Tetrahedron Vol. 38, No. 13, pp. 1949 to 1958, 1982
Printed in Great Britain.

0040-4020/82/131949-10$03.00/0
Pergamon Press Ltd.

ANT VENOM ALKALOIDS FROM *SOLENOPSIS* AND *MONOMORIUM* SPECIES

RECENT DEVELOPMENTS

TAPPEY H. JONES† and MURRAY S. BLUM
Department of Entomology, University of Georgia, Athens, GA 30602, U.S.A.

and

HENRY M. FALES
Laboratory of Chemistry, National Heart, Lung, and Blood Institute, Bethesda, MD 20205, U.S.A.

(*Received in U.S.A.* 18 *June* 1981)

Abstract—The chemistry and biology of the ant venom alkaloids from the genera *Solenopsis* and *Monomorium* are briefly reviewed. The usual 2,6-dialkylpiperidines found in four as yet unstudied species of *Solenopsis* are described. In addition, a monoalkylated 1-piperideine, that is a new natural product, is described from a fifth *Solenopsis* species. Finally, the venoms of *Monomorium latinode* and *M. subopacum* are shown to contain an array of 2,5-dialkylpyrrolidines.

INTRODUCTION

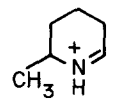
Ants in the genera *Solenopsis* and *Monomorium* produce a variety of monocyclic and bicyclic alkaloids in their poison glands. The biology and chemistry of these compounds have been the subjects of numerous investigations whose results are briefly considered here for each genus.

The venoms of fire ants, *Solenopsis* (*Solenopsis*) species, are characterized by a predominance of 2-alkyl-6-methylpiperidines[1-4] in admixture with a low concentration of proteinaceous constituents.[5] Initial investigations on the biological activities of one of these alkaloid-rich venoms (*S. invicta* = *saevissima*) established that the secretion produced edema and necrotic lesions when the ants stung human beings,[6] and in addition possessed antibacterial, antifungal, phytotoxic, and insecticidal properties.[7]

Subsequent investigations have established that these alkaloids exhibit a wide range of physiological activities and thus constitute broad-spectrum toxins which are admirably suited to function as defensive compounds. Fire ant alkaloids have been demonstrated to possess powerful hemolytic activity[8] and are responsible for the necrotoxicity[9] and antibiotic activity[10] of the venom. These compounds, which are capable of inhibiting Na^+ and K^+ "ATPases",[11] reduce mitochondrial respiration and uncouple oxidative phosphorylation at low concentrations.[12] In addition, they are capable of blocking neuromuscular junctions[13] and releasing histamine from mast cells,[14] the latter activity undoubtedly being associated with the well-developed algogenicity of the venom,[6] which is responsible for the ants' common epithet, fire ants. Although some allergic individuals are skin reactive to the alkaloids,[15] it is probable that systemic reactions resulting from fire ant stings are due to the proteins in the venom.[5]

†Present address: Department of Chemistry, U.S. Naval Academy, Annapolis, MD 21402, U.S.A.

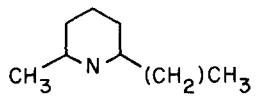
The *Solenopsis* (*Solenopsis*) venom alkaloids lend themselves quite well to analysis by GC/MS techniques. All the 2-alkyl-6-methylpiperidines (**1**, **2**) (Fig. 1) show a strong ion at $m/z = 98$ due to alpha cleavage of the alkyl group, an M-CH_3, and an M-1 ion, although unless they contain an unsaturated side chain (**2**) the molecular ion is very weak.[1] Upon carbon-skeleton chromatography they



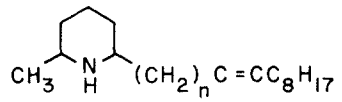
m/z=98

produce only n-alkanes with the same carbon number as the parent compound. Initially, the piperidine ring and the side chain double bond geometry were suggested by IR spectroscopy. Ultimately, the natural alkaloids were compared directly with synthetic compounds having well-established structure and stereochemistry.[1] The relative stereochemistry of the ring substituents has been determined by direct gas chromatographic comparison using polar liquid phases such as Carbowax 20M or SP-1000, which are capable of separating double bond isomers and the 2,6-disubstituted piperidine ring configurational isomers. Under these conditions, the *cis*-2,6-disubstituted piperidines elute first probably because the nitrogen is more sterically hindered to solvation by the 2,6-diequatorial substituents.[1] These facts have proven invaluable in determining the ring stereochemistry in all the monocyclic ant venom alkaloids reported to date. This method has shown that the side chain double bonds in the piperidines **2** are always *Z*, and that *trans*-2,6-disubstitution about the piperidine ring predominated in *S. invicta*.[1] In several other species, however, the *cis*-disubstituted piperidine is the major component.[4]

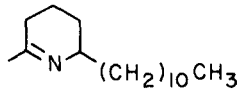
Although a number of syntheses have been reported



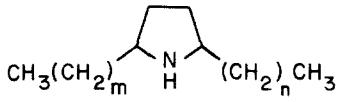
1, n=8, 10, 12, 14



2, n=3, 5, 7

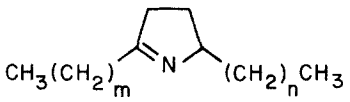


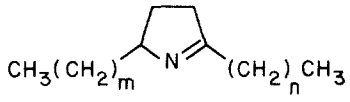
3



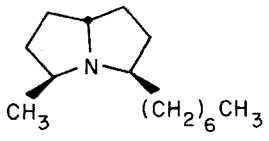
4

m=1, n=6
m=3, n=4, 6
m=5, n=4





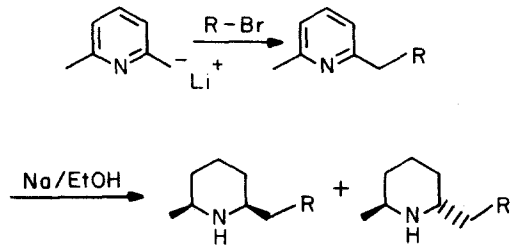
5, m=1, n=4, 6



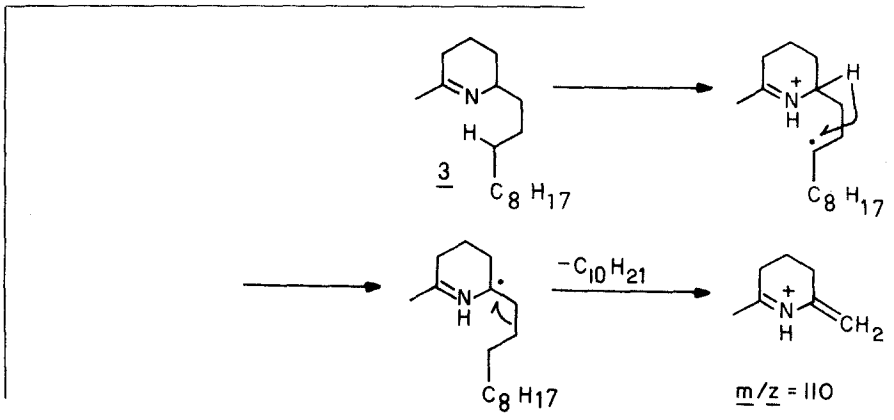
6

Fig. 1. *Solenopsis* venom alkaloids.

since the piperidine ant venom alkaloids were first prepared,[16,17] the original synthesis is still superior in providing fair yields of compounds with *trans*-stereochemistry and excellent yields of compounds with *cis*-stereochemistry.[1] This method is based on the alkylation of the lithium derivative of 2,6-lutidine with the appropriate alkyl bromide, followed by selective reduction of the resulting 2-alkyl-6-methylpyridine either by catalytic hydrogenation or with sodium in ethanol.



The 1-piperideine 3 found in *S. xyloni*, shows a characteristic fragmentation ion at $m/z = 110$ as the base peak in its mass spectrum, apparently due to proton transfer to nitrogen, followed by migration of the 6-proton and cleavage of the side chain as shown. In this case a mixture of both possible piperideines was pre-

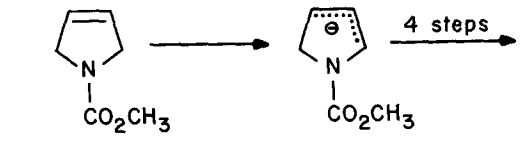


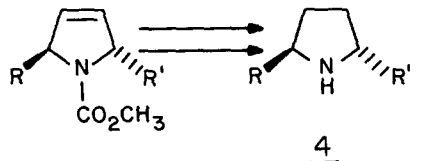
pared by treatment of piperidine **1**, n = 12, with t-butyl-hypochlorite. The two isomeric imines have different gas chromatographic retention times and different mass spectra, so that direct comparison was possible.[2]

Many species of *Solenopsis* belonging to the subgenus *Diplorhoptrum*, a taxon that is characterized by great taxonmic complexity,[18] are called thief ants in reference to the propensity of these diminutive insects to steal larvae from the nests of other species of ants.[19] This plundering *modus vivendi* is made possible by the presence of powerful venomous repellents, which are secreted in offensive contexts by the raiding thief ants.[20] It has also been established that one *Solenopsis* (*Diplorhoptrum*) species utilizes 2-butyl-5-heptyl-pyrrolidine (**4**, m = 3, n = 6) in order to effectively repel several species of host ants that are normally raided.[21] A synthetic sample of **4**, m = 3, n = 6, was as active a repellent as the ant-derived compound.[21]

In general, thief ants are not noted for their stinging abilities. However, *S. punctaticeps*, a species more closely related to thief ants than fire ants, was reported to sting human beings.[22] Reactions to the stings were mild and were characterized by transient edema and pruritis.

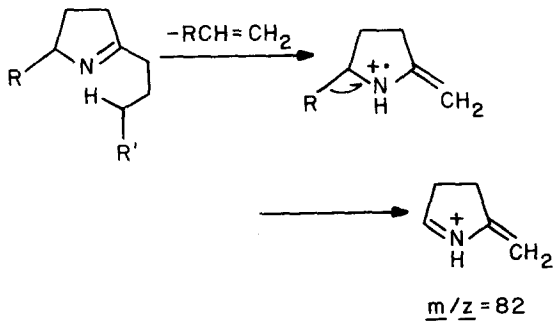
The mass spectra of the 2,5-dialkylpyrrolidines **4** found in these ants display two intense ions corresponding to α-cleavage of the side chains as well as a weak parent ion, which defines their C–N skeletons, but not their stereochemistry.[22] A number of syntheses have been reported for these compounds, including procedures based on the Hofman–Loffler reaction,[22] the borohydride reduction of the corresponding pyrrolines formed by the Mundy rearrangement,[23] the direct alkylation of N-nitrosopyrrolidine,[24] the catalytic hydrogenation of pyrroles,[25] and the reductive amination of 1,4-diketones.[26] Pyrrole hydrogenation gives predominantly *cis*-2,5-disubstituted pyrrolidines, and as with the 2,6-dialkylpiperidines, it was found that the *cis* pyrrolidines elute first on polar glc columns. Subsequently, direct comparison has shown that the *Solenopsis* pyrrolidines are the *trans* configuration. Recently a stereo-selective synthesis of the *trans* compounds has been developed which is based on the direct alkylation of 1-(methoxycarbonyl)-3-pyrroline.[27]





4

The mass spectra of the 2,5-dialkyl-1-pyrrolines (**5**) show the expected allylic cleavage ions relative to the C=N bond, as well as an odd electron ion from a McLafferty rearrangement and an ion at m/z = 82 resulting from the α-cleavage of an alkyl group from the odd electron ion.[22]



The 1-pyrrolines **5** have been prepared from their parent pyrrolidines by treatment of the N-chloropyrrolidines with aqueous alkali.[25] Also they may be formed inadvertently by catalytic dehydrogenation in GC–MS systems.[28]

To date, the pyrrolizidine **6** is the only known bicyclic *Solenopsis* alkaloid. All four possible isomers have been prepared by reductive amination of the corresponding triketone, and the stereochemistry of the natural product was determined by direct comparison.[29]

As with the *Solenopsis* species, there is one relatively well-known species in the genus *Monomorium*, that is the Pharaoh's ant, *M. pharaonis*. This tropical species has become a domestic pest in many nontropical countries and is known to be able to carry pathogenic bacteria and transmit disease.[30] Workers of *M. pharaonis*, which compete quite successfully with other species of ants at food sources, utilize their posion gland secretion as an effective repellent for foreign formicids.[20] Indeed the venom of this species can be used in much the same way as that of thief ants, *Solenopsis* (*Diplorhoptrum*) species,[20,21] in order to steal brood from the nests of other species of ants. In addition to this repellent function, some components in the venom may play roles as trail pheromones for the workers and queens of *M. pharaonis*.[30]

The venom of *M. pharaonis* is an alkaloid-rich secretion that contains both pyrrolidines **4**, m = 3, n = 4, and **9**, n = 4, 6, 8, as well as the indolizidines **7** and **8** (Fig. 2).[30–32] These alkaloids are present on the odor trails laid by the workers[31,32] and the synthetic compounds are somewhat active as trail pheromones,[31,33] although less active than faranal, a sesquiterpenoid produced in the Dufour's gland.[34] The trail-following activity of these alkaloids appears to be concentration dependent[35] and synergistic effects characterize the responses of the workers to mixtures of these alkaloids.[23]

One of the major components of the *M. pharaonis* venom is 3-butyl-5-methylindolizidine (**7**), an alkaloid that has been the subject of a number of chemical investigations. Although the structure of **7** was suggested by spectral data,[30] both the structure and stereochemistry of **7** were again only established by synthesis.[30,31] One approach was via alkylation of 2,6-lutidine with 1-hexene oxide. By varying the sequence of the subsequent cyclization and hydrogenation reactions, all four possible isomers of **7** could be prepared.[36] Although the stereochemistry of each isomer was assigned from known reaction pathways, it is supported by extensive conformational analysis based on nuclear magnetic resonance data.[37] The stereochemistry of the unsaturated indolizidine **8**, a minor component from *M. pharaonis*, is not reported.[32]

There are relatively few endemic species of

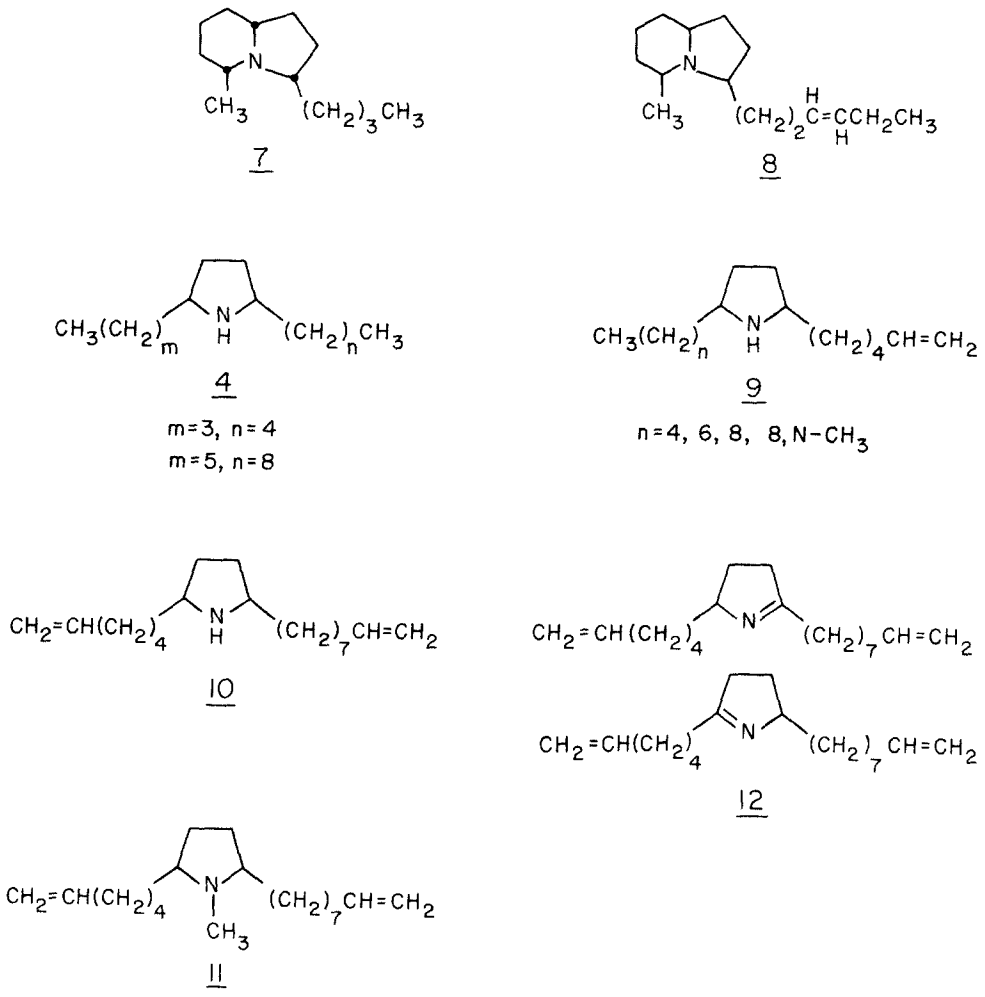


Fig. 2. *Monomorium* venom alkaloids.

Monomorium in North America, and these consist of a group of closely related forms.[18] Several introduced species of *Monomorium* (e.g. *M. floricola*) are now well established in the United States, but these are only found out-of-doors in the subtropical areas of Florida.

As is the case for the venom of *M. pharaonis*,[20] those of North American species of *Monomorium* appear to be utilized as repellents for other ant species. Workers of *M. minimum* have been observed to successfully repel workers of the larger and aggressive fire ant *Solenopsis invicta* when both species were competing at food sources.[38,39] The apparent widespread use of venom gland secretions as repellents by *Monomorium* species is indicated by the observation that this practice is common in Neotropical species as well.[40]

The venoms of *Monomorium* species have also been shown to contain the saturated 2,5-dialkylpyrrolidines (**4**) as well as the unsaturated pyrrolidines (**9** and **10**).[31,32,40] The terminal double bonds in the side chains of the pyrrolidines **9**, n = 8 and **10**, which are major components of the venom of several North American *Monomorium* species, were established by methoxymercuration–demercuration on a micro scale.[40] The alkaloids were prepared by reductive animation of the corresponding 1,4-diketones, conditions which the terminal double bonds tolerate quite well. Direct comparison with the synthetic *cis/trans* mixture showed that the natural alkaloids were all of the *trans* configuration.[40]

The N-methylpyrrolidine (**11**) had a mass spectrum similar to the corresponding N-H derivative, with all the major fragments shifted up by fourteen mass units. It could be prepared by reductive alkylation of the non-methylated pyrrolidine **10** with formaldehyde in formic acid.[40]

A major venom component in *M. ebeninum* is the isomeric pair of 1-pyrrolines (**12**) which showed the same McLafferty rearrangement, and α-cleavage behavior in their mass spectra as did the pyrrolines found in *S. punctaticeps*; they could be reduced in the same fashion to **10** with sodium borohydride.[22,40]

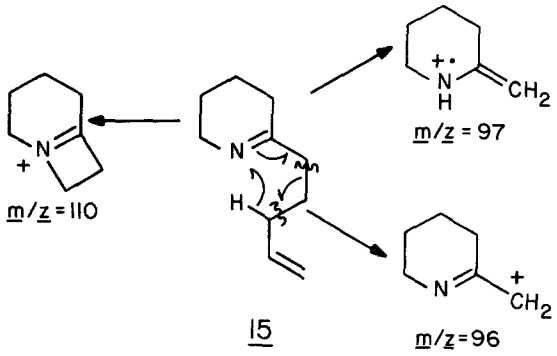
The alkaloidal venom components of four species of *Solenopsis* (*Diplorhoptrum*), one species of *Solenopsis* (*Euophthalma*), and of *Monomorium latinode* and *M. subopacum*, Old World species, are described in this report. Again, GC/MS techniques, coupled with micro-degradation and synthesis, provide the structures for these alkaloids, including a monoalkylated 1-piperideine (**15**) reminiscent of the Hemlock alkaloids.

RESULTS AND DISCUSSION

The methylene chloride extracts from three species of *Solenopsis* (*Diplorhoptrum*) and one species of *Solenopsis* (*Euophthalma*), *S. littoralis*, were examined by GC/MS and found to contain the alkaloids listed in Table 1. The 6-methyl-2-alkylpiperidines (**1**) have well documented mass spectra, and were readily identified.[1] Compared to the fire ants, these ants produce very small quantities of alkaloids. Only in the cases of *S. carolinensis* and *S. pergandei* was there sufficient material to carry out direct comparisons with authentic compounds, which demonstrated that in both cases the 2,6-dialkylpiperidines were of the *trans* configuration.

The N-methyl-2,6-dialkylpiperidines (**13**) are novel ant venom alkaloids whose structures were indicated by a base peak of $m/z = 112$ in their mass spectra and no higher mass ions that would indicate anything other than the loss of a Me group. These structures were confirmed by their identity with authentic samples prepared by reductive methylation of the corresponding N-H piperidine with formaldehyde and formic acid.[40] In the case of *S. pergandei*, the N-methylpiperidine **13**, n = 10, can constitute up to one fifth of the total alkaloids in the secretion, so that it is improbable that these compounds are artifacts.

In contrast to the well-known ant alkaloids in Table 1, the extracts of one species of *Solenopsis* (*Diplorhoptrum*), Puerto Rico species A, contained a single compound, 2-(4-penten-1-yl)-1-piperideine (**15**), whose mass spectrum is shown in Fig. 3. The weak molecular ion at $m/z = 151$ suggested the formula $C_{10}H_{17}N$, while the base peak at $m/z = 97$ suggested an α-substituted 1-piperideine system because of its odd electron nature (α-substituted 1-piperideines undergo a McLafferty rearrangement to produce an ion of this mass).[2] Direct allylic cleavage affords the accompanying ion at $m/z = 96$. The presence of the ion at $m/z = 97$ also suggests that the remaining double bond is located terminally as is shown, since location at the 3′ position would be expected to inhibit the McLafferty rearrangement. A terminal double bond also facilitates explanation of the ion at $m/z = 110$ (M-41), which is considered to arise via simple allylic cleavage as shown. In confirmation of this structure, an NMR spectrum was obtained on the crude extract after taking up the sample in dilute hydrochloric acid, washing the acid layer with ether, making the sample basic and reextracting. Although the NMR spectrum was not of high quality, no methyl doublets or triplets could be discerned. However, in the olefin region



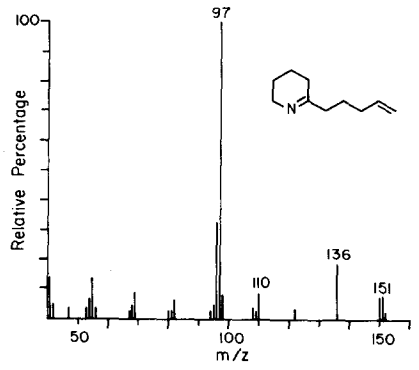
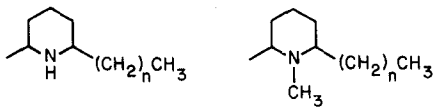


Fig. 3. Mass spectrum of 2-(4-penten-1-yl)-piperidine (**15**).

Table 1.



1 **13**

Solenopsis littoralis	++ (n=12)	
Solenopsis pergandei	++ (n=10)	+ (n=10)
Solenopsis carolinensis	++ (n=8)	- (n=8)
Solenopsis sp. B (Puerto Rico)	++ (n=8)	

++ = major component, + = minor component, - = trace amount.

part of the characteristic ABC pattern of a terminal olefin could be identified at δ 4.74, 4.92, and 5.01, identical in appearance to that of 4,6,8-trimethylnonene (Varian catalogue #1, 298).

The presence of a 1-piperideine system was confirmed by sodium borohydride reduction of the natural material (Scheme 1) to give 2-(4-penten-1-yl)-piperidine (**16**) whose mass spectrum is shown in Fig. 4, having a molecular ion at $m/z = 153$ and a base peak at $m/z = 84$ due to cleavage of the entire pentenyl side chain from the piperidine ring. On the other hand, catalytic hydrogenation of the natural material in methanol produced 2-pentylpiperidine (**17**), showing a mass spectrum with a molecular ion at $m/z = 155$ and the expected base peak at $m/z = 84$ for the 2-piperidyl ion (Fig. 4). This experiment confirmed the carbon nitrogen skeleton of **15** and was supported by the catalytic hydrogenation of 2-pentylpyridine to give a sample of **17** with identical gas chromatographic and mass spectral characteristics.

Although 2-(4-penten-1-yl)-1-piperideine (**15**) has been prepared as a synthetic intermediate via the Grignard addition of 4-penten-1-yl magnesium bromide to O-methylvalerolactim,[41] a sequence based on the Mundy N-acyllactam rearrangement is far superior in ease of operation.[42] Thus, N-(5-hexenoyl)-piperidone (**14**), prepared by acylation of piperidone with 5-hexenoyl chloride,[16,43] was heated in the presence of calcium oxide to give **15** directly (Scheme 1). The synthetic material had both an identical gas chromatographic retention time and mass spectrum as the natural ant alkaloid. In addition, pure samples of **16** and **17** were prepared from **15** by sodium borohydride reduction and catalytic hydrogenation respectively, and their mass spectra were identical to those of **16** and **17** derived from the natural material. These reductions of **15** to **16** and **17** were readily confirmed by the presence or absence of the appropriate double bond bands in their IR spectra and by the appearance of N-H and Bohlmann bands in the IR spectra of **16** and **17** (Experimental). It was also found that the terminal double bond of **15** could be selectively hydrogenated using ethyl acetate as the solvent to give 2-n-pentyl-1-piperideine (**18**). Continuing the hydrogenation in the presence of added acetic acid permitted complete reduction to **17**.

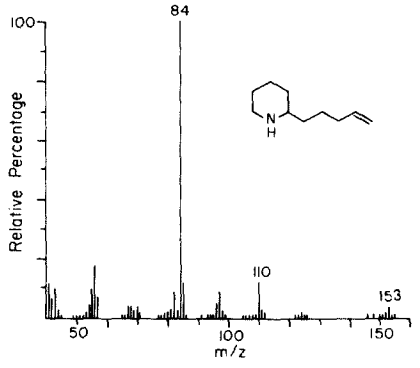


Fig. 4. Mass spectrum of 2-(4-penten-1-yl)-piperidine (**16**).

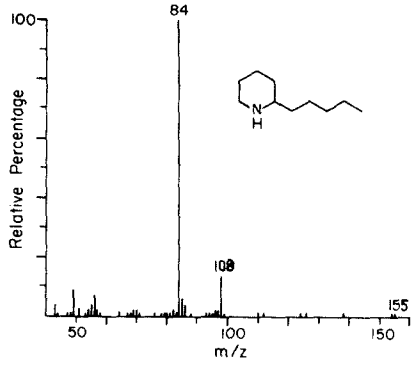
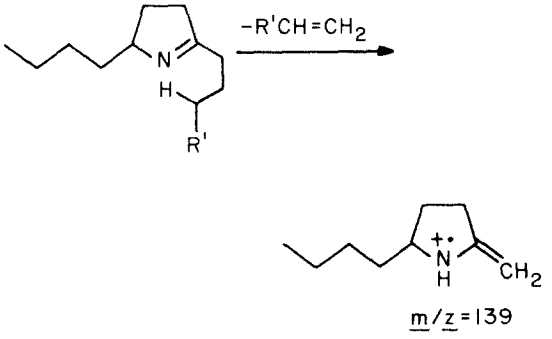
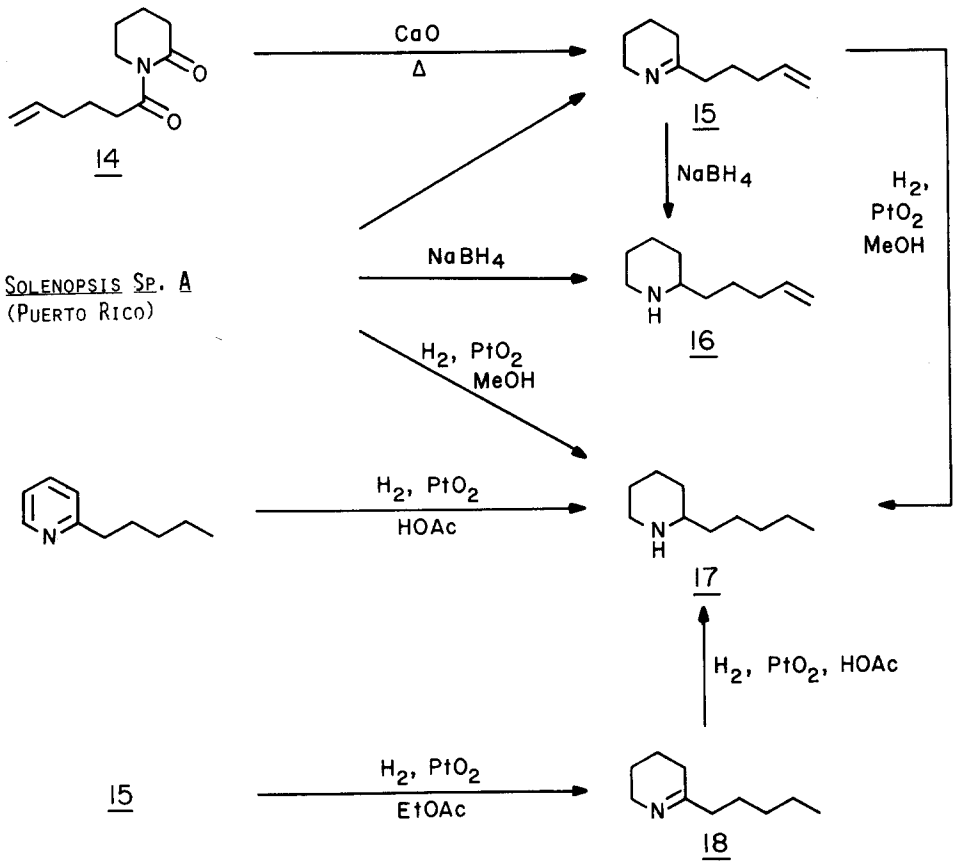


Fig. 5. Mass spectrum of 2-pentylpiperidine (**17**).

The alkaloidal venom components found in the methylene chloride extracts of *Monomorium latinode* are shown in Fig. 6, lettered in their order of elution from a nonpolar GC column. The major components of the mixture were B and E (**4** m = 3, n = 4 and n = 6 respectively) which made up 7 and 85% of the total alkaloids present and were readily identified from their well known mass spectra.[22] The 5-pyrrolines A and D were present on the order of about 2% each, and in contrast to other species of *Monomorium* and to *Solenopsis punctaticeps* in which 1-pyrrolines appear as mixtures of both possible C=N bond isomers,[22,40] only the 2-butyl-5-alkyl-5-pyrrolines were detected. These compounds show an intense odd electron ion at $m/z = 139$ in their mass spectra resulting from the McLafferty rearrangement as shown.



There is no detectable ion at $m/z = 143$ or $m/z = 171$ as would be expected for the pyrrolines isomeric with A and D. An additional minor component from *M. latinode* is N-methyl-2-butyl-5-heptylpyrrolidine (**18**) comprising about 3% of the alkaloids. The structure of this compound was suggested by its mass spectrum in which the α-cleavage and parent ions were fourteen mass units higher than those of N-H pyrrolidine **4**, m = 3, n = 6. This assignment was confirmed by reductive N-methylation of an authentic sample of **4**, m = 3, n = 6, with formaldehyde in formic acid to give a single product having a mass spectrum identical to the natural alkaloid. Finally, an unidentified component, C, was detected, whose mass spectrum had the following intense ions: $m/z = 207$ (M+), 150, and 94(100) and which comprised about 1% of the alkaloids present. When the *M. latinode* extracts were chromatographed using polar GC columns, this component eluted first, indicating that it is less polar than the other components. Since it is such a minor component, little could be done to further elucidate its structure. The mixture of venom alkaloids from *M. subopacum* was found to resemble that of *M. latinode*.[45]



Scheme 1.

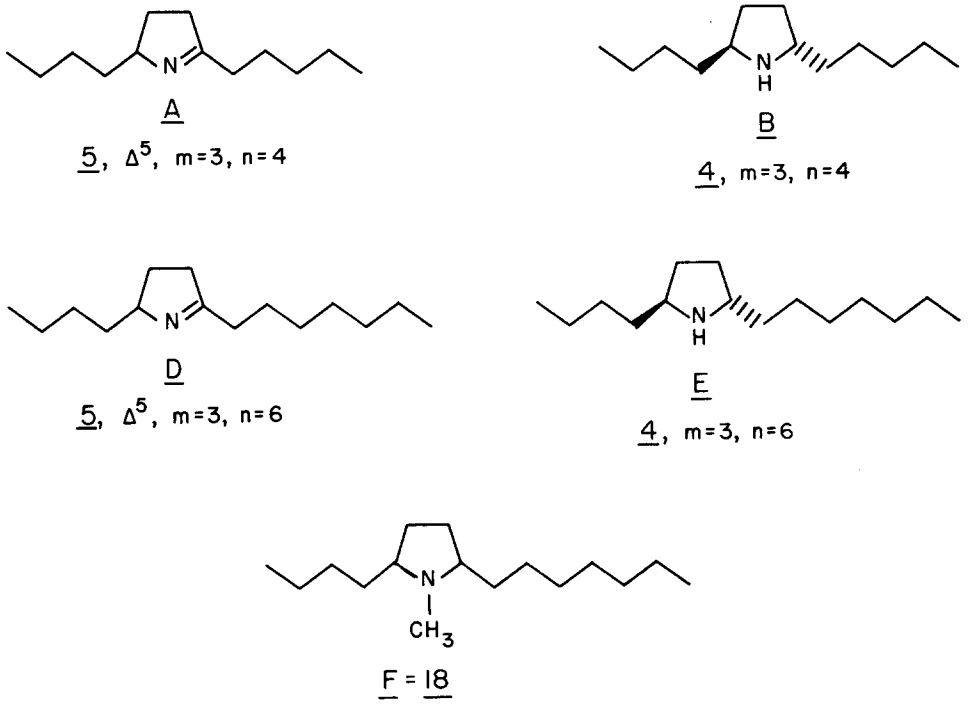


Fig. 6. *Monomorium latinode* alkaloids.

Although the N-methylpiperidines (**13**) from the *Solenopsis* (*Diplorhoptrum*) and the N-methylpyrrolidine **18** from *M. latinode* are new natural products, from a structural standpoint, the occurrence of 2-(4-hexen-1-yl)-1-piperideine **15** as an ant alkaloid is the most notable result of this investigation. This alkaloid differs from all previously reported *Monomorium* and *Solenopsis* alkaloids in having an even numbered carbon chain. In this respect as well as in having a 2-substituted-1-piperideine ring, **15** is quite reminiscent of the Hemlock alkaloids, especially γ-coniceine, the alkaloid present in largest quantities in growing *Conium maculatum*.[44] The well-known toxicity of the Hemlock alkaloids leaves little doubt as to the biological potency of the ant alkaloid **15**.

While alkaloidal venoms appear to be characteristic of myrmicine species in the genera *Monomorium* and *Solenopsis*, there are indications that species in each of these taxa produce idiosyncratic compounds. Unsymmetrical 2,6-dialkylpiperidines have only been detected as poison gland products of *Solenopsis* species, although the present investigation has considerably expanded their subgeneric distribution. These compounds, which had previously been identified in a wide range of *Solenopsis* (*Solenopsis*) species,[1-4] are also produced by a species in the subgenus *Euophthalma* (*S. littoralis*) and by several species in the subgenus *Diplorhoptrum* (*S. pergandei* and *S. carolinensis*). These *Diplorhoptrum* species are also distinctive in being the only members of the genus *Solenopsis* known to date to produce N-methylpiperidines as well.

In contrast to the members of the subgenus *Solenopsis*, those in the subgenus *Diplorhoptrum* are biosynthetically conservative in terms of both the amount and number of alkaloids that are produced in their poison glands. For example, whereas some species of *Solenopsis* (*Solenopsis*) synthesize relatively large amounts of the *cis* and *trans* isomers of five 2,6-dialkylpiperidines,[1,2,4] *Solenopsis* (*Diplorhoptrum*) species generally synthesize trace amounts of a single nitrogen heterocycle. Indeed with the exception of the N-methyl concomitants, **13**, of the 2,6-dialkylpiperidines identified in the *S.* (*Diplorhoptrum*) venoms studies in this investigation, a single alkaloid has characterized the poison gland products of each species in this subgenus studied to date.

On the other hand, *S.* (*Diplorhoptrum*) species may produce a greater variety of nitrogen heterocycles than *S.* (*Solenopsis*) species. With the exception of a piperideine identified in the venom of only one of more than thirty *S.* (*Solenopsis*) species analyzed,[2] unsymmetrical 2,6-dialkylpiperidines have been identified as characteristic natural products of every species in this subgenus that has been examined.[4] By contrast, analyses of considerably fewer species in the subgenus *Diplorhoptrum* have resulted in the identification of 2,5-dialkylpyrrolidines and 2,5-dialkylpiperidines and the unique piperideine **15** described in the present report. It will not prove surprising if additional classes of alkaloids are detected in the venoms of additional *S.* (*Diplorhoptrum*) species, most of which are found in tropical areas.

The venoms produced by North American species of *Monomorium* in the subgenus *Monomorium* contain a variety of alkaloids that constitute variations on a 2-hexyl-6-nonylpyrrolidine theme.[40] Similarly, we have shown that several Neotropical species in this subgenus also produce these unsymmetrical dialkylpyrrolidines. The invariant C_6, C_9-pyrrolidine theme that characterizes the venoms of these New World species of *Monomorium* (*Monomorium*) contrasts markedly those of three Old World species in this genus, *M. pharaonis*, *M. latinode* and *M. subopacum*. Although both *M. pharaonis* and *M. latinode* are members of the subgenus *Monomorium*, their venoms are distinguished by the presence of a variety of unsymmetrical 2,5-dialkylpyrrolidines. This is also the case for the venom of *M. subopacum*, the only species in the Old World subgenus *Xeromyrmex* that has been analyzed.

The venom of *M. pharaonis* is particularly distinctive in containing, in addition to four dialkylpyrrolidines, two indolizidines.[32] On the other hand, one of the characteristic compounds detected in the venoms of several North American *Monomorium* species, 2-(5-hexen-1-yl)-5-nonylpyrrolidine, **9**, n = 8,[40] is also a trace constituent in the venom of *M. pharaonis*.[32] 2-(5-Hexen-1-yl)-5-heptylpyrrolidine (**9**, n = 6), another distinctive trace constituent in the venom of *M. pharaonis*, is an equally minor alkaloid in the venom of *M. subopacum*. The venom of *M. latinode*, on the other hand, contains a variety of alkaloids, some of which are new insect natural products (e.g. N-methyl-2-butyl-5-heptylpyrrolidine, **18**), whereas others have been detected in *S.* (*Diplorhoptrum*) species or in *M. pharaonis*. 2-Butyl-5-pentylpyrrolidine (**4**, m = 3, n = 4) occurs in *M. pharaonis* as well as in *S. punctaticeps*, while the heptyl homologue (**4**, m = 4, n = 6) occurs in *S. punctaticeps* and in *S. fugax*. An array of 1-pyrrolines is also known in *S. punctaticeps*, although the *M. latinode* 1-pyrrolines have not been previously reported. In terms of qualitative diversity, the venoms of *M. latinode* and *M. subopacum* are more comparable to the venom of *S. punctaticeps* than those of any other species of *Monomorium*. These results serve to further emphasize the possibility that taxonomy notwithstanding, new alkaloidal natural products may be forthcoming when the venoms of additional species of these two myrmicine taxa are subjected to analytical scrutiny.

EXPERIMENTAL

IR spectra were obtained from neat liquid films with a Perkin–Elmer 297 spectrophotometer. NMR spectra were recorded using a Varian T-60 or a JEOL FX-60 spectrometer. Mass spectra were obtained by using a LKB 2091 GC/MS or a LKB 9000 GC/MS fitted with columns packed with 10% SP-1000 or 3% OV-1 on Supelcoport. Combustion analyses were performed by Atlantic Microlabs, Atlanta, Georgia.

Solenopsis littoralis. Methylene chloride extracts of *S. littoralis* contained only one volatile component by GC/MS analysis which had the following mass spectrum: *m/z* (rel. %) 281(1, M+), 268(2), 99(2), 98(100), 84(1), 53(2), 51(5), 43(5), 41(4), which was identical to that of 2-methyl-6-tridecylpiperidine (**1**, n = 12).[1]

Solenopsis pergandei. Methylene chloride extracts of *S. pergandei* contained two components by GC/MS analysis. The major component had the following mass spectrum: *m/z* (rel. %), 253(1, M+), 252(1), 238(8), 99(15), 98(100), 83(5), 81(2), 71(6), 70(7), 69(6), 57(10), 56(10), 55(15), 43(17), 41(15), which was identical to that of 2-methyl-6-undecylpiperidine (**1**, n = 10).[1] The natural material was the *trans* isomer by glc comparison (SP-1000) with an authentic sample. The second component had the following mass spectrum: *m/z* (rel. %) 267(1, M+), 266(1), 253(1), 252(2), 113(6), 112(100), 71(3), 70(5), 69(3), 57(5), 55(7), 43(4), 41(5). This spectrum was identical to that of 2,N-dimethyl-6-undecylpiperidine (**13**, n = 10), prepared by warming a small amount of **1**, n = 10, with formic acid and formaldehyde overnight.[40] Five samples of extracts of this species were examined, and the N-methylpiperidine was found to constitute between 10% and 35% of the total alkaloids present. Treatment of the natural

mixture with acetic anhydride left the mass spectrum and GC retention time of the N-methyl compound unchanged.

Solenopsis carolinensis. Methylene chloride extracts of *S. carolinensis* contained two components by GC/MS analysis. The major component had the following mass spectrum, *m/z* (rel. %) 225(0.5, M+), 224(2), 210(5), 99(10), 98(100), 71(1), 70(4), 69(2), 57(2), 55(5), 43(5), 41(5), which was identical to that of 2-methyl-6-nonylpiperidine (**1**, n = 8). The natural material was the *trans* isomer by glc comparison with an authentic sample. The second component had the following mass spectrum, *m/z* (rel. %), 239(0.5, M+), 238(1), 225(1), 224(2), 113(8), 112(100), 71(2), 70(1), 69(2), 57(3), 55(5), 43(3), and 41(2), which was directly analogous to the N-methylpiperidine from *S. pergandei*, and indicated **2**, N-dimethyl-6-nonylpiperidine (**13**, n = 8). Four samples of this species were analyzed, and the N-methyl compound was found to constitute 5% or less of the alkaloidal mixture from this species.

Solenopsis sp. B (Puerto Rico). Methylene chloride extracts from this unidentified *Solenopsis* species contained one volatile component by GC/MS analysis, whose mass spectrum was identical to that reported above for 2-methyl-6-nonylpiperidine (**1**, n = 8).

Solenopsis sp. A (Puerto Rico). Methylene chloride extracts of *Solenopsis* sp. A (Puerto Rico) showed a single peak eluting at 134° on an OV-17 column programmed at 10°/min. Isothermally it eluted at 9.8 min at 100° and had the mass spectrum shown in Fig. 3. The NMR spectrum (FX-60) showed the typical ABC pattern of the terminal protons of a terminal olefin with signals at δ 4.72, 4.92, and 5.01 (actually a pair of broad doublets δ = 4.96 (1H, br d, J = 18 Hz), and δ = 4.87 (1H, br d, J = 10 Hz)), identical in appearance to those of 4,6,8-trimethyl-1-nonene (Varian catalogue #1, 298). There was also a broad multiplet at δ = 3.42 (2H, $-CH_2N=C$).

A small sample of the crude extract was treated with $NaBH_4$, producing a single volatile compound, whose mass spectrum is shown in Fig. 4 (*m/z* = 153, M+). A second sample of the crude extract was taken up in MeOH and hydrogenated in the presence of PtO_2 to a major volatile product whose mass spectrum is shown in Fig. 5 (*m/z* = 155, M+). There also appeared to be a small amount of the N-methyl piperidine present when methanol was used as a solvent.

N-(5-*Hexenoyl*)-*piperidone* (**14**). A soln containing 5.6 g 2-piperidone (57 mmol) and 9 ml pyridine in 150 ml anhyd. benzene was cooled in an ice bath, and a soln containing 7.1 g 5-hexenoyl chloride[43] in 20 ml anhyd. benzene was added over 20 min. The mixture was stirred at room temp. overnight and worked up in the usual manner[16] to provide after distillation, 8.5 g (77% yield) of **14** as a colorless liquid; b.p. = 104–106° (0.4 mm Hg), IR 3070, 1690, 1640, 1475, 1455, 1370, 1340, 1327, 1290, 1190, 1170, 1155, 1070, 995, and 905 cm^{-1}, NMR δ = 5.6 (1H, d of d of t, J = 18, 10, and 6 Hz, CH_2=C<u>H</u>–), 4.96 (1H, br d, J = 18 Hz, *trans* $C\underline{H}_2$=CH–), 4.87 (1H, br d, J = 10 Hz, *cis* $C\underline{H}_2$=CH–), 3.66 (2H, br t, $-C\underline{H}_2-N(CO)_2$), 2.8 (2H, t, J = 7 Hz, $CH_2=CHCH_2CH_2C\underline{H}_2CO$), 2.46 (2H, br m, ring $C\underline{H}_2CO$), 2.1–1.6 (8H, m). Glc analysis showed this product to be about 90% pure.

2-(4-*Penten*-1-*yl*)-1-*piperideine* (**15**). An intimate mixture of 3.0 g of **14** and 3.0 g CaO was heated to reflux under N_2 for 4 hr. The mixture was cooled, diluted with either, filtered and purified by kugelrohr distillation to give 0.9 g (39% yield) of **15** as a colorless liquid, about 90% pure; small, very pure samples were obtained by preparative glc. IR, 3070, 2920, 2850, 1665, 1640, 983, and 905 cm^{-1}; NMR δ = 5.6 (1H, d of t, J = 18, 10, and 6 Hz), 4.96 (1H, br d, J = 18 Hz), 4.87 (1H, br d, J = 10 Hz), 3.46 (2H, br m, $C\underline{H}_2$–N=C), 2.05 (6H, m, $(C\underline{H}_2)_2C$=N and $C\underline{H}_2CH=CH_2$), 1.6 (6H, m, 3 × CH_2). The mass spectrum of **15** is shown in Fig. 3. (Found C, 79.28; H, 11.39; N, 9.23. Calc. for $C_{10}H_{17}N$, C, 79.41; H, 11.33; N, 9.26). The GC retention time of this product was identical to that of the natural **15** from *Solenopsis* sp. A.

2-(5-*Penten*-1-*yl*)-*piperidine* (**16**). A soln containing 100 mg of **15** in 5 ml MeOH was treated with excess $NaBH_4$ and stirred overnight. The mixture was carefully acidified with dil. HCl and the solvents were removed *in vacuo*. The residue was treated with 50% KOH and extracted with ether. The ethereal extracts were dried over anhyd. K_2CO_3, filtered, and the solvents removed to give a single volatile compound by glc analysis. IR 3280, 3070, 2920, 2840, 2785, 2720, 1640, 1325, 1115, 1050, 985, and 905 cm^{-1}. The mass spectrum of **16** is shown in Fig. 4. This product had an identical GC retention time with that of the borohydride reduction product from the natural **15**.

2-*n*-*Pentylpiperidine* (**17**). A slow stream of H_2 was passed through a soln containing 100 mg of **15** and 10 mg PtO_2 in 5 ml MeOH until the starting material had been converted to a single product by glc analysis. Filtration and removal of the solvent *in vacuo* provided a single volatile product. IR 3280, 2920, 2850, 2790, 2730, 1450, 1375, 1325, 1115, and 1050 cm^{-1}. The mass spectrum of **17** is shown in Fig. 5, and the product had an identical GC retention time with the hydrogenation product from natural **15**. Alternatively, a slow stream of H_2 was passed through a soln containing 50 mg 2-pentylpyridine and 5 mg PtO_2 in AcOH to give a single volatile product whose mass spectrum was identical to that shown in Fig. 5.

2-*n*-*Pentyl*-1-*piperideine* (**18**). A small portion of synthetic **15** was hydrogenated in the presence of PtO_2 using EtOAc as the solvent to give only the side-chain reduced product, **18**, MS, *m/z* (rel. %) 153 (2, M+), 152(17), 138(1), 124(9), 110(21), 97(100), 86(22), 82(7), 55(9), 41(12). Addition of AcOH to the mixture and further hydrogenation converted this product completely to the saturated amine **17**.

Monomorium latinode. GC/MS analysis of *M. latinode* extract using a 2 m × 2 mm column packed with 3% OV-1 revealed a mixture of six volatile compounds, A–F, lettered in their order of elution (Fig. 6).

(A) MS, *m/z* (rel. %) 195 (1, M+), 194(2), 172(2), 166(6), 152(18), 139(42), 138(15), 106(16), 82(100), 55(12), 43(11), 42(8), 41(23), indicative of 2-butyl-5-pentyl-5-pyrroline (**5**, Δ^5, m = 3, n = 4) comprising about 2% of the mixture.

(B) MS, *m/z* (rel. %), 197 (3, M+), 196(%), 140(88), and 126(100), and otherwise identical to that of an authentic sample of 2-butyl-4-pentylpyrrolidine (**4**, m = 4, n = 4)[25]; comprising about 7% of the mixture.

(C) An unidentified component having the following mass spectrum: *m/z* (rel. %) 207 (45, M+), 192(19), 179(12), 178(30), 165(33), 164(25), 151(30), 150(85), 136(23), 123(55), 122(27), 110(13), 109(30), 108(52), 94(100), 71(19), 68(22), 67(20), 55(40), 43(25), and 41(60), and comprising about 1% of the mixture.

(D) MS, *m/z* (rel. %) 223 (1, M+), 222(2), 208(2), 194(4), 180(6), 166(10), 152(30), 139(50), 126(12), 110(10), 96(12), 83(20), 82(100), 55(25), 43(10), 41(25), indicative of 2-butyl-5-heptyl-5-pyrroline (**5**, Δ^5, m = 3, n = 6) comprising about 2% of the mixture.

(E) MS, *m/z* (rel. %), 225 (1, M+), 224(3), 168(85), 126(100), and otherwise identical to that of an authentic sample of *trans*-2-butyl-5-heptylpyrrolidine (**4**, m = 3, n = 6)[25] and comprising about 87% of the mixture.

(F) MS, *m/z* (rel. %) 239 (1, M+), 208(1), 192(1), 184(1), 183(9), 182(71), 181(1), 166(1), 154(1), 150(1), 142(1), 141(9), 140(100), 138(1), 126(1), 110(1), 109(1), 98(1), 97(1), 96(3), 95(1), 94(1), 84(2), 83(4), 82(6), 81(1), 71(1), 70(3), 69(3), 68(1), 67(2), 58(3), 55(7), 44(2), 43(2), 42(5), and 41(5), and was otherwise identical to the mass spectrum obtained from an authentic sample of N-methyl-2-butyl-5-heptylpyrrolidine (**18**), prepared by treatment of a small sample of **4**, m = 3, n = 6, with formic acid and formaldehyde.[40]

The configuration of component E was found to be *trans* by direct comparison to an authentic sample of *cis* and *trans* **4** m = 3, n = 6, using a GC column packed with 10% SP-1000 on Supelcoport.

When the *M. latinode* sample was chromatographed with a 2 m × 2 mm column packed with 10% SP-1000, the order of elution remained unchanged except that the unknown component C was the first to elute.

Acknowledgements—The authors wish to thank Dr. W. F. Buren, Department of Entomology, University of Florida, Gainesville FL, for the identification of *S. carolinensis*, *S. littoralis*, and *S. pergandei*. Specimens of these ants are in his collection. We are

grateful to Dr. C. A. Collingwood for identifying *M. subopacum*. The authors would also like to thank Dr. T. Abe for providing *M. latinode* from Okinawa, and Dr. J. Torres for providing *Solenopsis* sp. A and *Solenopsis* sp. B. from Puerto Rico, and Mr. R. R. Snelling for the identification of *M. latinode*. Specimens of *M. latinode* and the two unidentified *Solenopsis* species are deposited in the collection of the Los Angeles County Museum of Natural History, Los Angeles CA. This work was supported in part by a grant from the University of Georgia Research Foundation.

REFERENCES

[1]J. G. MacConnell, M. S. Blum and H. M. Fales, *Tetrahedron* **27**, 1129 (1971).
[2]J. M. Brand, M. S. Blum, H. M. Fales and J. G. MacConnell, *Toxicon* **10**, 259 (1972).
[3]J. G. MacConnell, R. N. Williams, J. M. Brand and M. S. Blum, *Ann. Ent. Soc. Am.* **67**, 134 (1974).
[4]J. G. MacConnell, M. S. Blum, W. F. Buren, R. N. Williams and H. M. Fales, *Toxicon* **14**, 69 (1976).
[5]H. Baer, T.-Y. Liu, M. C. Anderson, M. Blum, W. H. Schmid and F. J. James, *Ibid.* **17**, 397 (1979).
[6]M. R. Caro, V. J. Derbes and R. Jung, *Arch. Derm.* **75**, 475 (1957).
[7]M. S. Blum, J. R. Walker, P. S. Callahan and A. F. Novak, *Science* **128**, 306 (1958).
[8]G. A. Androuny, V. J. Derbes and R. C. Jung, *Ibid.* **130**, 449 (1959).
[9]D. C. Buffkin and F. E. Russell, *Toxicon* **10**, 526 (1972).
[10]D. P. Jouvanez, M. S. Blum and J. G. MacConnell, *Antimicrob. Ag. Chemother.* **2**, 291 (1972).
[11]R. B. Koch, D. Desaiah, D. Foster and K. Ahmed, *Biochem. Pharmac.* **26**, 983 (1977).
[12]E. Y. Cheng, L. K. Cutkomp and R. B. Koch, *Ibid.* **26**, 1179 (1977).
[13]J. Z. Yeh, T. Narahashi and R. R. Almon, *J. Pharmac. Exp. Ther.* **194**, 373 (1975).
[14]G. W. Read, N. K. Lind and C. S. Oda, *Toxicon* **16**, 361 (1978).
[15]F. K. James, H. L. Pence, D. P. Driggers, R. L. Jacobs and D. E. Horton, *J. Allergy Clin. Immunol.* **58**, 110 (1976).
[16]R. K. Hill and T. Yuri, *Tetrahedron* **33**, 1569 (1977).
[17]T. Moriyama, D. Doan-Huynh, C. Monneret and Q. Khuong-Huu, *Tetrahedron Letters* 825 (1977).
[18]W. S. Creighton, *Bull. Mus. Comp. Zool.* **104**, 1 (1950).
[19]K. Holldobler, *Biol. Zbl.* **48**, 129 (1928).
[20]B. Holldobler, *Oecologica* **11**, 371 (1973).
[21]M. S. Blum, T. H. Jones, B. Holldobler, H. M. Fales and T. Jaouni, *Naturwissenschaften* **67**, 144 (1980).
[22]D. J. Pedder, H. M. Fales, T. Jaouni, M. Blum, J. MacConnell and R. M. Crewe, *Tetrahedron* **32**, 2275 (1976).
[23]F. J. Ritter and F. Stein, *U.S. Pat.* 4,075,320, 21 Feb. 1978.
[24]R. R. Fraser and S. Passannanti, *Synthesis* 540 (1976).
[25]T. H. Jones, M. S. Blum and H. M. Fales, *Tetrahedron Letters* 1031 (1979).
[26]T. H. Jones, J. B. Franko, M. S. Blum and H. M. Fales, *Ibid.* 789 (1980).
[27]T. L. MacDonald, *J. Org. Chem.* **45**, 193 (1980).
[28]H. M. Fales, W. Comstock and T. H. Jones, *Analytical Chem.* **52**, 980 (1980).
[29]T. H. Jones, M. S. Blum, H. M. Fales and C. R. Thompson, *J. Org. Chem.* **45**, 4778 (1980).
[30]F. J. Ritter, I. E. M. Rotgans, E. Talman, P. E. J. Verweil and F. Stein, *Experientia* **29**, 530 (1973).
[31]F. J. Ritter and C. J. Persoons, *Neth. J. Zool.* **25**, 261 (1975).
[32]F. J. Ritter, I. E. M. Bruggeman-Rotgans, E. Verkuil and C. J. Persoons, *Ch. Noisot* (Edited P. E. Howse, G. Le Masne), *Proc. Symp.* Pheromones and *Defensive Secretions* in *Social Insects*, pp. 99–103, Univ. Dijon (1975).
[33]R. J. Ritter, I. E. M. Bruggeman-Rotgans, P. E. J. Verweil, E. Talman, F. Stein, J. La Brijn and C. J. Persoons, *Proc. 8th Int. Cong. IUSSI*, 41–43. Pudoc Press, Wageningen (1977).
[34]F. J. Ritter, I. E. M. Bruggeman-Rotgans, P. E. J. Verweil, C. J. Persoons and E. Talman, *Tetrahedron Letters* 2617 (1977).
[35]F. J. Ritter, I. E. M. Bruggeman, P. E. J. Verweil, E. Talman, F. Stein and C. J. Persoons, *Proc. Conf. Regulation of Insect Development and Behavior*, Karpacz, Poland, June 23–28 (1980).
[36]P. E. Sonnet and J. E. Oliver, *J. Heterocyclic Chem.* **12**, 289 (1975).
[37]P. E. Sonnet, D. A. Netzel and R. Mendoza, *Ibid.* **16**, 1041 (1979).
[38]C. B. Urbani and P. B. Kannowski, *Envir. Ent.* **3**, 755 (1974).
[39]F. W. Howard and A. D. Oliver, *J. Georgia Ent. Soc.* **14**, 259 (1979).
[40]T. H. Jones, M. S. Blum, R. W. Howard, C. A. McDaniel, H. M. Fales, M. B. DuBois and J. Torres, *J. Chem. Ecol.* **8**, 285 (1982).
[41]R. Lukes, O. Cervinka, *Coll. Czech. Chem. Comm.* **24**, 1846 (1959).
[42]B. P. Mundy, K. B. Lipkowitz, M. Lee and B. R. Lansen, *J. Org. Chem.* **39**, 1963 (1974).
[43]M. F. Ansell and S. S. Brown, *J. Chem. Soc.* 1788 (1957); F. B. LaForge, N. Green and W. A. Gersdorff, *J. Am. Chem. Soc.* **70**, 3707 (1948).
[44]R. K. Hill, *Chemistry of the Alkaloids* (Edited S. W. Pelletier), p. 396. Van Nostrand, New York (1970).
[45]As this manuscript was being prepared, we had the opportunity to examine samples of *Monomorium subopacum* (Almería, Spain), a taxon for which no material had been previously available. The alkaloidal composition of the venom from this species was remarkably like that of *M. latinode*, major components being **4**, m = 3, n = 6 (90%), **4**, m = 3, n = 4 (3%), and the pyrrolines **5**, m = 3, n = 6 (1%). A fourth component (3%) had the following important ions in its mass spectrum: m/z = 251 (M+), 250, 168, and 152, indicative of **9**, n = 6.