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XANTHONES FROM *FRASERA ALBOMARGINATA* AND *F. SPECIOSA**

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Key Word Index—*Frasera albomarginata*; *F. speciosa*; Gentianaceae; roots; 1-hydroxyxanthones; identification.

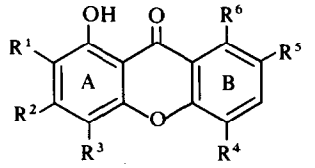
Abstract—Seven 1-hydroxyxanthones have been isolated from the roots of *Frasera albomarginata*. There were 1-hydroxy-3,7-dimethoxy-, 1-hydroxy-3,5-dimethoxy-, 1,8-dihydroxy-3,5-dimethoxy-, 1-hydroxy-2,3,4,7-tetramethoxy-, 1-hydroxy-2,3,4,5-tetramethoxy-, 1-hydroxy-3,4,7-trimethoxy- and 1-hydroxy-2,3,5-trimethoxyxanthone. Six 1-hydroxyxanthones were obtained from the roots of *F. speciosa*. These were 1-hydroxy-2,3,4,5-tetramethoxy-, 1-hydroxy-2,3,4,7-tetramethoxy-, 1-hydroxy-2,3,5-trimethoxy-, 1,7-dihydroxy-2,3,4-trimethoxy-, 1,7-dihydroxy-2,3-dimethoxy- and 1,3-dihydroxy-4,5-dimethoxyxanthone.

Previous papers of this series [1, 2] presented chemical evidence designed to show the chemotaxonomic relationship of *Frasera* to other related genera in the family Gentianaceae. One taxonomic problem in this area is the question of whether *Frasera* should be combined with *Swertia* or maintained as a separate genus [3]. As part of this study and in view of the possible role of xanthones as chemotaxonomic markers [4–7], the roots of *F. albomarginate* Wats. and *F. speciosa* have now been examined for their xanthone content.

Chromatography of the root extracts of *F. albomarginata* on silicic acid gave seven polysubstituted 1-hydroxyxanthones. These were, in order of elution from the column, compounds **1**–**7**. The structures assigned to these compounds followed from their NMR spectra and comparison of the NMR and UV spectra with literature values as well as direct comparison with reference samples in most cases.

Present in the extracts were the isomeric pairs of compounds, 1-hydroxy-3,7-dimethoxy (**1**) and 1-hydroxy-3,5-dimethoxyxanthones (**2**) as well as 1-hydroxy-2,3,4,7-tetramethoxy- (**4**) and 1-hydroxy-2,3,4,5-tetramethoxyxanthones (**5**). These isomeric pairs could arise from the two different modes of coupling of a common benzophenone precursor [4, 8]. Absent from the extracts, however, were the 5-methoxy isomer of 1-hydroxy-3,4,7-trimethoxyxanthone (**6**), i.e. compound **8**, and the 7-methoxy isomer of 1-hydroxy-2,3,5-trimethoxyxanthone (**7**), i.e. compound **9**. The presence of these 'missing' isomers might be expected on biogenetic grounds since they would result from the different coupling modes of the common benzophenone precursor which leads to **6** and **7** [4, 8].

After initial isolation, repeated rechromatography of the recombined mother liquors and mixed fractions resulted only in the isolation of further quantities of **1**–**7**.



1	$R^1 = R^3 = R^4 = R^6 = H$;	$R^2 = R^5 = MeO$
2	$R^1 = R^3 = R^5 = R^6 = H$;	$R^2 = R^4 = MeO$
3	$R^1 = R^3 = R^5 = H$;	$R^2 = R^4 = MeO$; $R^6 = HO$
4	$R^4 = R^6 = H$;	$R^1 = R^2 = R^3 = R^5 = MeO$
5	$R^5 = R^6 = H$;	$R^1 = R^2 = R^3 = R^4 = MeO$
6	$R^1 = R^4 = R^6 = H$;	$R^2 = R^3 = R^5 = MeO$
7	$R^3 = R^5 = R^6 = H$;	$R^1 = R^2 = R^4 = MeO$
8	$R^3 = R^4 = R^6 = H$;	$R^2 = R^3 = R^4 = MeO$
9	$R^1 = R^5 = R^6 = H$;	$R^1 = R^2 = R^5 = MeO$
18	$R^1 = R^5 = R^6 = H$;	$R^3 = R^4 = MeO$; $R^2 = HO$

* Part VI in the series 'Xanthones of the Gentianaceae'. For Part V see Stout, G. H. and Fries, J. (1970) *Phytochemistry* **9**, 235.

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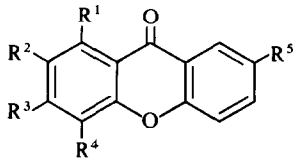

10 $R^1 = R^4 = HO$; $R^2 = R^3 = R^5 = MeO$
11 $R^1 = R^2 = HO$; $R^3 = R^4 = R^5 = MeO$
12 $R^1 = R^3 = HO$; $R^2 = R^4 = R^5 = MeO$
13 $R^1 = R^5 = HO$; $R^2 = R^3 = R^4 = MeO$
14 $R^5 = HO$; $R^1 = R^2 = R^3 = R^4 = MeO$
15 $R^4 = H$; $R^1 = R^3 = HO$: $R^2 = R^5 = MeO$
16 $R^4 = H$: $R^1 = R^2 = HO$: $R^3 = R^5 = MeO$
17 $R^4 = H$: $R^1 = R^5 = HO$: $R^2 = R^3 = MeO$

Efforts to isolate the two 'missing' metabolites (**8** and **9**) were unsuccessful, but their presence in the mother liquors at low concentrations cannot be definitely excluded.

With the exception of **2**, all of the xanthones found in *F. albomarginata* have been previously reported from other *Frasera* species [1, 2].

The root extracts of *F. speciosa* were also analyzed by column chromatography. The nonpolar fractions yielded six xanthones. The most nonpolar component from the column was identical with 1-hydroxy-2,3,4,5-tetramethoxyxanthone (**5**) isolated from other *Frasera* spp.

The NMR spectrum of the second, yellow, $FeCl_3$ positive, substance indicated that it had a strongly hydrogen-bonded 1-hydroxy group and three OMe groups. The downfield aromatic resonance indicated the presence of an 8-proton. This signal showed only *meta* coupling requiring the presence of 7-substituent. Since there were no resonances in the region of 6.3–6.8 ppm, this compound must have a 1,2,3,4,7-pentasubstitution pattern and is a dihydroxy trimethoxyxanthone. The formation of a diacetyl derivative supported the presence of two OH groups. 1,4-Dihydroxy-2,3,7-trimethoxy- (**10**) [9] and 1,2-dihydroxy-3,4,7-trimethoxyxanthone (**11**) [10] are known compounds but their reported physical constants indicated that neither could be identical with the substance from *F. speciosa*.

The NMR spectrum in benzene did not show any of the OMe signals shifted upfield relative to their position in $CDCl_3$ indicating the absence of such groups adjacent to an unsubstituted position [11]. This suggested that, of the two remaining possibilities, 1,3-dihydroxy-2,4,7-trimethoxy- (**12**) and 1,7-dihydroxy-2,3,4-trimethoxyxanthone (**13**), the latter structure was the most likely. That this was the case was shown by selective demethylation of the known 7-hydroxy-1,2-3,4-tetramethoxyxanthone (**14**) [11] with 30% HCl to give 1,7-dihydroxy-2,3,4-trimethoxyxanthone (**13**) identical by spectroscopic criteria with the natural material.

The NMR spectrum of the third nonpolar component showed the presence of a 1-OH group and two OMe signals. The downfield aromatic signal assignable to the 8-proton showed only *meta* coupling indicating again the presence of a 7-substituent. A one-proton aromatic singlet occurred at 6.52 ppm. These NMR data indicated a dihydroxy dimethoxyxanthone with a 1,2,3,7- or a 1,2,4,7-tetrasubstitution pattern. That the former was correct is indicated by the position of the aromatic singlet. The 2-proton in 1-hydroxy-3,4-dimethoxyxanthones [12] occurs at *ca* 6.3 ppm while the 4-proton occurs around 6.4 to 6.5 ppm in 1-hydroxy-2,3-dimethoxyxanthones [1, 2].

The UV spectrum of the third component from the column was very similar to that of **13**. The spectrum of either compound was unchanged upon addition of sodium acetate indicating the absence of a 3-OH group [13]. 1,2-Dihydroxyxanthones are reported to undergo decomposition in the presence of base [14]. The UV spectra of both **13** and the third component were very similar and unchanged in the presence of added NaOH after 1 hr. The UV data thus exclude 1,3-dihydroxy-2,7-dimethoxy- (**15**) and 1,2-dihydroxy-3,7-dimethoxyxanthone (**16**) leaving 1,7-dihydroxy-2,3-dimethoxyxanthone (**17**) as the only possible structure for the third substance.

Rechromatography of the combined mother liquors and mixed fractions from the column resulted in the isolation of additional amounts of **5** and **13** as well as small amounts of **4**, **7** and another dihydroxy dimethoxyxanthone. The NMR spectrum of this latter material indicated the presence of a 1-OH group and an 8-proton. The signal for the 8-proton was a quartet indicating the presence of 6,7 and 8-protons. A one-proton singlet at 6.22 ppm must be assigned to an isolated proton in the A-ring. The upfield position of this signal indicates that the proton must be located at the 2-position. The UV spectrum showed a pronounced acetate shift so that one of the OH groups must be located at the 3-position. Consideration of the UV data with the NMR results indicates that the compound must be 1,3-dihydroxy-4,5-dimethoxyxanthone, a known constituent of both *Frasera* [1] and *Swertia* spp. [9].

Xanthones in *Frasera* are characterized by their relatively high degree of *O*-methylation. With minor exceptions [1, 2], all OH groups are found *O*-methylated except those at the 1- and 8-positions. On the other hand, most of the xanthones reported [17] from *Swertia* and *Gentiana* species generally show a much lower degree of *O*-methylation. In fact, the degree of methylation and substitution pattern is very similar in *Frasera* and *Eustoma* spp. [18].

EXPERIMENTAL

F. albomarginata. Ground roots collected near St. George, Utah, were extracted with Me_2CO. Solvent was removed and the residue chromatographed on silicic acid. Fractions which gave a negative $FeCl_3$ test on TLC were discarded. Elution with C_6H_6 gave initially fractions containing **1**, mp 161–164° (EtOAc–hexane) followed by fractions containing **2**, mp 169–170° (EtOAc–hexane), green $FeCl_3$ test. Fractions eluted with mixtures of C_6H_6–$CHCl_3$ yielded swerchirin (**3**). Finally, elution with $CHCl_3$ gave fractions from which **6** and **7**, mp 183–187° (EtOAc–hexane), were recovered.

Recombination of the mother liquors from these operations, as well as those fractions which were mixtures, and rechromatography gave fractions from which further amounts of **1**, **2** and **3** were recovered. Fractions following **3** were worked up to give **4**, mp 112–114° [11], followed by **5**. Further chromatography of the mother liquors from the above operations yielded additional amounts of xanthones **1** to **7**.

F. speciosa. Ground roots collected near Yuba Pass in the Sierra Nevada mountains were extracted with Me_2CO. Chromatography of the extracts on silicic acid gave fractions eluted with C_6H_6 and C_6H_6–$CHCl_3$ mixtures from which **5** was recovered, identical by NMR and IR criteria with that of an authentic sample. Fractions eluted with $CHCl_3$ gave **13**, mp 164–168°; from EtOAc–cyclohexane; green-brown $FeCl_3$ test: λ_{max}^{EtOH} nm 236 (35000), 268 (48200), 301 (14000), 392 (8000), unchanged upon addition of NaOAc; $\lambda_{max}^{EtOH-NaOH}$ nm 247, 282, 341, 435; NMR 12.62 (*s*, 1H) 1-OH, 7.59 (*d*, $J = 2$ Hz, 1H) H-8, 7.5–7.2 (*m*, 2H) H-5 and H-6, 4.11, 3.91, 3.91 OMe ppm ($CDCl_3$); 3.9, 3.81, 3.76 methoxys ppm (C_6H_6). Further elution of the column with $CHCl_3$ gave **17**; mp 225–228° sublimed; green-brown $FeCl_3$ test; λ_{max}^{EtOH} nm 238, 262, 301, 376, unchanged upon addition NaOAc; NMR 12.81 (*s*, 1H) 1-OH, 7.45 (*d*, $J = 2$ Hz, 1H) H-8; 7.4–7.2 (*m*, 2H) H-5 and H-6; 6.52 (*s*, 1H) H-4; 3.9, 3.75 OMe ppm ($CDCl_3$–DMSO); M^+ 288.0640 (calc. for $C_{15}H_{12}O_6$, 288.0634).

Rechromatography of the mother liquors and the mixed fractions from the initial column gave **4** and **7** as well as additional amounts of **5** and **13**. Finally, **18** was obtained from the more polar fractions; NMR 12.47 (*s*, 1H) 1-OH; 7.62 (*q*, $J = 7$, 2 Hz, 1H) H-8; 7.4–7.2 (*m*, 2H) H-6 and H-5; 6.22 (*s*, 1H) H-2; 3.93, 3.83 OMe ppm ($CDCl_3$–DMSO); MS *m/e* (rel. int.): 289 (11), 288 (63), 274 (16), 273 (100), 245 (56), 230 (13).

Demethylation of **14**. The compound was refluxed with 30% HCl for 45 min. The product that separated upon cooling was collected by filtration and purified by chromatography on silicic acid to give **13**; mp 169–170.5° from EtOAc–cyclohexane; mmp 166–168° with natural material. (Found: C, 60.4; H, 4.47. $C_{16}H_{14}O_7$ requires: C, 60.2; H, 4.42%). The diacetate was obtained with Ac_2O–pyridine; mp 100–101° (MeOH); NMR 7.83 (*d*, $J = 2$ Hz, 1H) H-8; 7.6–7.2 (*m*, 2H) H-5 and H-6; 4.09, 3.98, 3.88 OMe; 2.47, 2.27 OAc ppm ($CDCl_3$). (Found: C, 60.6; H, 4.60. $C_{20}H_{18}O_9$ requires: C, 59.70; H, 4.51%).

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