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STRUCTURES OF TWO HIGHLY OXYGENATED IRIDOID GLUCOSIDES FROM *Globularia alypum*[1]

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Summary - Structures of two acylated iridoid glucosides 1 and 6 were determined on the basis of chemical transformation and spectroscopic evidence.

In a recent communication, we have reported[2] the structure of globularidin, an unusual iridoid glucoside lacking the typical bond between C-3 and C-4, isolated from *Globularia alypum* L.. Further investigation with the plant extract resulted in the isolation of two other new iridoids. The structure elucidation of these compounds constitutes the subject of this communication.

Globularimin (1), $C_{24}H_{30}O_{12}$ ($M^{+\cdot}$, 510 FD), $[\alpha]_D^{20}$ = -105.97 (c=0.64, MeOH), on hydrolysis with emulsin yielded D-glucose. Likewise, hydrolysis with methanolic NaOH (0.1 N) afforded cinnamic acid and *des*-cinnamoyl globularimin (2), $C_{15}H_{24}O_{11}$ ($M^{+\cdot}$, 380), $[\alpha]_D^{20}$ = -139.89 (c=0.64, MeOH). In the IR spectrum (KBr) of 1 significant bands appeared at 3400 (br., OH), 1702 (COO), 1638 (C=C), 1580, 1495 and 1450 cm^{-1} (aromatic ring). The UV absorption spectrum showed λ_{max} (MeOH):217 (log ε 4.08), 223 sh, 278 (4.38) nm, characteristic of a cinnamoyl ester chromophore. The 100 MHz ^1H NMR spectrum of 1 in CD_3OD exhibited, besides the signals due to five aromatic (7.62-7.30 ppm) and two olefinic protons (7.72 and 6.52 ppm, AB system, J=16 Hz) arising from the *trans*-cinnamoyl ester part of the molecule, signals at 6.22 (1H, dd, J=7 and 1.5 Hz, H-3), 5.54 (1H, d, J=5 Hz, H-1), 5.08 (1H, dd, J=7 and 3 Hz, H-4), 4.62 (1H, d, J=7 Hz, H-1'), 4.56 and 4.32 (2H, AB system, J=13 Hz, H-10), 2.72-2.30 ppm (2H, m, H-5 and H-9) and the signals due to glucose protons[3]. The 25.2 MHz ^{13}C NMR spectrum of 1 in CD_3OD showed apart from the signals due to cinnamoyl residue, signals corresponding to 15 carbon atoms, consistent with an iridoid glucoside structure. ^{13}C NMR spectral data of 1 and 2 (Table) clearly revealed the site of acylation. The spectrum of 1 differs from 2 mainly in the resonance value of C-10. The signal for C-10 in 1 appeared at 66.41 ppm whereas in 2 this signal is shifted 2.12 ppm upfield, thereby locating the site of acylation at C-10. Acetylation of 1 provided a hexa-

acetate 3, $C_{36}H_{42}O_{18}$ ($M^{+\cdot}$, 762), $[\alpha]_D^{20}$ = -81.08 (c=0.63, $CHCl_3$), in which one hydroxy group remained unaffected (IR, ^1H NMR and M-17 peak) indicating its tertiary nature. Prolonged acetylation, however, afforded the heptaacetate, 4, $C_{38}H_{44}O_{19}$ ($M^{+\cdot}$, 804), $[\alpha]_D^{20}$ = -81.83 (c=0.63, $CHCl_3$).

Taken together, these data support the gross structure 1 (disregarding the stereochemistry). On the basis of comparison of existing data [4] for the coupling constants, H-1, H-5 and H-9 can be placed α-, β-, and β- positions, respectively, leaving the configurations at the three carbinol centers in the cyclopentane ring undecided.

Due to the ambiguity in the interpretation of the proton-proton coupling constants in saturated five membered rings[5], the configuration at C-6, C-7 and C-8 was assigned with the aid of ^{13}C NMR[6,7,8]. It has been ovserved that a α-hydroxy group at C-8 causes deshielding at C-9 as compared to its α-counterpart and they absorb at 50 ± 1.5 ppm. This is corroborated by the shifts observed in the ^{13}C NMR spectra of 1 and 2, indicating thereby a β-hydroxy function at C-8. C-6 and C-7 in 1 and 2 absorb at rather lowfield and this indicates a *trans*-1,2-diol arrangement at these two carbons. Additional evidence regarding the stereochemistry at C-6 and C-7 can be obtained from ^1H NMR (360 MHz) of 4. Irradiation of the multiplet centered at 2.82 ppm (H-5) simplified both the signals at 4.85 ppm (tdd, $J_{5,7}$=2 Hz and $J_{6,7}$=2.5 Hz, H-6), and at 5.62 ppm (dd, $J_{5,7}$=1 Hz and $J_{6,7}$=2.5 Hz, H-7) to doublet, indicating thereby a long-range coupling (W-coupling) between H-5 and H-7 and demands a *cis*-relationship between these protons. $J_{5,6}$ is small (2 Hz) which demands a dihedral angle close to 90° between H-5 and H-6, necessiating a *trans*-relationship of these protons[9]. The above observations lends credence to structure 1 for globularimin. Globularimin can be visualized to have been derived from globularin 5 (or equivalent) by cleavage of epoxide ring.

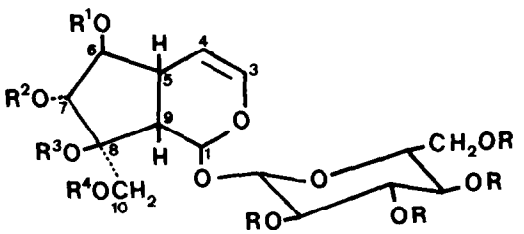
Consequently, a search has been made to isolate the other isomer 6, which can also be formed from 5 by the opening of epoxide from the other side. The structure of this compound 6, named globularinin, is based upon the following data.

Globularinin (6), $C_{24}H_{30}O_{12}$ ($M^{+\cdot}$, 510), $[\alpha]_D^{20}$ = -84.47 (c=0.64, MeOH). The presence of D-glucose and cinnamic acid in the molecule is confirmed by hydrolytic experiments. The UV and IR spectra of 6 were very similar to that of 1. The 100 MHz ^1H NMR spectrum of 6 in CD_3OD revealed the signals, with their assignments in parenthesis, at 6.31 (1H, dd, J=6 and 1 Hz, H-3), 5.28 (1H, d, J=6 Hz, H-1), 5.12 (1H, dd, J=6.5 and 3 Hz, H-4), 4.65 (1H, d, J=9 Hz, H-1'), 4.55 and 4.34 (2H, AB system, J=12 Hz, H-10), 2.84-2.58 (1H, m, H-5), 2.40 ppm (1H, dd, J=10 and 6 Hz, H-9), and the signals arising from glucose[3] and *trans*-cinnamoyl protons. The ^{13}C NMR data of 6 are given in the Table. The placement of cinnamoyl

Table. ^{13}C NMR Data of 1, 2, 6 and 7*

Compd.	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1	93.48	140.45	105.84	38.38	83.76	85.38	80.23	48.89	66.41
2	93.34	140.39	106.54	37.32	83.14	86.42	80.33	48.04	64.29
6	96.29	140.61	106.40	38.86	78.63	78.63	81.36	44.59	69.01
7	95.16	141.61	105.27	37.16	78.34	79.34	81.03	43.70	66.37

* The spectra were recorded in CD_3OD. In 7 few drops of DMSO-d_6 were added to increase the solubility. Chemical shifts in ppm relative to $(CH_3)_4Si$. Additional signals arising from glucose. Compds 1 and 6 in addition those from cinnamoyl part.

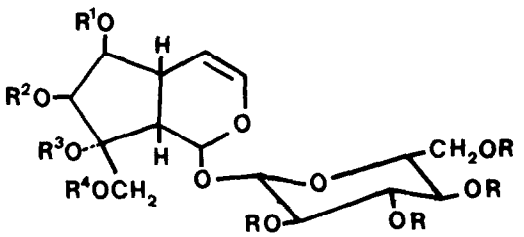


1. $R=R^1=R^2=R^3=H$; $R^4=C_6H_5CH=CH-CO$

2. $R=R^1=R^2=R^3=R^4=H$

3. $R=R^1=R^2=Ac$; $R^3=H$; $R^4=C_6H_5CH=CH-CO$

4. $R=R^1=R^2=R^3=Ac$; $R^4=C_6H_5CH=CH-CO$

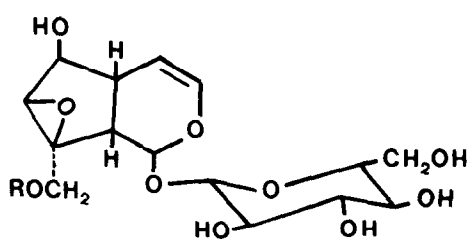


6. $R=R^1=R^2=R^3=H$; $R^4=C_6H_5CH=CH-CO$

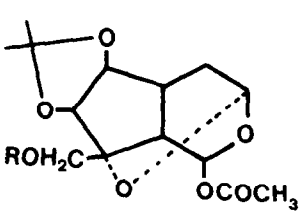
7. $R=R^1=R^2=R^3=R^4=H$

8. $R=R^1=R^2=Ac$; $R^3=H$; $R^4=C_6H_5CH=CH-CO$

9. $R=R^1=R^2=R^3=Ac$; $R^4=C_6H_5CH=CH-CO$



5. $R=C_6H_5CH=CH-CO$



10. $R=C_6H_5CH=CH-CO$

group at C-10 was made, as before, by comparison of 6 and 7. Acetylation of 6 afforded a hexaacetate 8, $C_{36}H_{42}O_{18}$ ($M^{+\cdot}$, 762), $[\alpha]_D^{20}$ = -97.06 (c=0.61, $CHCl_3$). Prolonged acetylation, however, provided a heptaacetate 9, $C_{38}H_{44}O_{19}$ ($M^{+\cdot}$,804), $[\alpha]_D^{20}$ = -95.03 (c=0.50, $CHCl_3$). Definite proof for the structure 6 for globularinin was gained from its transformation to 10 (structure established by ^1H and ^{13}C NMR). Treatment of 6 with acetone-$HClO_4$ at room temperature (45 min) followed by acetylation gave 10. This established the stereochemistry at C-5, C-6, C-7, C-8 and C-9 of the aglucone, as the ring must be *cis*-fused and 8-OH group α-oriented for the cyclization to proceed[10]. In addition formation of acetonide demonstrated the *cis*-diol function at C-6 and C-7.

The occurrence together in the same plant of globularin 5 and its corresponding two *trans*-diols globularimin 1 and globularinin 6, and globularidin [2], is perhaps unique. Globularin thus act as a link between the two compounds (1 and 6) and the recently reported[2] dihydrocompound, globularidin.

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References and Notes

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