Seco-cyclopentane Glucosides from *Menyanthes trifoliata*: Foliamenthin, Dihydrofoliamenthin, and Menthiafolin

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Menyanthes trifoliata is rich in glycosides, of which loganin (I) is the only one to have been isolated[1] in the pure state. Extensive fractionation† of the remaining material by countercurrent distribution has now afforded sweroside (IIa), of known structure and absolute stereochemistry,[2,3] together with three new glycosides, foliamenthin, menthiafolin, and dihydrofoliamenthin. The first two have been obtained crystalline and all three have proved to be of crucial importance for research on the biosynthesis of indole alkaloids (see accompanying papers)[4]. The essential data are now presented which establish structures (VIa) for menthiafolin and (VIIa) for dihydrofoliamenthin, and which characterise foliamenthin.

Foliamenthin, $C_{26}H_{36}O_{12}$, has m.p. 194—196°, $[\alpha]_D$ — 63° (MeOH), and it yielded a penta-*O*-acetyl derivative [*m/e* 750 (M^+), 525, 403, 331]. The u.v., i.r., and n.m.r. spectra of the glycoside and its penta-acetate supported the presence of the following groups: –O·CO–C(|)=CH–O–, –C(|)=C(|)–CO_2–, and two Me–C(|)=CH– residues. At this stage, we learned of Professor Arigoni's studies on foliamenthin: by informing us of his results, he gave considerable help to our structural work. Comparison of the two specimens of foliamenthin penta-acetate confirmed identity and, by friendly agreement, research on foliamenthin continued in Zürich whilst our efforts were concentrated on the other two glycosides.

† We thank Dr. R. S. Kapil who carried out preliminary isolation work on the glycosides.

The i.r. spectrum of menthiafolin (VIa), $C_{26}H_{36}O_{12}$, m.p. 186°, $[\alpha]_D$ − 68° (MeOH), showed strong unresolved carbonyl absorption in the range 1685—1740 cm.$^{-1}$ (at half-band height), due to overlapping peaks from the functions –O·CO–C(=)=CH–O– and –CH=CMe–CO_2– as was evident from the n.m.r. spectrum of menthiafolin tetra-*O*-acetate (Table); the u.v. spectrum was in agreement (λ_{max} 228, sh 245 mμ). The general composition of menthiafolin tetra-acetate was clear from its mass spectrum [*m/e* 708 (M^+), 693, 525, 361, 331] which allowed the recognition of three main units. The fragment at *m/e* 525 corresponds to the loss of $C_{10}H_{15}O_3$ from the parent ion and so to the favoured cleavage (*a*) in (VIb). Similar fission at (*b*) (VIb) accounts for the ion of *m/e* 361. Finally, that part of menthiafolin which is present in both fragments formed by cleavage at (*a*) or at (*b*) must comprise $C_{10}H_{10}O_3$, by difference. The intense peak at *m/e* 331 is assigned to (III), the normal fragment[5] from tetra-*O*-acetylglucosides.

Methanolic alkali cleaved menthiafolin to yield some menthiafolic acid but mainly the corresponding methyl ester, $C_{11}H_{15}O_3$, $[\alpha]_D$ + 11° ($CHCl_3$), λ_{max} 225 mμ (log ε 4·1). The mass spectrum showed M^+ 198 together with significant peaks at *m/e* 183, 180, 121, and 71. These fragmentations and the n.m.r. spectrum (Table) identified methyl menthiafolate as the linalool derivative (XII) and confirmation was achieved by synthesis (see later). The stereochemistry of the αβ-unsaturated ester function was assigned by comparing the chemical shift of the C-7′ proton with the position of signals from protons in substances of known configuration.[6]

The water-soluble product from alkaline cleavage of menthiafolin was characterised by conversion into the penta-*O*-acetate (Vb), λ_{max} 240 mμ (log ε 3·82), which was a mixture of C-5 epimers as shown by t.l.c. and n.m.r. Cleavage at (*a*) and (*b*), [see (Vb)] was again observed in the mass spectrum [*m/e* 584 (M^+), 525, 331, 237]. Reduction of the water-soluble product with borohydride afforded sweroside (IIa), which gave a tetra-*O*-acetate (IIb), m.p. 167—168°, $[\alpha]_D$ − 174° ($CHCl_3$), identical with the same derivative of natural sweroside.[2,3]‡

Menthiafolin must now be assembled from two units which give rise to the lactol acetates (Vb) and to the ester (XII). The evidence outlined above allows only one structure (VIa) which, apart from the configuration at C-1§ and C-5 is a complete representation of menthiafolin.

The work on dihydrofoliamenthin (VIIa),

Assignment of n.m.r. spectra determined[a] *at 100 and 220 MHz (τ values)*

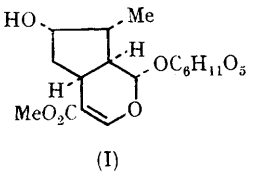
Substance	3 + 4	5	9	Position of proton 1′	2′	4′	7′	9′	CH_2OAc of glucose	No. of OAc groups (*ca.* τ 8·0)
Foliamenthin[b] (VIIIa)	4·7m	3·48m	2·43d	—	c	8·35m	3·30	8·24d	—	—
Foliamenthin penta-acetate[8]	c	3·32m	2·40d	5·45d	c	8·30m	3·04t	8·20m	5·70dd 5·90dd	5
Menthiafolin tetra-acetate (VIb)	c	3·35m	2·40d	c	4·09dd	8·68s	3·06t	8·13d	5·70dd 5·90dd	4
Dihydrofoliamenthin penta-acetate (VIIb)	c	3·40m	2·40d	5·49d	c	8·25m	—	8·78d	5·76dd 5·90dd	5
The lactol acetates (Vb)	c	3·20m 3·53d	2·42d	—	—	—	—	—	5·71dd 5·87dd	5
Methyl menthiafolate (XII)	—	—	—	4·80dd (*trans*) 4·92dd (*cis*)	4·06dd	8·69s	3·21dt	8·17d	—	—
Methyl dihydrofoliamenthate (XIV)	—	—	—	5·90d	4·68t	8·28m	c	8·84d	—	—

[a] Spectra determined in $CDCl_3$ unless otherwise stated; integration was in agreement with assignments given. [b] Determined in MeOD. [c] Obscured by other signals.

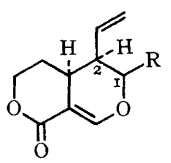
‡ Kindly provided by Prof. H. Inouye.

§ It is probable that menthiafolin and its analogues are biosynthesised by cleavage of loganin without disturbance of the C-1 centre; on this basis, the glucose residue at C-1 of menthiafolin (VIa) would be α-oriented. However, the C-1 glucose residue of sweroside (IIa) has been assigned the β-configuration by n.m.r.[3] and by unpublished evidence (H. Inouye, S. Ueda, and Y. Takeda, *Tetrahedron Letters*, 1968, 3453). This stereochemical anomaly is being investigated.

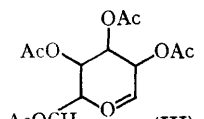
$C_{26}H_{38}O_{12}$, $[\alpha]_D$ — 65° (MeOH), followed closely the foregoing approach; it is only necessary therefore to outline the main results. The absence of an $\alpha\beta$-unsaturated ester function was clear from the u.v. and i.r. spectra of dihydrofoliamenthin (λ_{max} 245 mμ, ν_{max} 1740 and 1710 cm.$^{-1}$) and the



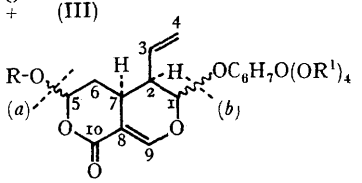
(I)



(IIa) R= O·$C_6H_7O(OH)_4$
(IIb) R= O·$C_6H_7O(OAc)_4$

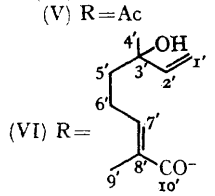


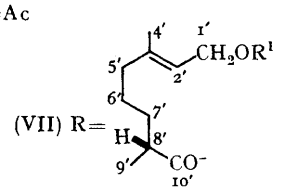
(III)

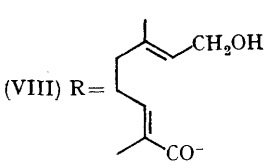


Series a, R^1=H
Series b, R^1=Ac

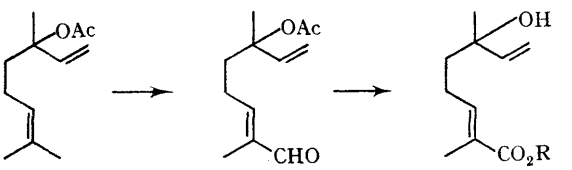
(IV) R=H
(V) R=Ac



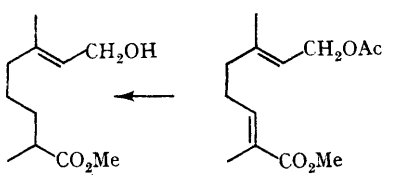




mass spectrum of the corresponding penta-*O*-acetate showed it to be two hydrogens richer than the corresponding derivatives of foliamenthin and menthiafolin. The breakdown pattern proved that the additional hydrogen atoms lie in the acyclic component [*m/e* 752 (M^+), 525 (cleavage *a*), 405 (cleavage *b*)] and this was confirmed by cleavage with methanolic alkali. The resultant methyl ester (XIV), $[\alpha]_D$ — 22° ($CHCl_3$), had no appreciable u.v. absorption at longer wavelength than 215 mμ, ν_{max} 1721 cm.$^{-1}$. No parent ion was observed in the mass spectrum of (XIV) but this structure was supported by the composition of the fragments at *m/e* 182, 169, 141, 123, 88; synthesis of (XIV) provided confirmation (see later). The illustrated absolute configuration at C-8′ rests at this stage on optical comparison with known standards;[7] chemical correlations are in progress.



(IX) (X) (XI) R=H
(XII) R=Me



(XIV) (XIII)

The water-soluble product from cleavage of dihydrofoliamenthin (VIIa) was shown to be identical with that from menthiafolin (VIa) by acetylation to form the C-5 epimeric penta-*O*-acetates (Vb) and by reduction to give sweroside (IIa). As argued for menthiafolin, these results lead to structure (VIIa) for dihydrofoliamenthin, so named because of its relationship to foliamenthin[8] (VIIIa).

Synthesis of the esters (XII) and (XIV) involved oxidation of linalool acetate (IX) with selenium dioxide[9] to generate the aldehyde (X) which was further oxidised with silver oxide to the acid (XI). The corresponding ester was identical with that obtained from menthiafolin (VIa). When the synthetic ester (XII) was heated with acetic acid, it underwent allylic rearrangement. The product (XIII) was reduced, with ethanol and sodium amalgam, to the dihydro-ester (XIV), which was spectroscopically and chromatographically indistinguishable from the ester derived from dihydrofoliamenthin (VIIa).

[2-^{14}C]Geraniol has been administered to *Menyanthes trifoliata* plants and dihydrofoliamenthin was isolated (5% incorporation). Alkaline cleavage showed that the total activity is divided between the ester (XIV) and the lactol (IV)

in the approximate ratio 3 : 1. These results support the derivation of both C_{10} units of dihydrofoliamenthin (VIIa) from geraniol and degradations to locate the labels are in progress.

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