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REVISED STRUCTURES FOR THE FLAVONES CIRSITAKAOSIDE AND CIRSITAKAOGENIN

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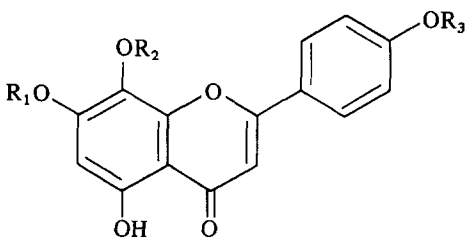
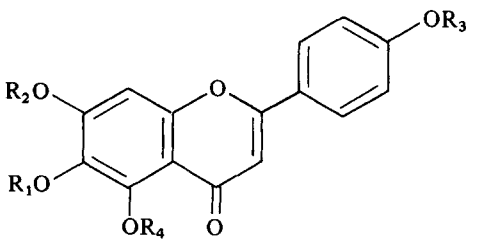
Key Word Index—*Cirsium japonicum* var *takaoense*, Compositae, cirsitakaoside, cirsitakaogenin, 5, 7-dihydroxy-8, 4′-dimethoxyflavone 7-*O*-glucoside, 5, 4′-dihydroxy-6, 7-dimethoxyflavone 4′-*O*-glucoside, cirsimarin

Abstract—The previously proposed structures for cirsitakaoside (5, 7-dihydroxy-8, 4′-dimethoxyflavone 7-*O*-β-D-glucoside) and its aglycone, cirsitakaogenin, are shown to be incompatible with the published data Reinterpretation of these data indicate that cirsitakaoside is 5, 4′-dihydroxy-6, 7-dimethoxyflavone 4′-*O*-β-D-glucoside and that cirsitakaogenin is its aglycone These compounds are known as cirsimarin and cirsimaritin, respectively, and published physical data for them confirm their identity with cirsitakaoside and cirsitakaogenin

In the course of a study of the flavonoids in the liverwort *Bucegia romanica* [1], a new flavonoid glycoside was isolated which is considered to be the 7-*O*-glucuronide of 5, 7-dihydroxy-8, 4′-dimethoxyflavone (**1**) The aglycone of this compound, however, differed chromatographically (and in a number of other ways) from the 5, 7-dihydroxy-8, 4′-dimethoxyflavone which had been isolated previously [2] and named cirsitakaogenin A reassessment of the data supporting the structure of cirsitakaogenin was therefore undertaken, and as a result it is concluded that the structure of cirsitakaogenin is 5, 4′-dihydroxy-6, 7-dimethoxyflavone (**3**) and of cirsitakaoside is 5,4′-dihydroxy-6, 7-dimethoxyflavone 4′-*O*-D-glucoside (**4**)



1 R_1 = Glur, R_2 = R_3 = Me
2 R_1 = H, R_2 = R_3 = Me



3 R_1 = R_2 = Me, R_3 = R_4 = H
4 R_1 = R_2 = Me, R_3 = Glc, R_4 = H
5 R_1 = R_3 = Me, R_2 = rutinosyl $(OAc)_6$, R_4 = OAc
6 R_1 = R_3 = Me, R_2 = R_4 = OAc

The evidence presented by the previous workers unquestionably supports their contention that cirsitakaogenin is a dihydroxy-dimethoxyflavone with a free 5-hydroxyl group and that cirsitakaoside is its mono-*O*-glucoside However, certain of the published spectral data which are discussed below are strongly supportive of the newly proposed structures but not of those originally described

Absorption spectra

The sodium acetate shift reagent causes band II of the aglycone spectrum to move from 274 to 272 nm indicating that in the aglycone the 7-hydroxyl is substituted [3] Further, the shift of band I from 332 to 385 nm is characteristic of 4′-hydroxyflavones and not 4′-methoxyflavones [3]

^1H NMR spectra

The chemical shift of the H-6 signal in the acetate of the aglycone at δ6 87 is virtually the same as that reported for the acetate of the glycoside, which indicates that the acetylated aglycone does not possess an additional acetate function at C-7 If it were acetylated at C-7 a downfield shift of *ca* 0 17 ppm should be evidenced [as reported by the authors for the H-8 signal in the pectolinarin acetate (**5**) pectolinarigenin acetate (**6**) pair]

In the spectrum of the glycoside, although the H-2′,

H-6′ signals at δ7 70 have the same chemical shift as in pectolinarin, the H-3′, H-5′ signals at δ6 97 appear at lower field than in pectolinarin (δ6 88) This is not accounted for if cirsitakaoside has a 4′-methoxyl but would be expected if instead the 4′-hydroxyl is glycosylated (cf spectra of penduletin and its 4′-*O*-glucoside [3]) Also, acetylation of the aglycone causes marked downfield shifts of the H-2′, H-6′ and H-3′, H-5′ signals consistent with the presence of a free 4′-hydroxyl in the aglycone

Mass spectra

In the mass spectrum of the aglycone no B-ring fragment is reported which contains a 4′-methoxyl whereas two were found containing a 4′-hydroxyl (B_1^+ at *m/z* 118 and B_2^+ at *m/z* 121) Further, the A-ring fragments, *m/z* 182 and 153, can also be accounted for if the A-ring contains a 5-hydroxy-7, 8 (or 6, 7)-dimethoxy substitution pattern [4]

From the analysis of data as presented above, there seems little doubt that cirsitakaogenin has one hydroxyl and two methoxyls in the A-ring, one 4′-hydroxyl in the B-ring and (in the glycoside) the glucose is attached to the 4′-hydroxyl The only question remaining is the substitution pattern of the A-ring which can be 5,7,8 or 5,6,7 The authors of the original paper rely very much on the often misleading [5] Gibbs test to distinguish these possibilities, but a more positive solution to the problem may be obtained by reference to the ^{1}H NMR spectra of model compounds Two models are available [3] with the relevant A-ring oxygenation patterns, herbacetin 8-methyl ether (3,5,7,4′-tetrahydroxy-8-methoxyflavone) and penduletin (5,4′-dihydroxy-3,6,7-dimethoxyflavone) The TMS-ethers of these compounds exhibit A-ring proton signals at δ6 12 and 6 47, respectively Since the A-ring proton in cirsitakaoside TMS-ether resonates at δ6 48 this evidence clearly supports a 5-hydroxy-6,7-dimethoxy oxygenation pattern (the nature of the derivatization of the 7-hydroxyl does not affect this reasoning [3]) Support for the 5,6,7-oxygenation pattern is also provided by the absorption spectrum, band I of which exhibits a bathochromic shift of only 26 nm on the addition of aluminium chloride [6] It is, therefore, concluded that the structures of cirsitakaogenin and cirsitakaoside are 5,4′-dihydroxy-6,7-dimethoxyflavone (**3**) and its 4′-*O*-β-D-glucoside (**4**), respectively

Compounds **3** and **4** have both been isolated previously from *Cirsium* and other species [3, 7–11] and named cirsimaritin and cirsimarin Published data for the known compounds are in good agreement with those reported for cirsitakaogenin and its 4′-*O*-glucoside Cirsimaritin is reported to have a mp of 257° [7] and 263–265° [8] and cirsimarin 243° [7], compared with 259–260° for cirsitakaogenin and 241–247° for cirsitakaoside The absorption spectra of cirsimaritin (methanol, sodium acetate and aluminium chloride [9, 10]) and the ^{1}H NMR spectrum of the diacetate in chloroform [10] are also essentially identical with those of cirsitakaogenin Finally, the chemical shifts of the B-ring protons in the ^{1}H NMR spectrum of cirsitakaoside are, as expected, identical with those reported for the other known 4′-*O*-glycoside of cirsimaritin, the 4′-*O*-rutinoside [11] *

* The difference between the H-8 signals (δ6 7 in cirsimaritin 4′-*O*-rutinoside and 6 48 in cirsitakaoside) is accounted for if the 5-hydroxyl (which is difficult to trimethylsilylate in 6-methoxy-5,7-dihydroxyflavonoids [3]) has not been trimethylsilylated in cirsitakaoside [3]

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NOTE ADDED IN PROOF

Professor N Morita, coauthor of the original paper (ref [1]) has now confirmed, by mmp determinations, that cirsitakaoside is identical with cirsimarin and that cirsitakaogenin is identical with cirsimaritin