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PYRROLIZIDINE ALKALOIDS FROM *HACKELIA CALIFORNICA* AND *GNOPHAELA LATIPENNIS*, AN *H. CALIFORNICA*-HOSTED ARCTIID MOTH

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ABSTRACT.—Two new pyrrolizidine alkaloids, 7-*O*-acetyl-9-*O*-latifolylretronecine [**1**] and 9-*O*-latifolylretronecine [**2**], were isolated from *Hackelia californica* after Zn reduction. The alkaloids are analogues of latifoline, which was previously found in *Hackelia floribunda*. Neither of the new pyrrolizidines could be isolated prior to Zn reduction; hence they were presumed to be present in the plant as *N*-oxides. Female *Gnophaela latipennis* moths and larvae raised on their natural host plant, *H. californica*, contained an alkaloid which was different from the plant isolates. Spectral evidence showed that this alkaloid was callimorphine, 9-*O*-(2-acetoxy-2-methyl)-butanoylretronecine, a pyrrolizidine reported earlier from other moth pyrrolizidine alkaloid specialists, but not from their host plants. Callimorphine was also found in wild-caught *Gnophaela vermiculata* (host plant unknown).

The tribe Eritricheae of the Boraginaceae contains, among other genera, two whose greatest diversity occurs in the western United States, *Hackelia* (1) and *Mertensia* (2). Species of these genera are under current study in our laboratories (3,4) as part of our interest in biologically active pyrrolizidine alkaloids and in the chemistry of insect/plant interactions. In the first study of *Hackelia* (3), we reported the isolation of the pyrrolizidine alkaloid latifoline and its *N*-oxide from *Hackelia floribunda* (Lehm) Johnston. Recently, *Hackelia californica* (Gray) Johnston was reported to be a major feeding host plant for larvae of the strikingly aposematic (warningly or brightly patterned) black and white moth *Gnophaela latipennis* (Boisduval) (Arctiidae: Pericopinae) (5). Other identified host plants for *G. latipennis* were also in the Boraginaceae: *Cynoglossum occidentale* Gray and *Cynoglossum grande* Dougl. ex Lehm., as well as unidentified *Mertensia* and *Myosotis* species. Warningly colored Lepidoptera whose larvae consume pyrrolizidine-containing plants often sequester these alkaloids as defensive substances (6–8). Defensive pyrrolizidines can also be obtained by adults via nectaring (9), and the alkaloids can also be metabolically converted to pheromones (8, 10–12). We report here the results of a study on the alkaloid content of *H. californica* leaves used as a food source by *G. latipennis* larvae and on the alkaloid content of the insects. Alkaloid presence in adult *Gnophaela vermiculata* Grote & Robinson, caught in the field, was also investigated.

RESULTS

H. CALIFORNICA.—Preliminary isolation studies on small leaf samples by the procedure of Hartman and Zimmer (13) established the presence of alkaloids, but only as *N*-oxides, as alkaloids were recovered only after Zn dust treatment of the acidic extraction solution. A large scale isolation, with Zn reduction, yielded a crude alkaloid fraction (0.8%, dry wt basis) that showed one major, one minor, and one trace alkaloid by tlc analysis. The major and minor alkaloids were isolated by vacuum liquid chromatography (vlc), but the trace alkaloid could not be recovered pure.

The major and minor alkaloids were characterized as 7-*O*-acetyl-9-*O*-latifolylretronecine [**1**] and 9-*O*-latifolylretronecine [**2**] as follows. Fab hrms established the molecu-

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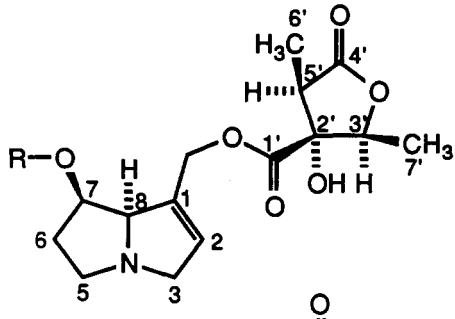
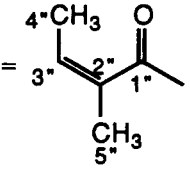


1 R= $CH_3C(=O)$— (2" 1")

2 R=H



3 R=

lar formula of **1** as $C_{17}H_{23}O_7N$ and of **2** as $C_{15}H_{21}O_6N$. That **1** was an acetyl derivative of **2** was evidenced by the molecular formula difference and the close correspondence of their ^{1}H-nmr spectra (Table 1). Differences were a 3H singlet at 1.96 ppm in **1** that was lacking in **2** and a ^{1}H broad singlet that appeared at 5.30 ppm in **1** but at 4.35 ppm in **2**. The ^{1}H-nmr spectrum of **1** was very similar to that of latifoline [**3**], isolated previously (3) from *H. floribunda*. The only differences between the spectra for **1** and **3** were those expected from replacement of the angelyl group in **3** with the acetyl group in **1**. The ^{13}C-nmr spectrum of **1** in comparison with that of **3** was also consistent with the

TABLE 1. ^{1}H-nmr Spectral Data for Compounds **1**, **1** *N*-Oxide, and **2**, (ppm, Multiplicity, *J* in Hz).

Proton	Compound		
	1[a]	**1** *N*-Oxide[b]	**2**[c]
6′	1.16 d (6.50)	1.18 d (7.00)	1.18 d (7.00)
7′	1.29 d (6.50)	1.31 d (6.50)	1.34 d (6.60)
2″	1.96 s	2.03 s	—
6	2.01–2.06 m	2.14 m 2.19 m	1.92–2.03 m
5b	2.62–2.67 m	3.71 td (6.00, 11.9)	2.72 dd (10.00, 17.00)
5′	2.93 q (6.50)	2.94 q (7.00)	2.97 q (7.00)
5a	3.28 dd (7.70, 9.80)	3.88–3.96 m	3.21–3.28 m
3a	3.34 m	4.49 m	3.42 m
3b	3.90 dd (3.50, 15.00)	4.52 br s	3.90 br d (17.00)
8	4.20 br s	5.02 br d	4.20 br s
3′	4.37 q (6.50)	4.39 q (6.50)	4.43 q (6.60)
9	4.68 d (15.00)	4.74 d (15.00)	4.86 d (10.00)
	4.95 d (15.00)	4.76 d (15.00)	4.94 d (10.00)
7a	5.27 dd (3.00, 3.00)	5.67 m	4.35 br s
2	5.80 d (3.00)	5.87 d (2.30)	5.89 br s

[a]500 MHz and ^{1}H-^{1}H COSY.
[b]270 MHz.
[c]300 MHz.

assigned structure (Table 2). Alkaloid **1** was converted to the *N*-oxide, and the *N*-oxide was characterized by ^{1}H- and ^{13}C-nmr spectroscopy (Tables 1 and 2). This aided in spectral interpretation because only the resonances at C-3, C-5, and C-8 (or those of their attached protons) were shifted significantly in the ^{13}C- (or ^{1}H-) nmr spectrum of the *N*-oxide as compared to the base **1**. Assignments in the ^{1}H nmr spectrum of **1** were also assisted by high field ^{1}H-^{1}H COSY and nOe experiments. Mass spectral fragmentation patterns (see Experimental) were also consistent with the assigned structures.

Larvae of *G. latipennis* were collected near Chester, California from *H. californica* and fed on the same plant material until pupation and subsequent eclosion. Alkaloid isolations were conducted on larvae, frass excreted by the larvae, pupae, and adult females. No adult males were obtained and the number of female adults was also small since many larvae failed to reach the pupal stage and some which did pupate failed to eclose. Alkaloids were not present in the frass. Alkaloids could be isolated from larvae, pupae and adults in small amounts without prior Zn reduction by the same procedure as was used for the plant material. If larvae, pupae, or adults were not dried before analysis, and the modified procedure of Brown (9), which includes Zn reduction, was used, alkaloid yields were much higher. Tlc results and subsequent NH_3 cims (14) indicated the presence of one major component, mol wt 297, and a minor component, mol wt 155, in most of the life stages analyzed. Neither **1** nor **2** was present in the moth crude alkaloid isolate, nor was the mol wt 297 alkaloid detectable in the crude alkaloid isolate from *H. californica*.

The mass spectral fragmentation pattern of the major component could not be in-

TABLE 2. ^{13}C-nmr Spectral Data for Compounds **1**, **1** *N*-Oxide, and **3** *N*-Oxide (ppm).

Carbon	Compound		
	1	**1** *N*-Oxide[a]	**3** *N*-Oxide[b]
4′	174.3	174.8	175.1
1′	171.1	171.2	170.7
1″	170.0	169.3	165.7
1	132.0	131.1	130.8[c]
2	128.5	123.0	122.4
2′	83.4	83.9	83.7
3′	79.5	80.2	81.7[d]
8	75.5	93.8	93.8
7	74.1	72.7	72.3
3	63.2[d]	78.6	80.3[d]
9	62.8[d]	61.3	61.3
5	53.3	69.5	69.6
5′	45.6	46.4	46.7
6	34.0	32.5	32.7
2″	20.8	20.7	—
7′	13.4	13.9	14.1
6′	8.2	8.6	8.8
3″	—	—	140.9
2″	—	—	126.3[c]
4″	—	—	20.4
5″	—	—	16.0

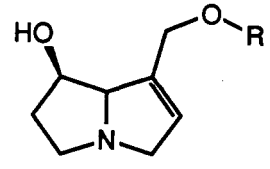
[a]67.5 MHz.
[b]25 MHz.
[c]A revision of the earlier assignment (3).
[d]Interchangeable.

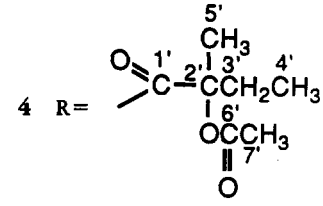
terpreted in terms of possible derivatives or metabolites related to **1** or **2**, but it was essentially identical with that reported (15) for callimorphine [**4**], a pyrrolizidine isolate from adults of several lepidopteran species. The ^{1}H- and ^{13}C-nmr spectra (Table 3), not

TABLE 3. ^{13}C-nmr and ^{1}H-nmr Spectral Data for Compound **4** (ppm, Multiplicity, *J* in Hz).

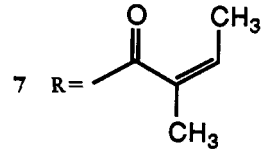
Position	^{13}C[a]	^{1}H[b]
6'	172.15	—
1'	170.23	—
1	132.40	—
2	130.25	5.88 d (1.4)
2'	80.95	—
8	78.71	4.23 br s
7	71.03	4.27 br s
9	62.89[c]	4.76 d (13.0)
		4.66 d (13.0)
3[a]	62.18[c]	3.44 ddd (1.7, 3.4, 15.0)
3[b]		3.88 d (15.0)
5[a]	53.91	3.36 dd (6.7, 9.2)
5[b]		2.76 ddd (6.7, 9.2, 11.8)
6	35.74	1.98–2.04 m
3'	30.98	1.8–2.00 m (buried)
7'	21.09	2.05 s
5'	20.67	1.54 s
4'	7.62	0.91 t (7.5)

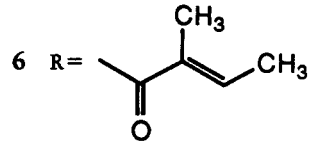
[a]67.5 MHz.
[b]300 MHz.
[c]Interchangeable.





5 R=H





previously reported, were in complete accord with structure **4**. The minor mol wt 155 component had ^{1}H-nmr and mass spectra and tlc value identical with those for standard retronecine [**5**]. With very heavy spotting, tlc plates showed additional very minor alkaloidal components in the insect isolates, but none could be isolated pure. The NH_3 cims of mixtures showed an $[M + H]^+$ peak at 238 for one of these components; this is consistent with a formulation as either 9-angelylretronecine [**6**] or 9-tiglylretronecine [**7**].

Once these components were found (or suggested to be present) in the insect, we looked in detail at the NH_3 cims of the crude alkaloid isolate from the *H. californica* plant. The presence of both **5** and **6** (or **7**) in extremely small amounts was indeed indicated, but no peak corresponding to that for **4** could be seen even at trace levels.

Similar black and white aposematic adult moths were encountered flying in central Utah and identified as *G. vermiculata*. Tlc analysis of the crude bases extractable from these adults showed callimorphine to be the major alkaloid.

DISCUSSION

H. CALIFORNICA ALKALOIDS.—Although the alkaloids **1** and **2** are new, they are simple analogues of latifoline [**3**], which was the major alkaloid of *H. floribunda* (3). Because about 45 species of *Hackelia* are known (1), additional species need to be analyzed if the scope of alkaloid structure variations within the genus is to be assessed. A number of *Hackelia* species were originally placed in the genus *Lappula*, but it has been suggested (1) that *Hackelia* is more closely related to *Eritrichum*. Echinatine was reported (16) from *Lappula glochidiata* and lasiocarpine from *Lappula intermedia* (17). These are mono- and diesters of the necine base heliotridine. Thus, *Hackelia* and *Lappula* differ in the necine base stereochemistry of their pyrrolizidine alkaloids in the few cases so far reported. Macrocyclic esters have not been reported from either genus. There are no literature reports as yet on alkaloids of *Eritrichum*.

GNOPHAELA ALKALOIDS.—The presence of bitter (or toxic) pyrrolizidine alkaloids as defensive substances in aposematic lepidoptera has been demonstrated several times (6,8,9). There are some interesting variations in those cases where the pyrrolizidines were sequestered via larval consumption of pyrrolizidine-containing plants. Thus, senecionine, integerrimine, and a trace of seneciphylline were found in both *Senecio spathulatus* A. Rich and the hosted *Nyctemera annulata* Boisduval moth (6). Alkaloids were in higher concentration in the moth than in the plant and occurred as the *N*-oxide and free base (about 70:30) in both the plant and the moth. Callimorphine [**4**] has been reported as a minor component, along with plant alkaloids, in a number of arctiid moths (15). In these cases, as in ours, **4** was not found in the host plant. The structure of **4** was previously proven by comparison of gc retention times and mass spectra of synthetic **4** and derivatives as compared with the isolate and by identification of retronecine and the necic acid from hydrolysis of the isolate (15). The absolute configuration of the acid is unknown. In our case, the major alkaloid in the moths is **4** and we could find none of the two major plant alkaloids **1** and **2**.

Callimorphine was termed a "metabolite" (15) as its origin was not determined. No suggestions were made as to its possible mode of formation, nor have any further studies on callimorphine appeared in the literature.* Our studies have shown that pyrrolizidines do not appear in the larval frass, and because no **1** or **2** is found in the larvae or later life stages of the insect, these compounds must be rapidly metabolized by the larvae after consumption. A direct conversion of the necic acid of **1** or **2** to that of **4** would

*NOTE ADDED IN PROOF: See, however, M. Wink, D. Schneider, and L. Witte, *Z. Naturforsch.*, **43c**, 737 (1988).

have to involve a chemically unlikely series of complex transformations. A more likely sequence might involve hydrolysis of the **1** and **2** ester functions to yield **5** and reesterification with a new acid (presumably plant-obtained) to form **4**. The proper acid would be that resulting from addition of HOAc to angelic (or tiglic) acid or from hydration of one of these acids followed by acetylation. The unacetylated necic acid, 2-hydroxy-2-methylbutanoic acid, has previously been found (18) as one of the acylating acids of some *Veratrum* alkaloids. Alternatively, **4** could arise from a similar sequence of hydration and acetylation reactions on **6** or **7**. We are currently exploring ways to confirm or negate these hypotheses for the insect production of callimorphine.

EXPERIMENTAL

INSTRUMENTATION.—^{1}H-nmr spectra were recorded on Bruker-IBM WP-270, WP-200, or ACE-300 spectrometers. 2D-nmr and ^{1}H-^{1}H COSY spectra were recorded on Bruker 500 or ACE-300 spectrometers. ^{13}C-nmr spectra were recorded on Bruker IBM WP-270 or the Bruker ACE-300. All spectra were in $CDCl_3$. Optical rotation was done on a Autopol III automatic polarimeter (Rudolph Research). NH_3 cims were obtained on a VG Micromass 16F spectrometer with a Systems Industries Interface and a Digital PDP8-A computer.

ORGANISMS.—Descriptions of *H. californica* and *G. latipennis* biology in northern California and identifications of the organisms have been published (5). Fourth-instar larvae of *G. latipennis* were collected June 7, 1987, on *H. californica* plants 6.4 air km NE of Chester, Plumas Co., California, in Section 26 on Mud Creek Rim (1676 m). Larvae were fed on *H. californica* until pupation. Upon eclosion (June 28), adults were papered and sent to Colorado for analysis along with air-dried whole aboveground *H. californica*. Free-flying adults were captured at the same time. In 1988, larvae and fresh plant material of their host were collected on June 20 and shipped to Colorado. Some last-instar larvae were frozen immediately for later analysis and others raised on plant material. Frass was collected during the growth period. As pupae formed, some were frozen for later analysis, while others were held until adult eclosion. Adults were frozen immediately. Adults of *G. vermiculata* were collected in flight on July 16 near milepost 32 on the east side of US Highway 40 south of Heber, Utah. Live moths were express-mailed to Colorado and frozen until analysis. Identification was by Dr. B. Kondratieff, Department of Biology, Colorado State University. Specimens are in the CSU Insect Collection (B. Kondratieff, curator).

PLANT ISOLATION PROCEDURES.—In a general procedure (13), 10 g of dry, ground plant material (or a similar amount of fresh or fresh frozen plant) was extracted with 100 ml of MeOH by stirring overnight. The mixture was filtered and evaporated in vacuo to a gummy residue which was triturated well with 50 ml of 1 M HCl and filtered. The filtrate was divided into two equal parts. One part was washed with hexane (15 ml) and then Et_2O (15 ml). To the aqueous solution was added concentrated NH_4OH to pH 9, and the solution was then extracted with 5 × 10 ml of $CHCl_3$. The organic phase was tested for alkaloids by tlc (iodoplatinate visualization). Only traces of alkaloids were detected in the concentrated residue. The second part of the aqueous extract was stirred with 1 g of Zn dust at 25° overnight, filtered, washed, made basic, and extracted as above. Tlc examination of the extract with iodoplatinate visualization showed a major alkaloid at R_f 0.50, a trace at 0.20 and a minor alkaloid spot at 0.13 [Si gel, $CHCl_3$-MeOH (1:1)]. The residue was subjected to NH_3 cims for screening (14), and protonated molecular ions were detected at *m/z* 354 (major) and 312 (minor). No peak was detected at *m/z* 298, which would be expected for **4**. At high sample pressure, minor peaks were seen at *m/z* 238 and 156.

The procedure with Zn dust reduction was used to obtain 0.86 g of crude alkaloid mixture from 104 g of dried plant material. Vlc (19,20) was used for separation of the alkaloids: 60–200 mesh Si gel, 30-ml sintered glass funnel, eluents of pure $CHCl_3$, $CHCl_3$/MeOH mixtures, and pure MeOH (16 total fractions of 20 ml each). Fractions 4–6 were combined and evaporated to yield 188 mg of pure **1**, R_f 0.50, while fractions 3 and 7–9 contained mainly **1** (47 mg). Fractions 10–14 (36 mg) were mixtures of mainly **1**, **2**, and a trace alkaloid, while fractions 15 and 16 yielded 20 mg of pure **2**, R_f 0.13.

7-O-*Acetyl*-9-O-*latifolylretronecine* [**1**].—An oil: $[\alpha]^{25}D$ +25.9 (c = 1.11, EtOH); hrfabms $[M+H]^+$ 354.1548; calcd for $C_{17}H_{23}O_7N$, 354.1553; fabms *m/z* (rel. int.) 354 (50), 221 (13), 195 (45), 161 (27), 119 (100); ^{1}H nmr see Table 1.

9-O-*Latifolylretronecine* [**2**].—An oil: $[\alpha]^{25}D$ +37.6 (c = 0.71, EtOH); hrfabms $[M+H]^+$ 312.1446; calcd for $C_{15}H_{21}O_6N$, 312.1447; fabms *m/z* (rel. int.) 312 (40), 195 (40), 161 (20), 119 (100); ^{1}H nmr see Table 1.

SYNTHESIS OF **1** *N*-OXIDE.—To 50 mg of **1** in 10 ml MeOH was added dropwise 0.5 ml 30% H_2O_2 and 30 mg of PtO_2. After stirring overnight, the mixture was filtered and evaporated, and the residue was

purified by preparative tlc [Si gel, $CHCl_3$-MeOH (1:1)] to yield 15 mg of **1** *N*-oxide: an amorphous solid; $[\alpha]^{25}D + 23.3$ ($c = 0.67$, EtOH); ^1H nmr see Table 1.

INSECT ISOLATION PROCEDURES.—Insects were analyzed separately. Each insect was placed in a 10-ml culture tube and macerated in aqueous MeOH 10% w/v for 5 min [MeOH-H_2O (4:1) for larvae and pupae, MeOH-H_2O (9:1) for adults]. The MeOH was filtered and evaporated under reduced pressure. The residue was taken up in 1 ml of 2 N H_2SO_4 and 1 ml of $CHCl_3$ and both layers placed in a culture tube. Contents were mixed by shaking and were finally centrifuged. The organic layer was drawn off and the aqueous layer washed twice with 1 ml of $CHCl_3$. In one case the aqueous layer was made basic, then extracted with $CHCl_3$, but only trace amounts of alkaloids were detected in the $CHCl_3$ extract. Larger amounts were obtained if Zn dust was added to the acidic aqueous layer and allowed to react for 2 h. The mixture was centrifuged and the supernatant removed to a new tube. This was made basic to pH 10 by drop-by-drop addition of either saturated NaOH solution or concentrated NH_4OH. Use of NH_4OH gave larger yields of alkaloids and was used in all subsequent extractions. The basic solution was extracted twice with equal volumes of $CHCl_3$-MeOH (3:1) and once with a larger amount of $CHCl_3$. In each case the organic layer was added to the test tube, mixed, and centrifuged. The organic layers were removed, dried over Na_2SO_4, combined, and tested for alkaloids by tlc as above. A major alkaloid (R_f 0.28) was detected for almost all insects and minor alkaloids at R_f 0.07 and 0.64 for a few [Si gel, $CHCl_3$-MeOH (1:1)]. Residues of some insects were subjected to NH_3 cims for screening as above. Protonated molecular ions were detected at *m/z* 298 (major), 238 (minor), and 156 (minor). No peaks were detected at *m/z* 312 or 354, which would be expected for **1** and **2**.

All insect alkaloid fractions containing **4** were combined, giving 19 mg of material. Mini vlc was used to isolate **4**: 60–200 mesh Si gel, 11 ml plastic Bio-Rad chromatography column, eluents of pure $CHCl_3$ and $CHCl_3$/MeOH mixtures (20 total fractions 2 mls each).

Fractions 7–13 contained traces of the R_f 0.64 alkaloid, which appeared to be a mixture upon heavy spotting. The amount obtained pure was insufficient for characterization. Fractions 14–20 were mainly **4**. Fraction 17 was essentially pure **4** and was used for nmr characterization (Table 3).

ACKNOWLEDGMENTS

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