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6-O-ACETYLMELITTOSIDE AND OTHER IRIDOIDS
FROM *CASTILLEJA* SPECIES¹

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ABSTRACT.—The new iridoid 6-O-acetylmelittoside and several known iridoids were isolated from *Castilleja sessiliflora*, while known iridoids were isolated from *Castilleja foliolosa*, *Castilleja exilis*, *Castilleja minor*, and *Castilleja chromosa*. Iridoid content was identical for *C. exilis* and *C. minor*, whose identity as separate taxa has sometimes been questioned. The phenylpropanoid glycoside verbascoside was identified in each of the species.

In a continuation of studies on iridoid and phenylpropanoid glycosides of *Castilleja* (Scrophulariaceae) (1–3), we have analyzed several additional species. *Castilleja sessiliflora* Pursh is a unique species of the western U.S. plains and is the only member of Section Sessiliflorae (4). *Castilleja exilis* A. Nels. and *Castilleja minor* (A. Gray) A. Gray are very similar but geographically distinct species of western Colorado, Utah, the southwest U.S., and northern Mexico. Unlike the perennial *Castilleja* so far studied chemically, these two species are annuals and are considered to be very closely related (5). *Castilleja chromosa* A. Nels. occurs mostly west of the continental divide in the intermountain region, while *Castilleja foliolosa* H.&A. is a western California species.

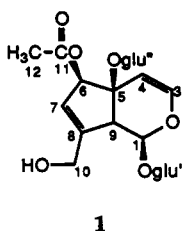
The results of the iridoid glycoside analyses are given in Table 1. Of the compounds isolated, 6-O-acetylmelittoside [**1**] from *C. sessiliflora* is a new

substance whose structure was elucidated by comparison of the ¹H- and ¹³C-nmr spectra with those of melittoside (6). Resonances for two sugars, an acetyl group, and the aglycone were evident. Key differences between the spectra of **1** and those of melittoside were the 5.50 ppm ¹H and 84.7 ppm ¹³C resonances for **1** (4.58 ppm and 79.9 ppm, respectively for melittoside) assignable to H-6 and C-6. Complete assignments for the ¹H- and ¹³C-nmr spectra of **1** are given in the Experimental section, along with key melittoside comparisons.

C. exilis and *C. minor* have indistinguishable glycoside contents, in accord with their morphological closeness (5). The iridoid content of *C. chromosa* is very similar to that of *Castilleja integra* (3). These, as well as biological and biogeographical considerations, show *C. integra* and *C. chromosa* to be more closely related to each than to other *Castilleja* species. Melittosides so far have been reported in *Castilleja* only from *Castilleja wightii* (7), but occur in several species, previously assigned to *Orthocarpus*, that have recently been reassigned to *Castilleja* (8,9).

EXPERIMENTAL

PLANT COLLECTIONS.—Collections were as follows: *C. chromosa* FRS 196, June 16, 1981 on a hill south of State Highway 303 at Bearcreek, Carbon Co., Montana; *C. sessiliflora* FRS 243, May 17, 1985, at the northeast end of Bonny Reservoir, Yuma Co., Colorado; *C. foliolosa* FRS 340, March 16, 1988 on Highway 198 just east of the Monterey Co. line in Fresno Co., California; *C. exilis* FRS 273, August 21, 1985, just west of Ferron, Emery Co., Utah; *C. minor* DRG



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¹Part 19 in the series Chemistry of the Scrophulariaceae. For Part 18, see C.A. Boros, D.R. Marshall, C.R. Caterino, and F.R. Stermitz, *J. Nat. Prod.*, **54**, 506 (1991).

TABLE 1. Glycosides Isolated from *Castilleja* Species.

Glycoside	Species				
	<i>sessiliflora</i>	<i>foliolosa</i>	<i>exilis</i>	<i>minor</i>	<i>chromosa</i>
6-O-Acetylmelittoside [1]	*	—	—	—	—
Melittoside	*	*	—	—	—
Verbascoside	*	*	*	*	*
Adoxoside	tr	—	—	—	*
Mussaenoside	tr	—	*	*	—
Geniposide	—	*	—	—	—
Geniposidic acid	—	*	—	—	—
Aucubin	—	*	—	—	—
Shanzhiside methyl ester	—	—	*	*	—
8- <i>epi</i> -Loganin	—	—	*	*	—
Catalpol	—	—	—	—	*
Macfadienoside	—	—	—	—	*
Adoxosidic acid	—	—	—	—	*
Salidroside	—	—	—	—	*

105B, northeast of Gateway, Mesa Co., Colorado in a wet area along State Highway 141. Vouchers (CSU herbarium) were identified by L.R. Heckard, Jepson Herbarium, University of California, Berkeley or D.H. Wilken, Department of Biology, Colorado State University.

ISOLATIONS.—Whole, air-dried and crushed *C. sessiliflora* (50 g), *C. foliolosa* (25 g), and *C. chromosa* (90 g) were each soaked in MeOH 48 h, filtered, and concentrated in vacuo. The residues were partitioned between H₂O and CH₂Cl₂, the aqueous phase was evaporated, and each residue was triturated several times with absolute MeOH. The MeOH was evaporated to leave crude iridoid residues: *C. sessiliflora* (1.7 g), *C. foliolosa* (0.86 g), and *C. chromosa* (4.2 g). In a typical purification scheme, the *C. sessiliflora* residue was chromatographed (vlc, Si gel, CH₂Cl₂/MeOH gradient elution, 16 fractions, 40 ml each). Fractions 8 and 9 (30% MeOH) yielded trace amounts of adoxoside and mussaenoside. Fractions 12–16 (50% MeOH) were combined (600 mg) and rechromatographed (vlc, C18 Si gel, H₂O/MeOH gradient, 20 fractions, 40 ml each): fraction 4 (20% MeOH) yielded melittoside (47 mg); fraction 7 (30% MeOH), 6-O-acetylmelittoside (73 mg); fraction 8 (40% MeOH), verbascoside (trace). Similarly, the *C. foliolosa* residue yielded geniposide, verbascoside, geniposidic acid, mellitose, and aucubin, eluted in order from a Si gel vlc (20–60% MeOH in CH₂Cl₂); while the *C. chromosa* residue yielded adoxoside, adoxosidic acid, verbascoside, salidroside, catalpol, and macfadienoside.

Dried above-ground parts of *C. minor* (62 g) were extracted 24 h in MeOH and filtered, and the MeOH was removed in vacuo. The residue

was distributed between H₂O and Et₂O, and the aqueous layer was evaporated. The residue was triturated with absolute MeOH and evaporated to yield 780 mg of residue. Of this, 280 mg was separated by preparative tlc [Si gel, CHCl₃-MeOH (65:35), double-developed] to yield 20 mg of a mixture of mussaenoside and 8-*epi*-loganin, 10 mg of shanzhiside methyl ester, and 46 mg of verbascoside. Similar results were obtained from 36 g of *C. exilis*.

IDENTIFICATIONS.—6-O-Acetylmelittoside: amorphous, white solid; $[\alpha]^{23}_D -59^\circ$ ($c = 0.52$, MeOH); ¹H nmr [D₂O, 300 MHz, ppm, compared to melittoside (6)] H-3 6.45 d (6.51), H-7 5.75 d (5.86), H-6 5.55 d (4.58), H-1 5.45 d (5.44), H-4 5.20 d (5.16), H-10 4.22 dd (4.28), H-9 3.45 d (3.35), H-12 2.1 s, H-1' 4.72 d, H-6' 3.80 t and 3.60 t, H-2'–H-5' 3.2–3.5 m; ¹³C nmr (D₂O, 75 MHz, ppm) 176.7 (C-11), 150.2 (C-8), 146.5 (C-3), 127.0 (C-7), 108.4 (C-4), 101.3 and 100.8 (C-1', C-1''), 97.9 (C-1), 84.7 (C-6), 82.8 (C-5), 79.1 and 78.6 (C-3', C-3''), 78.5 (C-5', C-5''), 76.0 and 75.7 (C-2', C-2''), 72.3 (C-4', C-4''), 63.5 (C-6', C-6''), 62.4 (C-10), 54.6 (C-9), 23.5 (C-12). Assignments were made from ¹H-¹³C HETCOR and ¹³C DEPT spectra.

All other iridoids were identified by tlc (or TMSi gc) and ¹H-nmr spectra in comparison with previously isolated samples (1, 3, 8).

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