lanessan (Flacourtiaceae[23]) is a tree which occurs abundantly in parts of South East Asia. Its seed oil (chaulmoogra oil[20]) is allegedly active against leprosy, and the seeds have been studied extensively.[24,25] However, although the plant has long been recognized as cyanogenic[26] and used as a source of β-glucosidase,[15,27] no glycosidic constituents responsible for the cyanogenesis have been isolated thus far.[26,28] Taraktogenos heterophylla (Blume) van Slooten[23] is closely related. We investigated leaf material of these plants and found mixtures of (7) and (8) in each case, in a ratio of 3:1 (T.heterophylla, total yield 0.21% of fresh weight) or 1:3 (H.anthelmintica, 0.24%). The compounds are readily separable by HPLC on silica gel.



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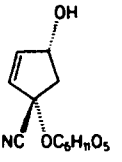

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^1H and ^{13}C NMR spectral data for (7) and (8) and their derivatives are collected in Tables 1 and 2. Comparison of the ^1H NMR spectra with those of (3) and (4)[3,4] reveals characteristc differences between the two pairs. The separation between the resonances of ring methylene protons is for (3) and (4) and their derivatives 0.18-0.69 ppm,[4] and for (7) and (8) and the derivatives 0.69-0.98 ppm (Table 1). This reflects the different numbers of oxygen atoms intimately juxtaposed to each hydrogen atom of the methylene group in the two pairs. Moreover, the chemical shift of the allylic protons in (3) and (4) (δ 4.98[4]) is significantly higher than for (7) and (8) (δ 4.81, Table 1), according to the change of relative stereochemistry at C-1. Thus the allylic oxygen atoms in (3) and (4) are trans,[3,4] and in (7) and (8) are cis.

Because of the low conformational free energy of the cyano group[29] as compared with oxygen functions,[30] the conformational equilibrium of the cyclopentene ring in (7) and (8) is expected to be significantly more biased (both allylic C-O bonds semiequatorial) than in (3) and (4) (one C-O bond semiequatorial, another semiaxial). Accordingly, the coupling constants in the cyclopentene ring are identical within the pairs but distinctly different between them. The differences in chemical shifts of olefinic protons, olefinic carbons, and anomeric protons and carbons between (7) and (8) parallel closely those observed for (3) and (4),[3,4] according to the chirality of C-1. In particular, the resonances of anomeric carbons and protons and of the cyanohydrin carbons (C-1) appear without exception at lower fields in the (1R) series than in the (1S) series,[2-4] both for the free glucosides and for their derivatives (Tables 1 and 2).

The absolute chirality of the aglucones of (7) and (8) is also apparent from application of the Brewster rules[31] to these systems. Thus, the rotatory contribution of the allylic hydroxy group, largely determined by its interaction with the double bond, should be negative for (7) and positive for (8).[31c] The rotatory contributions of the substituents at C-1 largely cancel each other, as the molecular rotations of epimeric β-D-glucopyranosides of unsubstituted cyanohydrin of

2-cyclopentene-1-one, $[M]_D$ -68° and -54° for the (1R) and (1S) form,[2] are very much like those of β-D-glucopyranosides with achiral aglucones.[4] The observed rotations of (7) and (8) should hence be dominated by the contribution from the free allylic hydroxy group. Indeed, the molecular rotations $[M]_D$ of (7) and (8) are -219° and +127°, respectively 151° more levorotatory and 181° more dextrorotatory than for the non-hydroxylated[2] counterparts. These differences correspond well to the molecular rotation of 2-cyclopentene-1-ol, $[M]_D$ ±165°.[4] The structures (7) and (8) are thus proved.

Finally, enzymatic hydrolysis of (7) and (8) with molluscan β-glucosidase[3,4] gave practically quantitative yields of the enantiomeric ketones (3) and (4), with spectroscopic and chirooptical properties identical with those reported before.[3,4,11] Because (8) is a C-1-epimer of (4), we propose the name epivolkenin for this glucoside. Similarly, (7) might take the trivial name epitetraphyllin B. Since this name, however, has been earlier erroneously used for (4),[3] we propose the name taraktophyllin for (7).

As in previously studied Passifloraceae, typically producing (3) and (4),[3,4] also the members of Flacourtiaceae investigated in this work contain mixtures of β-D-glucopyranosides of enantiomeric cyanohydrins. However, the enzymes involved in the biosynthesis of taraktophyllin and epivolkenin exhibit a different type of stereospecificity, the allylic hydroxy group at C-4 being introduced from the face trans to the cyano group of the cyclopentene ring, as in gynocardin (1). Whether (7) and (8) are equally broadly distributed as (3) and (4) has yet to be determined.

EXPERIMENTAL[32]

Plant material used in this work was collected in the National Botanical Garden, Meise, Bruxelles, Belgium, in April. The extracts were prepared in the usual way[2,4] using 85% aqueous methanol. The extract of H.anthelmintica (1.05 g, corresponding to 10 g of fresh leaves) was fractionated on silica gel (28 x 4 cm column), using ethyl acetate/acetone/dichloromethane/methanol/water 40:30:12:10:8, and the glucosides purified by HPLC on Lichrosorb RP-18 (7 μm, 25 x 1.6 cm column), eluted with methanol/water 1:4 (4 ml/min, retention time 11.8 min). The glucosides were separated by repeated HPLC on Lichrosorb Si60 (7 μm, 25 x 1.6 cm column), using ethyl acetate/methanol/water 85:13:2 (4 ml/min); retention times of (7) and (8) were 19.1 and 20.1 min (k' 0.75 and 0.84, separation factor 1.12, resolution 1.0). The yield was 6.2 mg of (7) and 17.5 mg of (8) (total yield 0.24% of fresh weight). Fractionation of 2.4 g of T.heterophylla extract (corresponding to 18 g of fresh leaves) in identical way afforded 25 mg of (7) and 13.2 mg of (8) (total yield of 0.21%), identical (^1H and ^{13}C NMR, $[\alpha]_D$) with the samples isolated from H.anthelmintica. Acetates and trimethylsilyl derivatives of the glucosides were obtained in usual way.[2,4,33]

Taraktophyllin (7): colourless syrup; $[\alpha]_D^{23}$ -75° (c 1, methanol). Pentaacetate: m.p. 126-127°C (corr.); $[\alpha]_D^{23}$ -48° (c 0.5, methanol); ν_{max}^{KBr} 1750 (s), 1735 (s), 1620 (w) cm^{-1}. Anal. $C_{22}H_{27}NO_{11}$: C, H, N.

Epivolkenin (8): colourless syrup; $[\alpha]_D^{23}$ +43° (c 1, methanol). Pentaacetate: m.p. 131-132°C (corr.); $[\alpha]_D^{23}$ +23° (c 0.5, methanol); ν_{max}^{KBr} 1750 (s), 1735 (s), 1620 (w) cm^{-1}. Anal. $C_{22}H_{27}NO_{11}$: C, H, N.

Enzymatic hydrolyses of the glucosides (ca. 10 mg) were carried out as previously described for (3) and (4).[3,4] Circular dichroism spectra of (5) and (6) were identical with those reported earlier.[3,4]

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