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ALKALOIDS FROM *CASTILLEJA MINIATA* AND *PENSTEMON WHIPPLEANUS*, TWO HOST SPECIES FOR THE PLUME MOTH, *AMBLYPTILIA (PLATYPTILIA) PICA*[1]

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ABSTRACT.—*Castilleja miniata* (Scrophulariaceae), a host plant for the plume moth *Amblyptilia (Platyptilia) pica* (Walsingham) was found to contain the dipiperidine alkaloids (−)-ammodendrine and (−)-*N'*-methylammodendrine, and the quinolizidine alkaloids (+)-13-α-hydroxylupanine, and (+)-tetrahydrorhombifoline. Incomplete structural evidence was also obtained for an unknown tetrahydrorhombifoline derivative and an artifact pyridine monoterpene alkaloid, probably cantleyine. Flowers of *Penstemon whippleanus* (Scrophulariaceae), another host plant for the plume moth, were found to contain the pyridine monoterpene alkaloid (+)-boschniakine and two incompletely characterized members of this class, probably 4-noractinidine and carbomethoxypedicularine or their isomers. Alkaloid or alkaloid metabolites (as yet unidentified) were present in the plume moths and larva that inhabit each plant species.

Castilleja miniata is a red-bracted "Indian paint brush" species that grows in the high altitudes in the Rocky Mountain west. It is closely related to *Castilleja rhexifolia* from which we reported the isolation and characterization of the pyrrolizidine alkaloid senecionine (1). It has been suggested that natural hybrids occur between the two species, and collections, which appear to be intermediate in form have sometimes been described as "*C. rhexifolia* aff. *miniata*" or "*C. miniata* aff. *rhexifolia*" (2). Chromosome counts on various collections of *C. miniata* have resulted in values of $n=12$, 24, 48, and 60 (2).[2] Different counts have been found for adjacent populations of *C. miniata* in the Yellowstone and Grand Teton National Park areas of Wyoming.

In the California mountains, *C. miniata* is a known host plant for the plume moth *Amblyptilia (Platyptilia) pica* (3). We discovered that *C. miniata* populations from the Grand Teton National Park area were also hosts to the plume moth and gave positive tests for alkaloids. The Colorado *C. rhexifolia* of our original work (1) also proved to be a host to the moth and contained alkaloids in addition to senecionine (4). Our screening program (5) had shown *Penstemon whippleanus* to be positive for alkaloids, and it was also now discovered to serve as a moth host. Certain other members of the Scrophulariaceae are also known hosts to the plume moth (3).

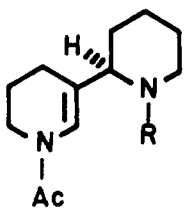
RESULTS

Castilleja miniata.—Isolation and characterization work, which concentrated on one specific population of *C. miniata*, resulted in positive identification of (−)-ammodendrine **1**, (−)-*N'*-methylammodendrine **2**, (+)-13-α-hydroxylupanine **3**, and (+)-tetrahydrorhombifoline **4**. Because ^{13}C-nmr spectra have not been published for **1**, **2**, and **4**, these data are given in the Experimental section. The 360-MHz ^{1}H-nmr spectra for each are available in a thesis (6). The gc/ms data (only) suggested the presence of hydroxy derivative **5**, 1-acetyl-1,2,3,4-tetrahydropyridine **6**, and lupanine **7**.

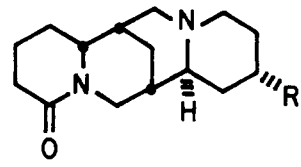
A look at our data for **5** is warranted. This alkaloid appeared at a slightly lower Rf

[1]This is the second paper in the series Chemistry of the Scrophulariaceae, for the first paper, see reference (1).

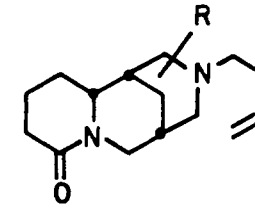
[2]"The difficulty of recognizing species boundaries in many genera characterized by a high proportion of polyploids is intrinsic and is not due to lack of perception on the part of the taxonomist." G. Ledyard Stebbins, *Topics in Plant Population Biology*. O.T. Solbrig, S. Jain, G.B. Johnson, and P.H. Raven, eds., Columbia University Press, New York, 1979, p. 21.



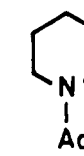
1: R=H
2: R=CH_3



3: R=OH
7: R=H



4: R=H
5: R=OH



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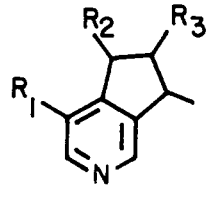
value on tlc than did tetrahydrorhombifoline and at a slightly greater retention time on gc. In the ei ms, tetrahydrorhombifoline itself shows no molecular ion peak but rather an M^+-41, which represents loss of the *N*-allyl side chain, while NH_3 ci ms (7) shows a high quasimolecular ion at *m/z* 249. These data and the fragmentation pattern are duplicated by **5**, with the exception that the M^+-41 in the ei ms and the quasimolecular ion in the NH_3 ci ms are exactly 16 mass units higher. This could be accommodated by an OH group in **5** placed somewhere on one of the rings. Neither ei nor ci mass spectra for **5** show peaks for loss of H_2O or OH. Loss of OH should be observed if the group were adjacent to nitrogen and loss of H_2O if there were an easy path for an E2-like elimination. A possible position for an OH group in **5** might be at one of the bridgeheads or on the bridge carbon. An *N*-oxide structure is also possible, but we have not observed good quasimolecular ions for *N*-oxides with NH_3 ci ms.

One alkaloid could be isolated only when an acid-base partition scheme with NH_4OH basification was used to prepare the crude alkaloid fraction. It was not formed when NaOH was used in place of NH_4OH. The ei ms and uv spectrum were identical with those reported for cantleyine (**8**). The ^{1}H-nmr spectra given in the literature for cantleyine differ somewhat (8, 9), but ours was quite close to that of one report (8). We were unable to free our material from contaminants, and this precluded obtaining meaningful optical rotation data.



8: R_1=R_2=H, R_3=OH
9: R_1=CHO, R_2=R_3=H
10: R_1=R_2=R_3=H
11: R_1=$COOCH_3$, R_2=COOH, R_3=H
12: R_1=R_3=H, R_2=COOH

Plants were collected from several locations at several different seasonal times in and near Grand Teton National Park where chromosome counts had previously been made (2). Partial isolation studies and tlc screening from several collections indicated that large deviations in alkaloid content did not occur. Only variability in tetrahydrorhombifoline content of some of the collections was noted. Since we had found unsaturated pyrrolizidines to be the main components of *C. rhexifolia*, chloranil and Ehrlich's reagent (10) were used as indicator sprays on some of the thin layer chromatograms, but no pyrrolizidine positives were obtained. Screening the crude alkaloid mixture by direct probe NH_3 ci gc/ms (7) confirmed the isolation work and, again, yielded nothing indicating the presence of pyrrolizidines. The tlc and gc analyses of the crude mixture identified the ammodendrines as the major components, with the quinolizidines secondary.

Tlc tests directly on larval contents and on a purified (acid-base partition) crude base fraction from larva and adult moths were positive for alkaloids. Isolation and characterization of these substances is underway.

Castilleja species are known semiparasites on the roots of other plants. In one of our collected locations, *C. miniata* was growing intermixed with *Lupinus argenteus* Pursh. Although we did not observe actual cases of parasitism, plume moths flushed from *C. miniata* occasionally lit on *L. argenteus*. A crude base fraction from *L. argenteus* was screened by tlc, because quinolizidines are typical constituents of *Lupinus* species. Five major and two minor alkaloid spots were noted in the extract of *L. argenteus*, but none were coincidental with *C. miniata* alkaloids by Rf value or spray reagent (iodoplatinate) color. There was no noticeable difference by tlc in alkaloid content between one population of *C. miniata* growing mixed with *L. argenteus* on a hillside and a second population (the major one studied) growing near-by, but close to the flood plain of Jackson Lake where *L. argenteus* did not occur. *L. argenteus* var. *stenophyllum* was reported (11) to contain α-isolupanine and thermopsine as the major alkaloids along with minor amounts of sparteine, dehydrolupinine, lupanine, anagyrine, and β-isosparteine.

Penstemon whippleanus.—Preliminary studies indicated that stems and leaves of *P. whippleanus* contained small amounts of alkaloids, while the blossoms were relatively high in alkaloid content. Larva of the plume moth, when presented with both leaves and blossoms, fed exclusively on the blossoms.

Tlc indicated that there were three alkaloids present in the blossoms, one major and two minor. Extremely heavy spotting showed trace amounts of others. An acid-base partition purification of the alcoholic extract residue left a crude base fraction from which the major alkaloid (+)-boschniakine (**9**) was positively identified. One minor, relatively nonpolar (tlc and gc) alkaloid was also a pyridine monoterpene by uv spectrum and its mass spectrum from gc/ms indicated a MW of 133. The only significant fragment was the base peak at *m/z* 118, which represented a methyl loss. The alkaloid is tentatively identified on this basis as the known 4-noractinidine **10** (12). The second minor alkaloid had MW 235 from the NH_3 ci gc/ms (7). The molecular ion was not visible in the ei spectrum, but instead showed an *m/z* 190 (M^+-45). Further fragment peaks (*m/z* 162, 146, 117) correlated with structure **11**, based upon the mass spectrum (13) of known pyridine monoterpene pedicularine (**12**). The crude base fraction contained nonalkaloidal material as well; *trans*-cinnamamide was a major component along with methyl *cis*- and *trans*-cinnamates and methyl ferulate.

DISCUSSION

This is the first report of quinolizidine alkaloids in the genus *Castilleja*, the only other report of any alkaloids being our finding (1,4) of pyrrolizidines in the closely related *C. rhexifolia*. Only one report of quinolizidines in the family Scrophulariaceae was that of sophoridine, sparteine, pachycarpine, sophoramine, and aloperine in *Leptorhabdos parviflora* (15). Our finding of quinolizidine alkaloids in one species of *Casilleja* and pyrrolizidines in a closely related species is an interesting confirmation of the suggestions that very similar enzyme systems are involved in the biosynthesis of these two classes of alkaloids (16). Only the precursor amino acids are different. The analogous case is that of *Cytisus* and *Crotalaria*, closely related Leguminosae genera, where the former accumulates only quinolizidines and the latter only pyrrolizidines. The case of *C. rhexifolia* and *C. miniata* is particularly interesting because it has been suggested that polyploidy in *Castilleja* is involved in speciation (2), and we may be observing alkaloid differences in rapidly evolving species.

The new alkaloids we have found are (−)-ammodendrine and (−)-*N'*-methylammodendrine (previously known in its (+) and (±) forms) and 1-acetyl-1,2,3,4-tetrahydropyridine. Although the latter has been known as a synthetic, we could not find reference to its isolation from a natural source.

The occurrence of pyridine monoterpenes in the two species is not exceptional, inas-

much as these alkaloids and their presumed precursor iridoids are well known from the Scrophulariaceae. Many iridoids have been reported from *Penstemon* species, but this is the first report of pyridine monoterpene alkaloids from the genus. Indeed, iridoids are so common to *Penstemon* that one wonders whether or not alkaloids have been overlooked in some of the studies. In the Colorado area, the only other *Penstemon* we examined was *P. virens*, and it was found to be devoid of alkaloids (5). It did not appear to host the plume moth.

The interactions of Lepidoptera with plants are well known, but in terms of alkaloid-containing plants, hosts up to now have been restricted to those containing pyrrolizidines, as far as we are aware. Preliminary results of direct tlc analyses on larva and on extracts of larva and adult moths that inhabit *C. miniata* and *P. whippleanus* were definitely positive for alkaloids. Work is progressing on the identification of these substances.

EXPERIMENTAL[3]

BIOLOGICAL MATERIAL.—*Castilleja miniata* (Dougl.) collections are given below. Voucher specimens were deposited in the Colorado State University (CSU) herbarium and identified by L.R. Heckard of the Jepson Herbarium, University of California, Berkeley:

FRS (CSU 65247) and FRS 215 (CSU 14248 and CSU 35726)—0.5 mi N of the north boundary of Grand Teton National Park, Wyoming, west side of Highway 89-287. FRS 216 (CSU 14184)—3.5 mi S of the north boundary of Grand Teton National Park, Wyoming, on the east side of Highway 89-287 on a hillside among aspen and *Lupinus argenteus* Pursh. FRS 218 (CSU 35727). Same as the last location, but on the west side of Highway 89-287 near the shore of Jackson Lake.

Penstemon whippleanus A. Gray was collected in the Cameron Pass area of Jackson County Colorado, near Highway 14 along Michigan Ditch, TAS-20 (CSU 57118), and identified by D. Wilken, Department of Botany, Colorado State University.

Adult moth specimens raised from larvae found on the above plants were submitted to the Systematic Entomology Laboratory, USDA, Smithsonian Institute, Washington, DC, and identified as *Amblyptilia pica* (Walsingham), Pterophoridae, Lepidoptera by D.C. Ferguson. *Amblyptilia* represents the reestablishment of an original generic name that was later subsumed (3) under *Platyptylia*.

When plants of either species were mature in the field, plume moths could occasionally be flushed, but did not appear to be common. This held true for *C. miniata* FRS 218, the major population studied, for June through August, the latter time approaching senescence. None of the plants of either species appeared to be heavily infested with larvae in the field or visibly damaged at any time during the season. Within one to two days after plants were picked, however, intense larval activity was noted on blossom heads, and from two to six larva could be found on each blossom head. Heavy feeding by larva was initiated only after plants had been picked. The picking apparently had an effect on the growth or instar-phase change of the larva. In the case of *C. miniata*, pressed herbarium specimens were found to contain observable larva or their remains several days after pressing and were heavily eaten around the blossom heads. Two such specimens are deposited (FRS 213-CSU 14273 and FRS 214-CSU 23604).

ALKALOID ISOLATIONS AND ANALYSES (*CASTILLEJA MINIATA*).—*C. miniata* (FRS 218 collection), 360 g of dried flower heads including bracts and 660 g of stems and leaves, were extracted separately by cold percolation with MeOH. The residues after evaporation were triturated with 0.5 N H_2SO_4 in portions and the combined solutions extracted with CH_2Cl_2. The aqueous layers were made basic to pH 9 with NH_4OH, extracted with $CHCl_3$, and the $CHCl_3$ solutions evaporated in vacuo. Tlc analyses indicated that these crude residues had similar alkaloid content, and hence, were combined to yield 1.0 g of crude alkaloid mixture. This residue was triturated with three 1-ml portions of Et_2O, which were combined, reduced to 1 ml, and injected on a medium pressure liquid chromatographic column of neutral alumina. Elution was with Et_2O-CH_2Cl_2 (1:1), which solution was gradually changed by decreasing the CH_2Cl_2 concentration and adding MeOH. The major alkaloid portion was eluted when the solvent system was Et_2O-CH_2Cl_2-MeOH (80:18:2). From this was obtained 16 mg of pure (−)-ammodendrine (**1**), 10 mg of (−)-*N'*-methylammodendrine (**2**), and 7 mg of (+)-tetrahydrorhombifoline (**4**). Other alkaloid fractions were mixtures, so they were combined, and further isolations were performed by plc on neutral alumina using a similar solvent system for elution. This yielded pure 22 mg of **2**, 12 mg of **1**, 12 mg of **4**, and 25 mg of (+)-13-α-hydroxylupanine (**3**). In addition, 5 mg of cantleyine (**8**) and 2 mg of **5** were isolated from the plc, but both contained impurities by ^{1}H-nmr.

[3]Routine data on instrumentation and general methods are available in a thesis (6).

The crude alkaloid residue was also analyzed by NH_3 ci gc/ms and these data (which corroborate the above work) have been published elsewhere (7). In addition, the gc-ms provided evidence for lupanine (**7**) and 1-acetyl-1,2,3,4-tetrahydropyridine (**6**).

(−)-*Ammodendrine* **1**.—This compound $[\alpha]^{23}D$ −20° (c 0.004, $CDCl_3$), had ir, ^{1}H-nmr, and mass spectra corresponding to those of the literature (17) for (+)-ammodendrine. As reported (17), some of the ^{1}H-nmr spectral peaks are doubled because of the presence of isomers from restricted rotation about the N-Ac bond. This is also observable in the ^{13}C-spectrum, which has not previously been reported. The values given here are the most intense of the two peaks where doublings occur. ^{13}C-nmr ($CDCl_3$): 168.02, 123.59, 121.08, 61.64, 47.46, 40.45, 31.81, 25.97, 25.10, 22.87, 21.71, 21.47.

(−)-*N'-Methylammodendrine* **2**.—Compound **2** $[\alpha]^{23}D$ −44° (c 0.02, $CDCl_3$) was identical with a standard sample of the (+)-compound except for optical rotation. The ir, ^{1}H-nmr, and mass spectra corresponded to those of the literature (17). ^{13}C-nmr ($CDCl_3$ (most intense peak where doubling occurred): 167.73, 122.31, 120.61, 70.52, 57.15, 44.25, 40.68, 31.98, 26.03, 24.57, 21.65, 21.42 (one peak involves two coincidental carbon resonances, probably that at 44.25 by intensity).

(+)-*13-α-Hydroxylupanine* (**3**).—This was identical by optical rotation, tlc, ^{1}H-nmr, and mass spectra with an authentic sample. The ^{13}C-nmr spectrum was essentially identical with that reported (18).

(+)-*Tetrahydrorhombifoline*.—Compound **4** was identical by optical rotation, tlc, ir, ^{1}H-nmr, and mass spectra with an authentic sample. The ^{13}C-nmr spectrum has not been reported previously. ^{13}C-nmr ($CDCl_3$): 168.78, 136.96, 115.07, 59.37, 58.90, 58.20, 54.05, 46.46, 34.09, 33.56, 33.15, 31.58, 29.36, 28.07, 20.25.

Hydroxytetrahydrorhombifoline (**5** .—Compound **5** appeared in tlc (Al_2O_3, Et_2O, double developed) at an Rf lower than tetrahydrorhombifoline and higher than hydroxylupanine. In the gc it appeared later than tetrahydrorhombifoline and before hydroxylupanine (7). It was not obtained pure except by gc/ms: ei ms (*m/z*, rel. int.) 262(1), 247(1), 223(100), 207(2), 124(11), 112(22), 109(3), 58(54); NH_3ci ms 265(100), 263(25), 249(8), 223(25), 112(5), 58(20). These data correspond quite closely with those from tetrahydrorhombifoline (6,7) except that the 223 base peaks in the ei ms and the quasimolecular ion in the NH_3 ci ms were exactly 16 mass units higher than in tetrahydrorhombifoline. The mass spectral data as well as the tlc and gc behavior indicate that this MW 264 alkaloid is probably an hydroxytetrahydrorhombifoline.

Cantleyine (**8**).—This compound had uv, ir, and mass spectra the same as those reported (8). The ^{1}H-nmr spectrum of our isolated sample showed presence of impurities, but the main peaks were very close to those reported (8) for cantleyine. One exception was our finding of δ 1.33 for the C-CH_3 instead of the δ 1.42 reported (8). The usual position for this resonance is, however, close to the 1.33 value. There is also ^{1}H-nmr data for cantleyine (9), which differs somewhat from ours or that of Sevenet, *et al.* (8). A value of δ 1.31 is, however, given for the C-CH_3. We were only able to isolate cantleyine (or show its presence by tlc) when basificaton was with NH_4OH and not with NaOH. It also appeared to be an artifact in other isolations (8,9).

Lupanine (**7**).—This compound was only observed by gc/ms. The ei ms showed *m/z* 248(42%), 247(38), 149(46), 136(100), and 97(28). This is nearly identical with that reported (19) for lupanine. The NH_3 ci ms showed a base peak quasimolecular ion at *m/z* 249, and the gc retention time was as expected for lupanine.

1-Acetyl-1,2,3,4-tetrahydropyridine (**6**).—Compound **6** was also identified only by gc/ms. Peak 1 in the gc (7) showed ei ms *m/z* 125(45%), 83(88), 82(100), 68(40), 54(22), and 43(35). This is essentially identical with the reported (20) spectrum for synthetic **6**.

ISOLATIONS AND ANALYSES (*PENSTEMON WHIPPLEANUS*).—Dried stems and leaves (185 g) were extracted in a Soxhlet with hexane and then MeOH. The MeOH was evaporated to a wet gum (39 g), which was treated by an acid-base partition as above to yield 30 mg of residue which, by tlc and mass spectral analyses, was mainly methyl ferulate. Small amounts of alkaloids could be seen by tlc.

Dried blossoms (150 g) were extracted similarly to yield 31 g of wet residue, which was treated by a similar acid-base partition. The first extraction of the basified solution was with $CHCl_3$, and it yielded 100 mg of residue. A second extraction was made with EtOAc, and this yielded 430 mg of residue. The 100-mg residue was dominated by one alkaloid that was purified by plc (Al_2O_3; 2:1, hexane-EtOAc) to yield 20 mg of boschniakine (**9**). Plc also yielded a mixture of *cis*- and *trans*-methyl cinnamates. A portion (320 mg) of the 430-mg residue was triturated with EtOAc-MeOH (100:1) to yield 130 mg of solubles, which were subjected to flash chromatography (Si gel, EtOAc-MeOH). Fractions 6-9 yielded a mixture of two substances, as evidenced by tlc. This was distributed between 1 M H_2SO_4 and $CHCl_3$. The $CHCl_3$ solution yielded a residue that was purified by mplc to give 5 mg of crystalline *trans*-cinnamamide. The aqueous acid was made basic with NaOH and extracted with $CHCl_3$ to yield a mixture of *trans*-cinnamamide and noractinidine (**10**).

A portion of the 430-mg residue was also analyzed by gc/ms. This corroborated the classical isolation studies and also provided evidence for carbomethoxypedicularine (**11**).

(+)-*Boschniakine* **9**.—This was identified by optical rotation, uv, ^{1}H-nmr (360 MHz), ^{13}C-nmr, and mass spectra and by a comparison with a standard sample. The 360-MHz ^{1}H-nmr spectrum is given in a thesis (6), while the previously unreported ^{13}C-nmr spectrum is given here. ^{13}C-nmr ($CDCl_3$): 191.40, 154.54, 150.80, 148.81, 145.72, 127.73, 37.12, 34.14, 30.70, 19.90.

trans-Cinnamamide was identified by mp, tlc, ir, 100-MHz ^{1}H-nmr, and mass spectra compared with a sample synthesized from *trans*-cinnamic acid.

Methyl ferulate and *cis* and *trans* methyl cinnamates were identified by mass spectra and 100-MHz ^{1}H-nmr spectra.

4-Noractinidine.—The presence of this compound was suggested by gc/ms (6) and uv of a mixture contaminated by some *trans*-cinnamamide. The uv showed λ max (MeOH) 262, 268 nm [Lit. (12) 260, 267 nm]. The mass spectra were corroborative: ei ms: 133(52), 118(100), 91(18); NH_3 ci ms: 134(100), 118(21). Thus, the main fragmentation was simply loss of a CH_3 as expected for 4-noractinidine (12), although isomeric structures cannot be ruled out. Boschniakine and 4-noractinidine have been linked biogenetically (14).

Carbomethoxypedicularine (**11**).—This is the suggested structure for an alkaloid of MW 235 with a relatively later gc retention time (6). Ei ms *m/z* 190(100%), 162(61), 146(20), 117(21), 104(42); NH_3 ci ms *m/z* 236(100], 190(95), 162(62), 146(30). The fragmentation pattern corresponds to that for pedicularine (**12**) (13) with the exception of the added carbomethoxy group. An isomeric structure cannot be ruled out.

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