Tetrahedron Vol. 38, No. 13, pp. 1939 to 1948, 1982
Printed in Great Britain.

0040-4020/82/131939-10$03.00/0
Pergamon Press Ltd.

ALKYLPYRAZINES FROM HYMENOPTERA

ISOLATION, IDENTIFICATION AND SYNTHESIS OF 5-METHYL-3-*n*-PROPYL-2-(1-BUTENYL)PYRAZINE FROM *APHAENOGASTER* ANTS (FORMICIDAE)

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(*Received in U.K. 24 December* 1981)

Abstract—Mandibular glands of *Aphaenogaster rudis* workers contain 5 - methyl - 3 - *n* - propyl - 2 - (1 - butenyl)pyrazine, a new natural product. This pyrazine and several of its isomers have been synthesized from the corresponding 2,3-, 2,5- or 2,6-dimethylpyrazines. Marked differences in the mass spectra of these multialkylated pyrazines are discussed. In addition, dimethylalkylpyrazines are reported from a variety of aculeate wasps.

Unlike most insects, Hymenoptera can be sources of diverse nitrogenous compounds. Table 1 summarizes previous work in this area. In the poison glands of ants, these include piperidines,[1-3] pyrrolidines,[4-7] an indolizine,[8,9] a methyl indole,[10] and a 3-substituted pyridine.[11] Ant mandibular glands and poison glands[12-17] and wasp mandibular glands[18-20] contain pyrazines. Although most of these are methylated at the 2 and 5 positions with further alkylation at the 3 position, some 2,6-dimethyl compounds are known. A dimethylpyrazine recently isolated from ants contains a terpenoid side chain,[16] and may correspond to one of two unidentified pyrazines in a wasp.[18]

The existence of these substituted dimethylpyrazines in natural product mixtures often is readily detected in the mass spectrometer. When the side chain of these pyrazines contains at least three carbons with a γ-hydrogen, a McLafferty rearrangement occurs giving a base peak at *m/z* 122. However, the existence of this *m/z* 122 ion establishes neither the length of the alkyl chain nor the substitution pattern (2,5 or 2,6). Retention times must be used to resolve these points when insufficient material is available to give meaningful mass spectra.

Here we report on pyrazines in the mandibular gland secretions of 13 genera including several families of wasps. Most of these data are from species that have not yet been studied. We also reinvestigated one species examined by Hefetz and Batra,[17] *Eumenes fraternus*, and report a different chemistry. We also demonstrate here that the mandibular gland of the ant *Aphaenogaster rudis* contains a uniquely multi-alkylated pyrazine. Establishing the identity of this compound has led to the synthesis of many pyrazines, the details of which are the major thrust of this paper.

Wasps, collected near Quantico, Virginia, Everglades National Park, Florida, and Frederick, Maryland, emitted a detectable chocolate-like odor when lightly held between the fingers. Methylene chloride extracts of heads or dissected mandibular glands were analyzed by combined gas chromatographic/mass spectroscopic (GC/MS) analysis and/or gas chromatography, and were shown to contain the substituted dimethylpyrazines listed in Table 2. In contrast to some earlier studies,[17,18] the retention time of synthetic standards was established to differentiate between the 2,5- and 2,6-isomers. A reexamination of *Eumenes fraternus*, previously analyzed by Hefetz and Batra, shows that the so-called 2,5 - dimethyl - 3 - (butylbutyl)pyrazine is actually 2,5 - dimethyl - 3 - isopentylpyrazine along with a small amount of the 2,6-isomer (Table 2). Hefetz and Batra[17] have reported the only 2,3-dimethyl substituted pyrazines in either ants or wasps. It should also be noted that in several cases 6 - methyl - 5 - hepten - 2 - one has been found accompanying the pyrazines. Neither its function not that of the pyrazines has been clearly defined.

Aphaenogaster rudis colonies were collected from mountainous regions near Athens, Georgia and Frederick, Maryland by lifting rocks and mouth aspirating the individuals. Fifty to five hundred ants were collected from each colony. Our original purpose was to establish the presence of methyl anthranilate in their mandibular gland secretions which would account for the prevalent grape-like odor.[21] Mouth aspiration, however, also indicated the presence of a material very irritating to the mouth and throat mucosa. Analysis of total ant extracts indicated another component in addition to the methyl anthranilate and the alkanes and alkenes characteristic of ant Dufour's glands.[22] This component eluted immediately after pentadecane and exhibited *m/z* 190 (M^+), 175 (M-15), 161 (M-29), 147 (M-43), and 133 (M-57) (base peak) with few smaller fragment ions. The extract also contained a small amount (10%) of an isomeric compound, eluting slightly earlier, which showed a base peak at *m/z* 147. In spite of mass collecting live material, extraction, and purification by either column or thin layer chromatography, enough of this unknown was never available for a satisfactory proton NMR spectrum. Both

Table 1. Nitrogenous compounds from ant and wasp poison and mandibular glands

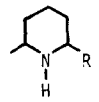
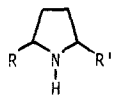
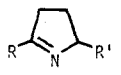
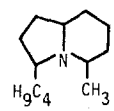
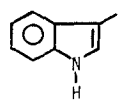
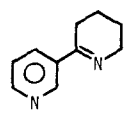
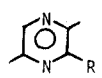
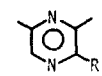
COMPOUND	STRUCTURE		SOURCE	ANT/ WASP	REF
c/t-2-Methyl-6-undecylpiperidine		R=C_{11}	Solenopsis saevissima	A	2,3
			S. xyloni	A	3
c/t-2-Methyl-6-tridecylpiperidine		R=C_{13}	S. saevissima	A	3
c/t-2-Methyl-6-pentadecylpiperidine		R=C_{15}	S. saevissima	A	3
2-Butyl-5-heptylpyrrolidine		R=C_7, R'=C_4	S. punctaticeps	A	4
			S. fugax	A	6
2-Ethyl-5-heptylpyrrolidine		R=C_2, R'=C_7	S. punctaticeps	A	4
2-Butyl-5-pentylpyrrolidine		R=C_5, R'=C_4	S. punctaticeps	A	4
5-Ethyl-2-heptyl-1-pyrroline		R=C_7, R'=C_2	S. punctaticeps	A	4
2-Ethyl-5-heptyl-1-pyrroline		R=C_2, R'=C_7	S. punctaticeps	A	4
2-Ethyl-5-pentyl-1-pyrroline		R=C_2, R'=C_5	S. punctaticeps	A	4
5-Ethyl-2-pentyl-1-pyrroline		R=C_5, R'=C_2	S. punctaticeps	A	4
5-Methyl-3-butyloctahydroindolizine			Monomorium pharaonis	A	8
Skatole			Pheidole fallax	A	10
Anabaseine			Aphaenogaster fulva	A	11
2,5-Dimethyl-3-ethylpyrazine		R=Et	Atta sexdens	A	15
2,5-Dimethyl-3-n-propylpyrazine		R=Pr	Iridomyrmex humilis	A	13
			Philanthus triangulum	W	18
2,5-Dimethyl-3-isobutylpyrazine		R=i-Bu	Stenodynerus fulvipes	W	17
2,5-Dimethyl-3-isopentylpyrazine		R=i-pentyl	Odontomachus hastatus	A	12
			O. clarus	A	12
			O. troglodytes	A	14
			Ponera pennsylvanica	A	20
			Hypoponera opacior	A	20
			Iridomyrmex humilis	A	13
			Ammophila fernaldi	W	19
			A. procera	W	19
			A. nigricans	W	19
			Rhytidoponera metallica	A	16
			Philanthus triangulum	W	18
			Argogorytes fargei	W	18
			A. mystaceus	W	18
			Nysson spinosus	W	18
			Stenodynerus fulvipes	W	18
			Pseudodynerus quadrisectus	W	18
2,5-Dimethyl-3-styrylpyrazine		R=styryl	Iridomyrmex humilis	A	13
2,5-Dimethyl-3-citronellylpyrazine		R=citronellyl	Rhytidoponera metallica	A	16
2,6-Dimethyl-3-ethylpyrazine		R=Et	Odontomachus brunneus	A	12

TABLE 1 (Cont.)

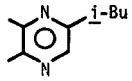
COMPOUND	STRUCTURE	SOURCE	ANT/ WASP	REF
2,6-Dimethyl-3-n-propylpyrazine	R=n-Pr	O. brunneus	A	12
		Ammophila urnaria	W	19
2,6-Dimethyl-3-n-butylpyrazine	R=n-Bu	Odontomachus brunneus	A	12
		Ammophila urnaria	W	12
2,6-Dimethyl-3-n-pentylpyrazine	R=n-pentyl	Odontomachus brunneus	A	12
2,3-Dimethyl-5-iso-butylpyrazine		Stenodynerus fulvipes	W	17
		Ancistrocerus antilope	W	17

Table 2. Alkylpyrazines from Eumenae, Tiphiidae, Sphecidae, Larridae, Nyssonidae and Philantidae wasps

FAMILY SPECIES (Male/Female)	COMPOUNDS (major is underlined)
	 R = n-Propyl (A) = n-Butyl (B) = isopentyl (C)
	 R = n-Propyl (D) = n-Butyl (E) = isopentyl (F) = n-Pentyl (G)
	6-Methyl-5-hepten-2-one (H)
	3-Octanone (I)
Tiphiidae	
Tiphia sp. (M & F)	C
Eumeninae	
Leptochilus acolhuus (F)	C, B
Stenodynerus floridanus	A, D
Parancistrocerus fulvipes (F)	A, C, E, F, H
P. rufovestis (M)	C, E
P. perennis (F)	C, E
P. sp. A (M)	C, E
P. sp. B (F)	C, E
Euodynerus fuscus	C, E
Monobia quadridens	G
Pachodynerus erynnis (F)	A, D, H
P. erynnis (M)	A, D, H
Ancistrocerus campestris (F)	C, E
A. campestris (M)	C, E
Eumenes fraternus	C, F
Sphecidae	
Eremnophila aureonotata	C, B
Larridae	
Tachytes guatemalensis	B, C
Nyssonidae	
Bicyrtes ventralis	B, C
Philanthidae	
Cerceris sp.	I

isomers were unstable when chromatographed and much more volatile than anticipated from their molecular weight. The unknown compound's pungent, burnt chocolate-like odor, a high resolution mass measurement indicating a molecular formula of $C_{12}H_{18}N_2$, and a weak absorption in the proton NMR spectrum of δ 8.1 led us to believe that these were pyrazines. Both compounds appeared unable to undergo a McLafferty rearrangement. Our experience with pyrazines[12,20] and the relatively simple fragmentation pattern of the unknowns suggested that they might be alkenyl substituted pyrazines with a simple allylic cleavage to form a base peak at *m/z* 133. The absence of alkenyl substituted pyrazines in the literature added to our naive view of the situation. A series of 2,3–, 2,5–, and 2,6-disubstituted pyrazines were synthesized as possible candidates for the unknown of mass 190 (Table 3) by the method in Scheme 1. When esters were used the ketonic products reduced with sodium borohydride, better yields and fewer side products were obtained than directly from the aldehydes.

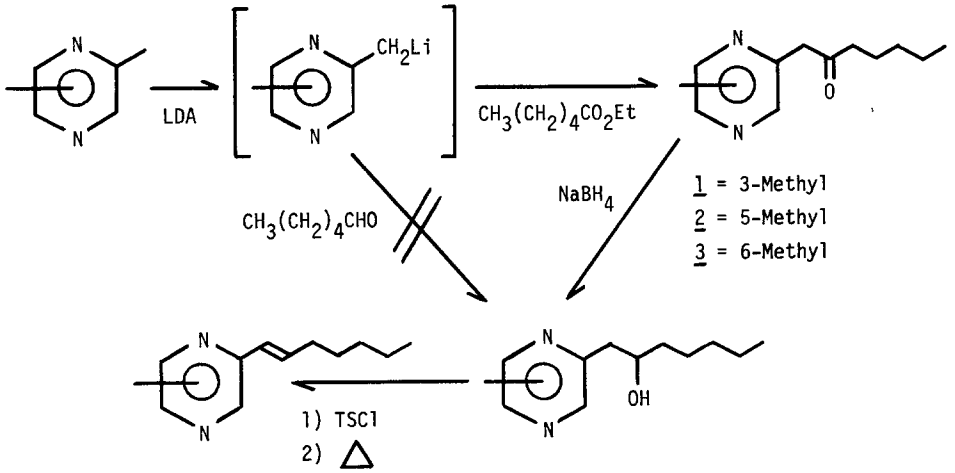
Table 3. Synthetic alkylpyrazines and their mass spectra

COMPOUND	MASS SPECTRUM m/z(%)
1-(3-Methyl-2-pyrazyl)-1-heptene (7)	190(22), 175(10), 161(15), 148(18), 147(100), 146(5), 145(5), 134(15), 133(62), 132(32), 131 (15), 121(15), 120(15), 119(45), 108(35), 67 (18), 66(18), 65(28), 42(25), 41(38)
1-(5-Methyl-2-pyrazyl)-1-heptene (8)	190(30), 175(5), 161(15), 148(20), 147(100), 145(8), 133(80), 132(25), 121(18), 120(35), 119 (8), 118(10), 108(35), 96(18), 65(20), 41(28)
1-(6-Methyl-2-pyrazyl)-1-heptene (9)	190(18), 175(18), 161(18), 148(15), 147(100), 145(10), 136(5), 133(35), 132(30), 131(5), 121 (5), 118(3), 108(20), 66(12), 65(10), 41(20)
cis-1-(2-Pyrazyl)-1-octene (10)	190(3), 189(6), 175(3), 161(3), 148(5), 147(15), 145(5), 134(15), 133(45), 132(8), 131(10), 120 (45), 119(100), 118(20), 107(5), 106(5), 94(15), 42(12), 41(11), 40(70)
trans-1-(2-Pyrazyl)-1-octene (11)	190(22), 175(5), 161(8), 147(18), 134(20), 133 (100), 132(8), 131(10), 120(25), 119(78), 118 (35), 117(5), 108(10), 107(40), 106(40), 105 (20), 94(25), 93(20), 79(15), 78(15), 65(25), 42(60), 41(20)
cis-5-Methyl-3-n-propyl-2(1-butenyl)pyrazine (12)	191(14), 190(80), 189(11), 175(54), 162(11), 161(79), 147(100), 146(22), 145(25), 133(40), 121(7), 119(7), 91(7), 73(11), 57(11), 55(11), 43(7), 42(22), 41(11)
trans-5-Methyl-3-n-propyl-2(1-butenyl)pyrazine (12)	191(6), 190(39), 189(5), 175(27), 162(23), 161 (65), 147(26), 146(12), 145(12), 133(100), 118 (3), 91(5), 77(6), 73(6), 65(5), 54(5), 43(3), 42(3), 41(9)
cis-3-Methyl-5-n-propyl-2(1-butenyl)pyrazine (13)	191(12), 190(100), 189(19), 175(81), 162(37), 161(81), 147(25), 146(12), 108(44)
trans-3-Methyl-5-n-propyl-2(1-butenyl)pyrazine (13)	191(3), 190(25), 189(12), 175(36), 162(100), 161(43), 147(29), 146(7), 133(7), 121(7), 120 (7), 42(7), 41(10)
cis-3-Methyl-2-n-propyl-6(1-butenyl)pyrazine (14)	191(3), 190(19), 189(6), 175(22), 162(100), 147(19), 146(6), 145(3), 133(6), 120(3), 79 (6), 77(6), 65(6), 53(6), 41(6)
trans-3-Methyl-2-n-propyl-6(1-butenyl)pyrazine (14)	191(4), 190(19), 189(8), 175(23), 162(100), 147(25), 146(8), 145(6), 133(6), 79(11), 77 (8), 65(6), 53(6), 42(2)

The temperature of the alkylation reaction was crucial, higher temperatures leading to mixtures of isomeric pyrazines. The specifics of this are being investigated.

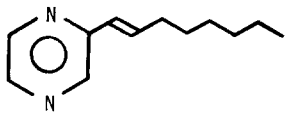
that the unknowns of mass 190 originated from these exocrine glands.

Chromatography of the crude extract on alumina with



Scheme 1.

Even though the general appearance of the synthetic *trans* pyrazines' mass spectra (**7**, **8**, **9**) was similar to that of the unknown of mass 190 none was identical. In fact, all (Table 3) exhibited a base peak at *m/z* 147 rather than the expected 133, indicating the rearrangement takes place before the cleavage. Using the same procedures, *cis*-**10** and *trans*-**11** were synthesized from methylpyrazine. The *trans* compound exhibited a base peak at *m/z* 133, but its spectrum did not match that of the natural product. Surprisingly, the *cis* isomer had its base peak at *m/z* 119.

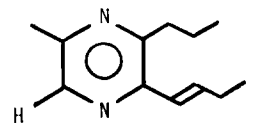


10 = cis

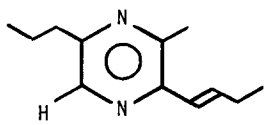
11 = trans

Although the general appearance of the mass spectra, the molecular formula, and the odor were consistent with the unknowns of mass 190 being pyrazines, it was evident that they had unique alkyl substitution.

Arduous effort during the spring, summer, and fall of 1980 produced 40,000 additional ants from the collecting site near Frederick, Maryland. These were two color morphs of *A. rudis*, but the extracts of both contained anabaseine in their poison glands[11] as well as methyl anthranilate and the unknowns of mass 190 in their head extracts. Gas chromatography of methylene chloride extracts of excised worker mandibular glands established pentane–ether mixtures (10–20% ether) gave the unknown of mass 190 contaminated with C_{16} and C_{18} acids as well as compounds of much higher molecular weight. Preparative gas chromatography of this gave material which exhibited the following proton NMR spectrum at 200 MHz; δ 8.2 (1H, s), 6.90 (1H, doublet of triplets, J = 16, 7 Hz), 6.6 (1H, d, J = 16 Hz), 2.8 (2H, t), 2.5 (3H, s), 2.3 (2H, m), 1.2 (3H, t), 1.0 (3H, t) with additional absorption between 1.3 and 1.9. Decoupling established that the multiplet at δ 2.3 is coupled to the absorption at 6.9 and that this in turn is coupled to the absorption at 6.6. The methylene group at 2.3 is also coupled to the Me group at 1.2. If one side chain on the aromatic ring is $-CH{=}CHCH_2CH_3$ and the proton at 8.2 represents a heteroaromatic proton, then the other subsitutents must be $-CH_3$ and $-CH_2CH_2CH_3$ with the CH_2 of the propyl group buried in the 1.3–1.9 absorption. Arrangement of these substituents on a pyrazine ring predicts that the unknown of mass 190 should correspond to one of structures **12–17** (ignoring *cis*/*trans* isomerism).



12



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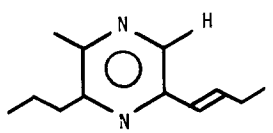
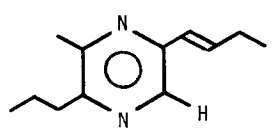


14



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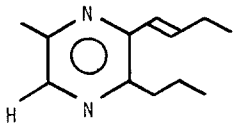

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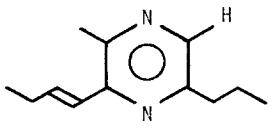
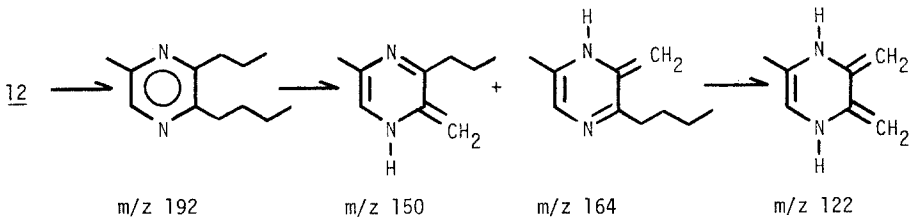


17

In order to differentiate among these six isomers and to resolve the apparent incompatibility of these proton NMR data with the mass spectral data mentioned previously (i.e. loss of a Bu side chain, M-57), the unknown was reduced catalytically (Pt and H_2) giving a mixture of two compounds with molecular weights of 192 and 198, respectively. The compound exhibiting *m/z* 192 (reduction of the butenyl group to a Bu group) showed the normal McLafferty rearrangements: *m/z* 164 (loss of ethylene), 150 (loss of propylene), and a double McLafferty loss to 122. The compound exhibiting *m/z* 198 exhibited two major fragments at *m/z* 100 and 98 in accord with reported fragmentation of piperazines.[23] This crucial data allows elimination of structures **14–17** and limits consideration to either structure **12** or **13** according to Scheme 3.

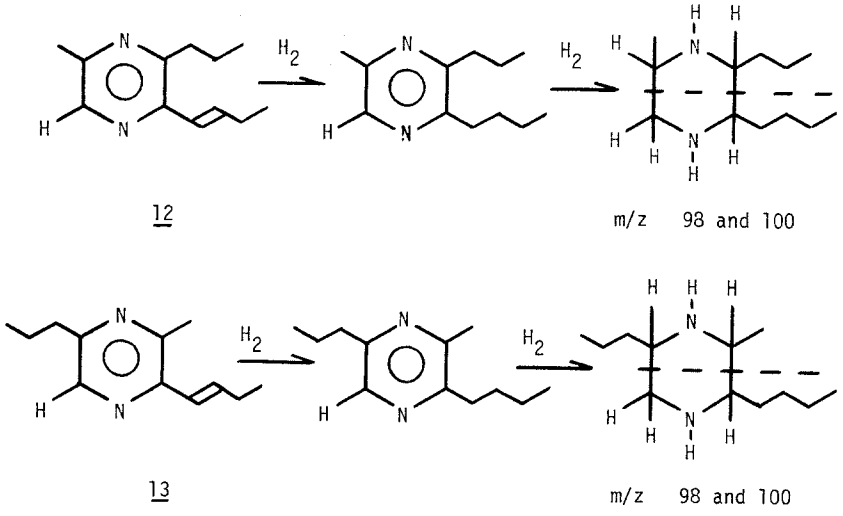
Any other arrangements of alkyl groups on the ring would lead to cleavages different from the observed *m/z* 98 and 100[23] (e.g. *m/z* 112, 114, 84, and 86 for **16** or **17**).

In order to determine which of these two isomers corresponded to the natural product, a mixture of **12** and **13** was synthesized according to Scheme 4 from 2,6-dimethylpyrazine (**18**). Analysis of this mixture by combined GC/MS gave surprising results. Not only did the four isomers (two *cis/trans* pairs) separate well from each other, but they exhibited completely different mass spectra. The first 190 isomer to elute from the GC column exhibited a base peak at *m/z* 147 and its mass spectrum was identical to that of the minor isomer of the natural product. The third 190 isomer to elute exhibited a base peak at *m/z* 133 and a mass spectrum which was identical in all respects with that of the major isomer of the natural product. This included two prominent metastable peaks at 136.4 (representing the loss of 29 mass units from the molecular ion *m/z* 190→161) and 109.9 (representing the loss of 28 mass units from the ion at *m/z* 161→133). The 190 isomer eluting fourth showed a base peak at *m/z* 162 (loss of 28) with practically no ion at *m/z* 133 while the remaining isomer (eluting second) had its base peak at 190 with large ions at 175 and 161. The first and third isomers were present in a ratio of 1:10 relative to the second and fourth isomers. In order to determine which set of these were the *cis/trans* isomers of **12** and which were the *cis/trans* isomers of **13**, **12** was synthesized by an alternate route giving a different contaminating isomer **14** by Scheme 5.

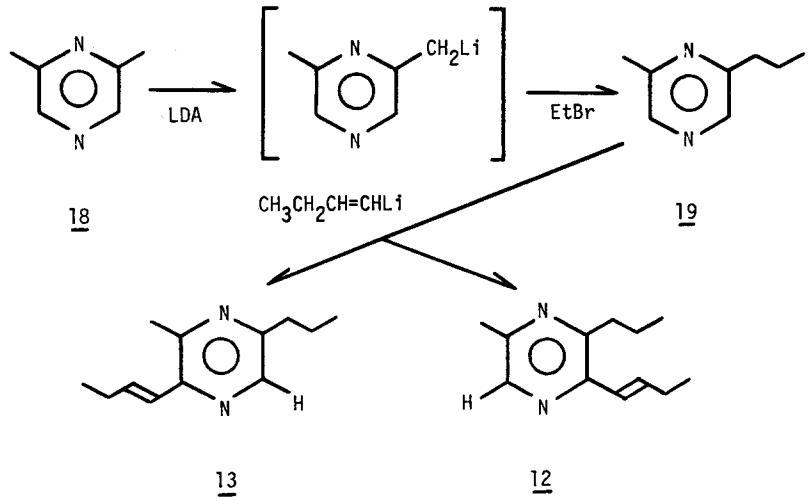


Scheme 2.

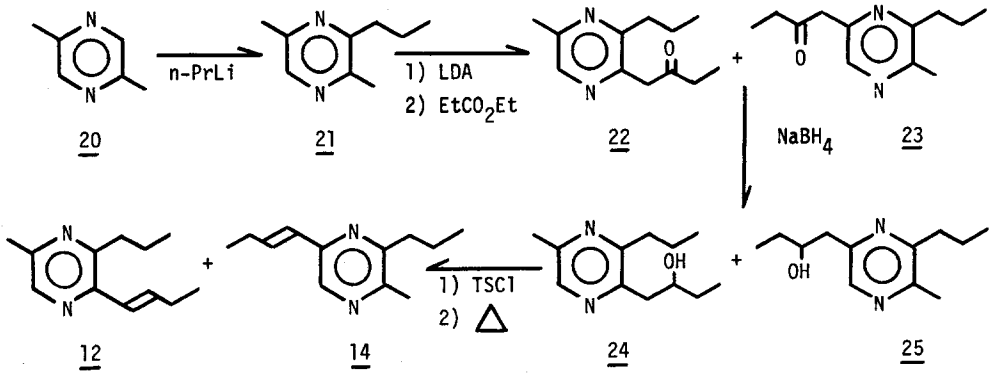
Unlike the previous two sets of *cis* and *trans* isomers which overlapped, the first two peaks eluting from the column were *cis* and *trans* isomers and corresponded exactly to the natural product with identical retention times and mass spectra. The second set eluting from the column exhibited a base peak at *m/z* 162 in accord with a normal McLafferty rearrangement including a metastable



Scheme 3.



Scheme 4.

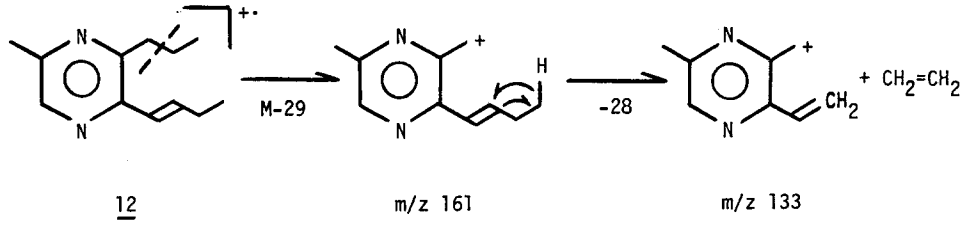


Scheme 5.

ion at 138.1 corresponding to this loss (190→162). In both syntheses of **12** an internal standard was available for gas chromatography. This was 2,6 - di - t - butyl - *p* - cresol (*m/z* 220) (an antioxidant added to commercial ether) which eluted on the tail of *trans*-**12**. Catalytic reduction of the separate pyrazines gave the piperazines which exhibited major peaks for the first two isomers at *m/z* 98 and 100 while the second two showed peaks at *m/z* 142, 140, 58, and 56 corresponding to reduction of **14** to its piperazine. A small amount of another isomer indicated that acylation had occurred to a slight extent on the propyl group of **21**.

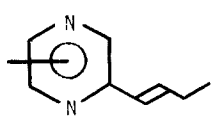
The metastable ions observed or **12** at 136.4 and 109.9 indicate that the apparent loss of a Bu group (M-57) is actually loss of Et followed by loss of ethylene (Scheme 6) and demonstrate the potential importance of metastable ions in assigning the structures of unknowns.

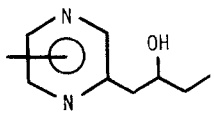
The presence of the same relative concentration of *cis*-**12** in all samples of natural extracts examined appears to indicate that it is real and not an artifact of the workup or chromatographic procedures. Tests of **12** and its isomers with live colonies of *Aphaenogaster rudis* are in progress and the results of the behavioral tests will be reported elsewhere.



Scheme 6.

Attempts to alkylate either **26** or **27** with propyl lithium gave a mixture of products, the molecular weights of which suggested that conjugate addition to the double bond was preceding alkylation of the ring. Similar attempts to alkylate their alcohol precursors **28** and **29** were unsuccessful.





26 = 3-Methyl

27 = 5-Methyl

28 = 3-Methyl

29 = 5-Methyl

The presence of the butenyl group adjacent to the propyl group in the natural product **12** hinders the McLafferty rearrangement of the latter group. This is strikingly evident because the synthesized isomeric products (*cis* and *trans* **14**, *trans* **13**) and dihydro **12**, *all* exhibit a normal rarrangement. Alkenes **26** and **27**, on the other hand, show simple allylic cleavage of the butenyl group. Although the 2,5- and 2,6-dimethyl - 3 - alkylpyrazines exhibit almost identical mass spectra, the introduction of an alkenyl group as a side chain gives spectra which differ significantly even between *cis* and *trans* isomers. This gross difference in the mass spectra of isomeric pyrazines was totally unexpected. However, it could be extremely useful in assigning structures to future pyrazine natural products. The relative intensities of the fragment ions (and molecular ion) varied somewhat in spectra taken on the three mass spectrometers used, *but* the overall losses (presence or absence of a McLafferty rearrangement) remained constant. This concept will be tested by the synthesis of additional unsaturated pyrazines.

EXPERIMENTAL

All m.p.s were taken on a Thomas–Hoover m.p. apparatus and are uncorrected. Proton NMR spectra were taken either on a Hitachi–Perkin Elmer R600 or a Nicolet NT200 supercon instrument in $CDCl_3$ with TMS as an internal standard in 5 mm tubes. Preparative gas chromatography was achieved on a Glowall 320 instrument equipped with an argon detector and a 2 m × 2 mm column of 3% OV-17 on Supelcoport 60/80. Analytical gas chromatography used the same instrument with a flame ionization detector. Mass spectra were obtained on three instruments: (1) a Finnigan 3200E automated gas chromatograph/mass spectrometer; (2) an LKB 9000 GC/MS; and (3) an LKB 2015 GC/MS. The latter two instruments were used to obtain metastable ions ad 3% OV-17 columns were used in all three mass spectrometers. A 10% SP-1000 column was used to establish the presence (or absence) of isomeric pyrazines in the early synthetic sequence.

General procedure for pyrazines. Alkylpyrazines were commercially available or prepared by the method of Klein and Spoerri[24] or the procedure of Bromwell *et al.*[25] **19** MS: 136 (M^+) (18), 135 (10), 121 (20), 108 (100), 94 (5), 81 (2), 67 (5), 66 (15), 53 (5), 42 (18), 41 (15). **21** MS: 150 (M^+) (6), 149 (6), 135 (20), 122 (100), 108 (3), 107 (6), 80 (3), 53 (10), 42 (22), 41 (6). Alkylation at higher temperatures than −78° gave mixtures.

General procedure for the preparation of pyrazyl ketones. The alkylpyrazine (0.11 mole) in anhyd ether was added to a soln of lithium diisopropylamide prepared from diisopropylamine (17 ml, 12.3 g, 0.12 mole) and n-BuLi (75 ml of 1.6 M soln in hexane, 0.12 mole) at 0° and subsequently cooled to −76°. A reddish ppt formed as soon as the pyrazine was added. After addition of pyrazine, the mixture was stirred for an additional ½ hr, and the appropriate ethyl ester (0.12 mole) in ether was added slowly. The mixture was stirred for an additional ½ hr, the cooling bath removed, and the reaction quenched with water. The ether soln was dried (Na_2SO_4), the ether removed on a rotary evaporator, and the residue purified by bulb to bulb distillation.

1(3 - *Methyl* - 2 - *pyrazyl*)*heptan* - 2 - *one* (**1**). 2,3-Dimethylpyrazine (5.0 g, 0.046 mole), LDA (0.048 mole) and ethyl hexanoate (6.6 g, 0.046 mole) gave 6.6 g (70%) of the title compound. MS: 206 (M^+), 191, 188, 163, 150, 135, 108 (100), 107, 80, 71, 55, 43, 41. NMR: 0.95 (3H, t), 1.2–1.8 (6H, m), 2.5 (3H, s), 2.6 (2H, t), 4.0 (2H, s), 8.35 (1H, d), 8.33 (1H, d, J = 2.7 Hz). (Found: 206.1406. $C_{12}H_{18}N_2O$ requires 206.1419).

1(5 - *Methyl* - 2 - *pyrazyl*)*heptan* - 2 - *one* (**2**). 2,5-Dimethylpyrazine (5.0 g, 0.046 mole), LDA (0.048 mole) and ethyl hexanoate (6.6 g, 0.046 mole) gave 5.7 g (60%) of the title compound. MS: 206 (M^+), 191, 188, 163, 150, 135, 109, 108 (100), 107, 99, 80, 71, 66, 55, 43, 41. NMR: 0.95 (3H, t), 1.2–1.6 (6H, m), 2.5 (3H, s), 2.55 (2H, t), 3.91 (2H, s), 8.34 (1H, s), 8.40 (1H, s). (Found: 206.1406).

1(6 - *Methyl* - 2 - *pyrazyl*)*heptan* - 2 - *one* (**3**). 2,6-Dimethylpyrazine (5.0 g, 0.046 mole), LDA (0.048 mole) and ethyl hexanoate (6.6 g, 0.046 mole) gave 5.7 g (60%) of the title compound. MS: 206 (M^+), 191, 188, 177, 163, 150, 135, 121, 108 (100), 107, 99, 80, 71, 66, 55, 43, 42, 41, 40. NMR: 0.95 (3H, t), 1.2–1.6 (6H, m), 2.6 (3H, s), 2.65 (2H, t), 3.91 (2H, s), 8.31 (1H, s), 8.34 (1H, s). (Found: 206.1410).

1(2-*Pyrazyl*)*octan*-2-*one.* 2-Methylpyrazine (10.3 g, 0.11 mole), LDA (0.11 mole) and ethyl heptanoate (12.3 g, 0.12 mole) gave 15 g (70%) of the title compound, m.p. 141.5–142.5. MS: 206 (M^+), 149, 136, 121, 113, 94, 85, 57, 43 (100), 41. NMR: 0.95 (3H, t), 1.2–1.6 (8H, m), 2.6 (2H, t), 4.0 (2H, s), 8.36 (2H, s), 8.25 (1H, s). (Found: 206.1415).

1(3-*Methyl*-2-*pyrazyl*)*butan*-2-*one.* MS: 164 (M^+), 149, 135, 109, 108 (100), 107, 93, 80, 67, 57, 53, 42, 41, 40. NMR: 1.05 (3H, t), 2.5 (3H, s), 2.55 (2H, q), 4.0 (2H, s), 8.32 (1H, d), 8.36 (1H, d, J = 2.7 Hz). (Found: 164.0948. $C_9H_{12}N_2O$ requires 164.0948).

1(5-*Methyl*-2-*pyrazyl*)*butan*-2-*one.* MS: 164 (M^+), 149, 135, 109, 108 (100), 107, 93, 82, 80, 67, 57, 53, 42, 41, 40. NMR: 1.0 (3H, t), 2.5 (3H, s), 2.55 (2H, q), 4.0 (2H, s), 8.32 (1H, s), 8.36 (1H, s). (Found: 206.1410).

1(5-*Methyl*-3-*n*-*propyl*-2-*pyrazyl*)*butan*-2-*one* (**22** and **23**). MS: 206 (M^+), 191, 178, 177, 163, 151, 150, 135, 122 (100), 109, 108, 82, 57, 42, 41, 40. NMR: 1.0 (3H, t), 1.1 (3H, t), 1.7 (2H, m), 2.5 (3H, s), 2.3–2.7 (4H, m), 4.0 (2H, s), 8.3 (1H, s). (Found: 206.1405. $C_{12}H_{18}N_2O$ requires 206.1419).

General procedure for the preparation of pyrazyl alcohols. The ketone (0.024 mole) in EtOH (10 ml) at 0° was treated with $NaBH_4$ (0.01 mole), the ice bath removed and the soln stirred for 4 hr. Extraction with ether was followed by washing with sat K_2CO_3 aq and drying over Na_2SO_4. Removal of the ether on a rotary evaporator gave the alcohol in essentially quantitative yield.

1(3-*Methyl*-2-*pyrazyl*)*heptan*-2-*ol* (**4**). MS: 208 (M^+), 190, 175, 161, 147, 137, 133, 121, 108 (100), 107, 80, 66, 55, 42, 41. NMR: 0.95 (3H, t), 1.2–1.6 (8H, m), 2.6 (3H, s), 2.9 (2H, m), 4.1 (1H, m), 4.6 (1H, s), 8.24 (1H, d), 8.26 (1H, d, J = 3 Hz). (Found: 208.1570. $C_{12}H_{20}N_2O$ requires 208.1576).

1(5-*Methyl*-2-*pyrazyl*)*heptan*-2-*ol* (**5**). MS: 208 (M^+), 190, 175, 161, 147, 137, 134, 133, 121, 109, 108 (100), 107, 95, 80, 66, 55, 43, 42, 41. NMR: 0.95 (3H, t), 1.2–1.6 (8H, m), 2.5 (3H, s), 2.9 (2H, m), 4.1 (1H, m), 4.7 (1H, s), 8.35 (1H, s), 8.40 (1H, s). (Found: 208.1570).

1(6-*Methyl*-2-*pyrazyl*)*heptan*-2-*ol* (**6**). MS: 208 (M^+), 207, 190, 175, 161, 151, 147, 137, 133, 121, 109, 108 (100), 107, 95, 83, 82, 81, 80, 66, 55, 43, 42, 41, 40. NMR: 0.95 (3H, t), 1.2–1.6 (8H, m), 2.5 (3H, s), 2.9 (2H, m), 4.1 (1H, m), 4.5 (1H, s), 8.30 (1H, s), 8.35 (1H, s). (Found: 208.1570).

1(2-*Pyrazyl*)*octan*-2-*ol.* MS: 208(M^+), 190, 161, 147, 133, 123, 94 (100), 93, 81, 55, 43, 41. NMR: 0.95 (3H, t), 1.2–1.6 (10H, m), 2.9 (2H, m), 4.1 (1H, m), 4.8 (1H, s), 8.25 (1H, s), 8.36 (2H, s). (Found: 208.1570).

1(3-*Methyl*-2-*pyrazyl*)*butan*-2-*ol* (**28**). MS: 166 (M^+), 165, 148,

137, 133, 109, 108 (100), 107, 95, 82, 80, 67, 59, 53, 42, 41, 40. NMR: 1.0 (3H, t), 1.6 (2H, m), 2.5 (3H, s), 2.8 (2H, m), 4.0 (1H, m), 4.8 (1H, s), 8.24 (1H, d), 8.26 (1H, d, J = 3 Hz). (Found: 166.1100. $C_9H_{14}N_2O$ requires 166.1106).

1(5-*Methyl*-2-*pyrazyl*)*butan*-2-*ol* (**29**). MS: 166 (M^+), 165, 148, 137, 133, 121, 109, 108 (100), 107, 95, 80, 66, 59, 42, 41. NMR: 1.0 (3H, t), 1.5 (2H, m), 2.5 (3H, s), 2.8 (2H, m), 4.0 (1H, m), 4.8 (1H, s), 8.32 (1H, s), 8.36 (1H, s). (Found: 166.1100).

1(5-*Methyl*-3-*n*-*propyl*-2-*pyrazyl*)*butan*-2-*ol* (**24** *and* **25**). MS: 208 (M^+), 207, 206, 190, 180, 179, 175, 151, 150 (100), 137, 133, 123, 122, 109, 108, 107, 81, 59, 43, 42. NMR: 1.0 (3H, t), 1.1 (3H, t), 1.7 (2H, m), 2.5 (3H, s), 2.7 (2H, t), 2.9 (2H, m), 4.1 (1H, m), 4.6 (1H, s), 8.3 (1H, s). (Found: 208.1570).

General method for the preparation of alkenes. The alcohol (5.0 g, 0.024 mole) in pyridine (20 ml) was treated with small portions of *p*-toluenesulfonyl chloride (5.0 g, 0.026 mole) keeping the temp at 10°. The mixture was stirred for 1 hr, then refluxed overnight. Water was added and the mixture extracted with ether. The ether extract was dried over $MgSO_4$ and the ether removed on a rotary evaporator. The residual ether soln was passed through a short Florisil column and distilled to give the pyrazyl alkene.

1(3-*Methyl*-2-*pyrazyl*)*hept*-1-*ene* (**7**). Yield 45%. MS: 190 (M^+), 175, 161, 147 (100), 133, 132, 119, 108, 92, 79, 77, 65, 41. NMR: 0.95 (3H, t), 1.2–1.6 (6H, m), 2.5 (3H, s), 2.6 (2H, m), 6.6 (1H, d, J = 16 Hz), 7.0 (1H, doublet of triplets), 8.25 (1H, d), 8.31 (1H, d, J = 2.5 Hz). (Found: 190.1460. $C_{12}H_{18}N_2$ requires 190.1470).

1(5-*Methyl*-2-*pyrazyl*)*hept*-1-*ene* (**8**). Yield 40%. MS: 190 (M^+), 175, 161, 147 (100), 133, 120, 108, 93, 77, 65, 52, 41. NMR: 0.95 (3H, t), 1.2–1.6 (6H, m), 2.5 (3H, s), 2.6 (2H, m), 6.6 (1H, d, J = 16 Hz), 7.0 (1H, doublet of triplets), 8.34 (1H, s), 8.40 (1H, s). (Found: 190.1460).

1(6-*Methyl*-2-*pyrazyl*)*hept*-1-*ene* (**9**). Yield 40%. MS: 190 (M^+), 175, 161, 147 (100), 133, 120, 107, 55, 41. NMR: 0.95 (3H, t), 1.2–1.6 (6H, m), 2.5 (3H, s), 2.6 (2H, m), 6.6 (1H, d, J = 16 Hz), 7.0 (1H, doublet of triplets), 8.30 (1H, s), 8.35 (1H, s). Found: 190.1460).

1(2-*Pyrazyl*)*oct*-1-*ene* (**10** *and* **11**). Yield 45%. MS(*cis*): 190 (M^+), 189, 175, 161, 147, 145, 134, 133, 120, 119 (100), 118, 94, 41. MS(*trans*): 190 (M^+), 175, 161, 147, 133 (100), 120, 119, 118, 107, 106, 105, 94, 93, 79, 78, 65, 51, 43, 41. NMR(*trans*): 0.95 (3H, t), 1.2–1.6(8H, m), 2.3 (2H, m), 6.39 (1H, d, J = 16 Hz), 6.84 (1H, m), 8.25 (1H, s), 8.36 (2H, s). (Found: 190.1460).

1(3-*Methyl*-2-*pyrazyl*)*but*-1-*ene* (**26**). Yield 45%. MS(*cis*): 148 (M^+), 147, 134, 133 (100), 132, 119, 108, 93, 79, 67, 52, 42, 41, 40. MS(*trans*): 148 (M^+), 147, 134, 133 (100), 132, 119, 108, 106, 92, 80, 79, 78, 77, 67, 54, 42, 41, 40. NMR(*trans*): 1.1 (3H, t), 2.3 (2H, m), 2.5 (3H, s), 6.4 (1H, d, J = 16 Hz), 6.85 (1H, m), 8.24 (1H, d), 8.26 (1H, d, J = 3 Hz). (Found: 148.0988. $C_9H_{12}N_2$ requires 148.1001).

1(5-*Methyl*-2-*pyrazyl*)*but*-1-*ene* (**27**). Yield 50%. MS(*cis*): 148 (M^+), 147, 134, 133 (100), 121, 120, 108, 94, 79, 66, 52, 42, 41. MS(*trans*): 148 (M^+), 147, 134, 133 (100), 121, 108, 93, 79, 65, 52, 42, 41, 40. NMR(*trans*): 1.1 (3H, t), 2.3 (2H, m), 2.5 (3H, s), 6.4 (1H, d, J = 16 Hz), 6.85 (1H, m), 8.2 (1H, s), 8.3 (1H, s). (Found: 148.0992).

1(5 - *Methyl* - 3 - *n* - *propyl* - 2 - *pyrazyl*)*but* - 1 - *ene or* 5 - *methyl* - 3 - *n*-*propyl* - 2 - (1 - *butenyl*)*pyrazine* (**12**) *and* 2 - *methyl* - 3 - *n* - *propyl* - 5(1 - *butenyl*)*pyrazine* (**14**). Yield 45%. MS(**12** *cis*): 190 (M^+), 175, 162, 161, 147 (100), 146, 145, 133, 121, 119, 91, 73, 57, 55, 43, 42, 41. MS(**12** *trans*): 190 (M^+), 175, 162, 161, 147, 146, 145, 133 (100), 118, 91, 77, 73, 65, 54, 43, 42, 41. NMR(**12** *trans*): 1.0 (3H, t), 1.2 (3H, t), 1.7 (2H, m), 2.3 (2H, m), 2.5 (3H, s), 2.8 (2H, t), 6.6 (1H, d, J = 16 Hz), 6.90 (1H, doublet of triplets), 8.2 (1H, s). MS(**14** *cis*): 190 (M^+), 175, 162 (100), 147, 146, 145, 133, 120, 79, 77, 65, 53, 41. MS(**14** *trans*): 190 (M^+), 175, 162 (100), 147, 146, 145, 133, 79, 77, 65, 53, 42. NMR(**14** *trans*): 1.0 (3H, t), 1.2 (3H, t), 1.7 (2H, m), 2.3 (2H, m), 2.5 (3H, s), 2.8 (2H, t), 6.6 (1H, d, J = 16 Hz), 6.90 (1H, doublet of triplets), 8.2 (1H, s). (Found: 190.1483).

5 - *Methyl* - 3 - *n* - *propyl* - 2 - (1 - *butenyl*)*pyrazine* (**12**) *and* 3 - *methyl* - 5 - *n* - *propyl* - 2 - (1 - *butenyl*)*pyrazine* (**13**). A magnetically stirred soln of 1 - bromo - 1 - butene[26] (2.56 g, 0.019 mole) in 84 ml of Trap mixture (tetrahydrofuran/ether/pentane, 4:1:1) was cooled under an argon atmosphere in a −120° bath (pentane/isopropyl alcohol/acetone, 4:1:1, liquid nitrogen) and combined within 10 min with t-BuLi (0.038 mole, 22 ml of a 1.9 M soln in pentane). The temp was kept between −120 and −110° for 1 hr, then warmed to −90°. 2-Methyl-6-n-propylpyrazine (2.6 g, 0.019 mole) in anhyd ether was added, stirring continued for 15 min at −78° and 20 min at room temp. The reaction was quenched by pouring it into a separatory funnel containing AcOH (1.15 g, 0.019 mole), sat NaCl aq and CH_2Cl_2. The CH_2Cl_2 soln was dried over Na_2SO_4 and analyzed by GC/MS. Although the yield of the products was poor, four pyrazines were formed: *cis* and trans **12** (1:10), and *cis* and *trans* **13** (1:10). No attempt was made to separate them as an alternative synthesis of **12** was available.

Acknowledgements—This work was started while R. M. Duffield was in the laboratory of Dr. M. S. Blum at the University of Georgia. We thank Mr. Arthur Griffiths, Ms. Patrice McCoy, and Mr. Gabe Hodziewich for technical assistance; Dr. Donald Whitehead for sobering comments; Dr. David Smith and Dr. Arnold Menke (Syst. Ent. Lab., IIBIII, AR-SEA, USDA, USNM) for identification of the ants and wasps, respectively; and Dr. H. M. Fales and Mr. William Comstock (NHLBI) for access to and use of the LKB mass spectrometers and facilities while on sabbatical leave. This work has been supported in part by NSF grant CHE7514564, MBS grant RR08016, and MARC training grants to Howard University providing fellowship support (JA) (GMO7799) and funds to purchase the Finnigan mass spectrometer (GM05001). NSF also provided partial funds for the purchase of the Nicolet NT 200 (PCM78-13235) and the Hitachi-Perkin Elmer R-600 (CHE-7822156). The Merck Foundation provided additional funds for the R-600. We thank Dr. Donna Maglott for extensive editing and Ms. Janet Wheeler for the artwork and capable assistance in all phases of production of the manuscript. We thank Mr. Noel Whittaker of NIAAMD, NIH for the high resolution mass measurements.

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