Tryptamine Derived Amides and Acetogenins from the Seeds of *Rollinia mucosa*[1]

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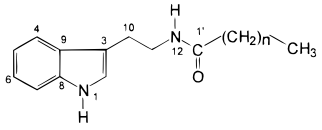
Bioactivity-directed fractionation of a $CHCl_3$−MeOH (1:1) extract prepared from the seeds of *Rollinia mucosa* led to the isolation of a mixture of eight novel tryptamine amides. Extensive HPLC allowed the isolation of the major component of the mixture, which was characterized as *N*-lignoceroyltryptamine (**6**) using a combination of spectroscopic and chemical methods. The minor amides were identified by GC−MS analysis as *N*-palmitoyltryptamine (**1**), *N*-stearoyltryptamine (**2**), *N*-arachidoyltryptamine (**3**), *N*-behenoyltryptamine (**4**), *N*-tricosanoyltryptamine (**5**), *N*-pentacosanoyltryptamine (**7**), and *N*-cerotoyltryptamine (**8**). Two lignans (pinoresinol dimethyl ether and magnolin) and six acetogenins [membranacin (**9**), desacetyluvaricin (**10**), rolliniastatin 1, bullatacin, squamocin, and motrilin] were also isolated. The cytotoxicity of membranacin (**9**) and desacetyluvaricin (**10**) against six human solid tumor cell lines was determined. The absolute configuration of the former is reported.

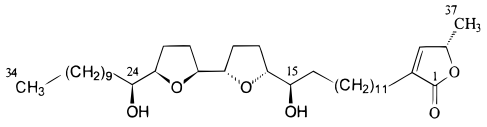
Rollinia mucosa (Jacquin) Baillon (Annonaceae) is a tree widely distributed in tropical America. The fruit of this plant, commonly known in Mexico as “anonillo”, “anonita del monte”, and “cherimoya”, is edible and employed in folk medicine as a therapeutic agent.[2]

Previous chemical investigations of the fruit, leaves, bark, and seeds of *R. mucosa* led to the isolation and identification of a number of cytotoxic and insecticide acetogenins,[3−12] lignans,[13,14] alkaloids,[14,15] steroids,[13] and fatty acid derivatives.[2] Recently, during the course of our search for bioactive compounds from Mexican medicinal plants, we reported from the seeds of this species the isolation of jimenezin, a novel cytotoxic acetogenin containing a hydroxylated tetrahydropyran ring along with an adjacent tetrahydrofuran ring and representing a novel carbon skeleton.[16]

Continuing our investigation on the seeds of *R. mucosa*, we have now isolated a mixture of eight novel amides derived from tryptamine, *N*-palmitoyltryptamine (**1**), *N*-stearoyltryptamine (**2**), *N*-arachidoyltryptamine (**3**), *N*-behenoyltryptamine (**4**), *N*-tricosanoyltryptamine (**5**), *N*-lignoceroyltryptamine (**6**), *N*-pentacosanoyltryptamine (**7**), and *N*-cerotoyltryptamine (**8**). Extensive HPLC of the mixture allowed the isolation of the major component of the mixture, which was characterized as *N*-lignoceroyltryptamine (**6**) by NMR, MS, and chemical methods. In addition, two lignans (pinoresinol dimethyl ether[17] and magnolin[13]) and six acetogenins [membranacin (**9**),[18] desacetyluvaricin,[19] rolliniastatin 1,[3] bullatacin,[20] squamocin,[21] and motrilin[22]] were obtained. Membranacin, motrilin, and pinoresinol dimethyl ether are isolated for the first time from this species. The cytotoxicity of membranacin (**9**) and desacetyluvaricin (**10**) against six human solid tumor cell lines was determined. The absolute configuration for **9** is reported.



Compound	n	Compound	n
1	14	**5**	21
2	16	**6**	22
3	18	**7**	23
4	20	**8**	24



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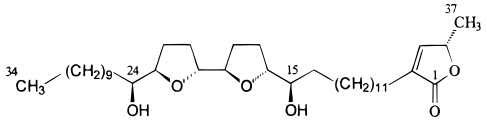

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Results and Discussion

N-Lignoceroyltryptamine (**6**) was obtained as a white solid that exhibited a [M + H] peak in the HRFABMS at *m*/*z* 511.4628, appropriate for a molecular formula of $C_{34}H_{58}N_2O$. Its UV spectrum showed absorptions typical of indole derivatives.[23,24] The NMR spectra (Table 1) clearly indicated that compound **6** was an amide of tryptamine and lignoceric acid. A prominent peak at *m*/*z* 143 (base peak) in the FABMS and EIMS further confirmed the tryptamine moiety. This peak, attributable to a vinylindole fragment, is generated from amide **6** through a McLafferty rearrangement.[23] The aromatic region of the NMR spectra of **6** showed the typical ABCD system [δ_H/δ_c 7.61 (dd, J = 8.0, 1.0 Hz, H-4)/118.8 (C-4), 7.38 (dd, J = 8.0, 1.0 Hz, H-7)/111.2 (C-7), 7.21 (ddd, J = 8.0, 8.0, 1.0 Hz, H-6)/122.3 (C-6), 7.13 (ddd, J = 8.0, 8.0, 1.0 Hz, H-5)/119.6 (C-5)] for the benzene ring and the signals for the pyrrol portion [δ_H/δ_c 7.04 (d, J = 2.5 Hz, H-2)/121.9 (C-2); δ_c 113. 3 (C-3); δ_H 8.04 (br s, H-1)] of the indole system. The absorptions for the ethylamine unit were observed at δ_H/δ_c 2.98 (t, J = 6.5 Hz, H-10)/25.4 (C-10) and 3.61 (td, J = 6.5 Hz, H-11)/39.7 (C-11), while the amide proton was found at δ_H 5.45 (H-12). Finally, the resonances of the acid moiety include those

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Table 1. ^{1}H (500 MHz, $CDCl_3$, *J* in Hz) and ^{13}C NMR (125 MHz, $CDCl_3$) Data of *N*-lignoceroyltryptamine (**6**)[a]

position	^{1}H	^{13}C	HMBC[b]
1	8.04 br s		
2	7.04 d (2.5)	121.9	C-3, C-9, C-8
3		113.3	
4	7.61 dd (8.0, 1.0)	118.8	C-8, C-6
5	7.13 ddd (8.0, 8.0, 1.0)	119.6	C-9
6	7.21 ddd (8.0, 8.0, 1.0)	122.3	C-8, C-4
7	7.38 dd (8.0, 1.0)	111.2	C-9, C-5
8		136.5	
9		127.5	
10	2.98 t (6.5)	25.4	C-2, C-3, C-9, C-11
11	3.61 td (6.5, 6.5)	39.7	C-3, C-10, C-1′, C-2′
12	5.45 br s		
1′		173.1	
2′	2.09 t (7.5)	36.9	C-1′, C-3′
3′	1.57 t, (7.5)	25.7	
4′−23′	1.25 (br s)	29.7, 295, 29.3	
24′	0.88 t (6.5)	14.1	

[a] Assigned by COSY, HMQC, and HMBC spectra. [b] Important long-range ^{1}H−^{13}C correlations.

Table 2. Brine Shrimp and Cytotoxicity Data for Compounds **9** and **10** from *Rollinia mucosa*

compound	BST[a] (μg/mL)	tumor cell line [ED_{50} (μg/mL)]					
		A-549[b]	MCF-7[c]	HT-29[d]	A-298[e]	PC-3[f]	PACA-2[g]
9	5.0×10^{-2}	4.0×10^{-1}	2.18	3.04	$<10^{-3}$	$<10^{-3}$	2.10
10	1.6×10^{-2}	4.7×10^{-1}	1.35	1.69	$<10^{-3}$	$<10^{-3}$	1.92
Adriamycin		8.9×10^{-3}	3.6×10^{-3}	3.7×10^{-3}	8.3×10^{-3}	5.6×10^{-3}	1.1×10^{-3}

[a] Brine shrimp lethality test. [b] Human lung carcinoma. [c] Human breast carcinoma. [d] Human color adenocarcinoma. [e] Human kidney carcinoma. [f] Human prostate adenocarcinoma. [g] Human pancreatic carcinoma.

of the amide carbonyl (δ_c 173.1), the methylenes α and β to the amide function, one terminal methyl group, and those for the remaining methylenes of the aliphatic chain. An HMQC experiment permitted unequivocal assignment of all proton-bearing carbons, while an HMBC experiment allowed assignment of the structure of the whole molecule. On acid hydrolysis **6** yielded lignoceric acid, identified as its methyl ester by GC−MS analysis.

The mixture of tryptamide derivatives was also isolated as a white powder. The FABMS of the mixture showed a series of eight [M + H] peaks (*m*/*z* 399, 427, 455, 483, 497, 511, 525, and 539) and a prominent peak at *m*/*z* 143. HRFABMS of the eight peaks gave molecular formulas of $C_{36}H_{62}ON_2$, $C_{35}H_{60}ON_2$, $C_{34}H_{58}ON_2$, $C_{33}H_{56}ON_2$, $C_{32}H_{54}ON_2$, $C_{30}H_{50}ON_2$, $C_{28}H_{46}ON_2$, and $C_{26}H_{42}ON_2$, respectively. This finding and the results of a GC−MS analysis indicated the presence of eight compounds in the mixture, including amide **6**. As in the case of compound **6**, the mass spectral data of the individual components exhibited the base peak at *m*/*z* 143 (vinylindole fragment), thus indicating that the eight substances were also tryptamine derivatives. The NMR spectra (see Experimental Section) of the mixture **1**−**8** were almost identical to those of pure compound **6**. Altogether, these evidences indicated that individual components of the mixture were *N*-palmitoyltryptamine (**1**), *N*-stearoyltryptamine (**2**), *N*-arachidoyltryptamine (**3**), *N*-behenoyltryptamine (**4**), *N*-tricosanoyltryptamine (**5**), *N*-lignoceroyltryptamine (**6**), *N*-pentacosanoyltryptamine (**7**), and *N*-cerotoyltryptamine (**8**). In the case of compound **6**, the identification of the major component of the mixture (58%), was confirmed by comparison of GC mobilities and by co-injection with **6** isolated in pure form during the course of this study by HPLC. The identity of the remaining amides was confirmed by GC−MS analysis of the methyl ester derivatives of the fatty acids obtained by acid hydrolysis of the mixture. The results of this analysis revealed that the fatty acids were palmitic, stearic, arachidic, behenic, tricosanoic, lignoceric, pentacosanoic, and cerotic acids. Identification of the methyl esters was made by comparison of their mass spectra with those of Public/NIST library.

The structure of membranacin (**9**) was reported previously, without determination of its absolute stereochemistry.[18] The *threo*/*cis*/*threo*/*cis*/*erythro* relative stereochemistry from C-15 to C-24 can be easily assigned on the basis of the chemical shifts values observed for these nuclei in the NMR spectra, which were identical to those previously described.[18] The absolute configuration of the stereogenic carbinol centers was established using the advanced Mosher's ester methodology.[25] Analysis of the $\Delta\delta_H(S - R)$ data (see Experimental Section) of the di-(*S*)- and di-(*R*)-MTPA ester derivatives **9s** and **9r** showed that the absolute stereochemistry of the chiral centers at C-15 and C-24 was *R* and *S*, respectively. The *S* configuration at C-36 was indicated by the negative Cotton effect at 238 nm.[26]

The cytotoxicity of acetogenins **9** and **10** against several cell lines is summarized in Table 2. Both compounds exhibited selective cytotoxicity against A-498 (human kidney carcinoma) and PC-3 (human prostata adenocarcinoma) cell lines. However, the amide **6** and the mixture of **1**−**8** were inactive against the six human tumor cell lines tested (ED_{50}> than 10 μg/mL in all cases) and were not toxic to *Artemia salina* (LC_{50} > 500 μg/mL in all cases). To our knowledge this is the first report of tryptamine-derived alkaloids from a member of the Annonaceae, a family well-known as a source of a variety of isoquinoline alkaloids.

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher−Johns apparatus and are uncorrected. UV spectra were obtained on a Shimadzu 160 UV spectrometer in MeOH solutions. CD spectra were recorded on a JASCO 720 spectropolarimeter at 25 °C in MeOH solution. IR spectra (film) were measured on a Perkin−Elmer 599 spectrometer. ^{1}H (500 MHz) and^{13}C NMR (125 MHz) spectra (all in $CDCl_3$) were obtained on a Varian Unity Plus 500 spectrometer. The

FABMS and HRFABMS data were obtained in a JEOL JMS-AX505HA mass spectrometer using a NBA matrix. GC−MS analyses were conducted on JEOL JMS-AX505HA. The GC column was HP 5% phenyl-methyl silicon (30 m × 0.32 mm i.d.). The linear temperature programming was from 150 to 300 °C, at the rate of 10 °C/min, and the carrier gas was He (1 mL/min). HPLC was carried out with a Waters HPLC instrument equipped with Waters UV photodiode array detector (900) set at 209−220 nm, using a Si gel column (19 mm i.d. × 300 mm). Control of the equipment, data acquisition, processing, and management of chromatographic information were performed by the millennium 2000 software program (Waters).

Plant Material. The seeds of *R. mucosa* (Annonaceae) were collected in September 1994, in Catemaco, Veracruz, México. A voucher specimen of the plant (no. CA94−3) is preserved in the Herbarium of the Instituto de Ecología (XAL), Xalapa, Veracruz, México.

Bioassays. Brine shrimp (*Artemia salina*) lethality test of the extract, fractions, and isolated compounds was performed according to the standard procedure.[27] Cytotoxicity against human solid tumors cells was measured at the Purdue Cell Culture Laboratory, using standard seven-day MTT assays for A-549 (human lung carcinoma),[28] MCF-7 (human breast carcinoma),[29] HT-29 (human colon adenocarcinoma),[30] A-498 (human kidney carcinoma),[28] PC-3 (human prostata adenocarcinoma),[31] and PACA-2 (human pancreatic carcinoma).[32] Adriamycin was used as a positive control.

Extraction and Isolation. The air-dried and ground seeds of *R. mucosa* (663 g) were extracted and treated as previously described[16] to yield 14 secondary chromatographic fractions (F_1−F_{14}). HPLC separation [7.3 mL/min, hexane−*i*PrOH−MeOH (90:5:5)] of active fraction F_4 (120 mg, brine shrimp lethality test LC_{50} 41.9 μg/mL) afforded a mixture of *N*-acyltryptamines (20 mg). Of this mixture 12 mg were subjected to extensive HPLC separation employing the same conditions. This process allowed the isolation of compound **6** (7 mg; retention time 23.0 min). HPLC purification [7.5 mL/min, hexane−*i*PrOH−MeOH, (92:4:5)] of active fraction F_5 (500 mg, BST $LC_{50} = 2.2$ μg/mL) afforded two known acetogenins [**9** (12 mg) and **10** (31.4 mg)] and two known lignans [pinoresinol dimethyl ether (18.4 mg) and magnolin (9.5 mg)] with retention times of 17.9, 20.5, 24.2, and 26.4 min, respectively. Finally, four additional acetogenins were isolated from the active fraction F_7 (500 mg, BST $LC_{50} = 4.5 \times 10^{-1}$ μg/mL) by HPLC [8.3 mL/min, hexane−*i*PrOH−MeOH, (88:6:6)]: rolliniastatin 1 (26.5 mg), bullatacin (21.4 mg), squamocin (57 mg), and motrilin (17 mg); retention times: 32.5, 36.9, 39.3, and 46.21 min, respectively.

***N*-Lignoceroyltryptamine (6):** white crystals; mp 114−115 °C; UV (MeOH) λ_{max} (log ϵ) 281.5 (3.1), 222 (3.76), 205.5 (3.68); IR ν_{max} (film) 3390, 3265, 2957, 2920, 2849, 1673, 1562, 1111 cm^{-1}; ^1H and ^{13}C NMR (Table 1); FABMS (NBA) *m/z* (rel int) 511 $\{MH\}^+$ (15), 143 (100); EIMS *m/z* 143 (100), 129 (18); HRFABMS (NBA) *m/z* 511.4610 $[M + H]^+$ calcd for $C_{34}H_{58}ON_2$ + H 511.4628.

Mixture of Amides 1−8: white powder; IR ν_{max} (film) 3391, 3266, 2956, 2921, 2850, 1675, 1563, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 8.07 (br s, H-1), 7.07 (d J = 2.5 Hz, H-2), 7.64 (dd J = 8.0, 1.0 Hz, H-4), 7.14 (ddd J = 8.0, 8.0, 1.0 Hz, H-5), 7.23 (ddd J = 8.0, 8.0, 1.0 Hz, H-6), 7.39 (dd J = 8.0, 1.0 Hz, H-7), 2.99 (t J = 6.5 Hz, H-10), 3.63 (td J = 6.5, 6.5 Hz, H-11), 5.48 (br s, H-12), 2.10 (t J = 7.5 Hz H-2′), 1.60 (m, H-3′), 1.26 (sa, $-CH_2$), 0.89 (m, $-CH_3$); ^{13}C NMR (125 MHz) δ 122.0 (C-2), 113.5 (C-3), 119.0 (C-4), 119.8 (C-5), 122.5 (C-6), 111.4 (C-7), 136.7 (C-8), 127.7 (C-9), 25.6 (C-10), 39.9 (C-11), 173.2 (C-1′), 37.0 (C-2′), 25.9 (C-3′), 29.9, 29.7, 29.6, 29.3 ($-CH_2$), 14.3 ($-CH_3$); FABMS (NBA) *m/z* $\{MH\}^+$ 539, 525, 511, 497, 483, 455, 427, and 399; HRFABMS (NBA) *m/z* 539.3599 $[M + H]^+$ calcd for $C_{36}H_{62}ON_2$ + H 539.4881; 525.4736 $[M + H]^+$ calcd for $C_{35}H_{60}ON_2$ + H 525.4754; 511.4618 $[M + H]^+$ calcd for $C_{34}H_{58}ON_2$ + H 511.4628; 497.4484 $[M + H]^+$ calcd for $C_{33}H_{56}ON_2$ + H 497.4501; 483.4357$[M + H]^+$ calcd for $C_{32}H_{54}ON_2$ + H 483.3437; 455.4105 $[M + H]^+$ calcd for $C_{30}H_{50}ON_2$ + H 455.4121; 427.3852 $[M + H]^+$ calcd for $C_{28}H_{46}ON_2$ + H 427.3867; 399.3599 $[M + H]^+$ calcd for $C_{26}H_{42}ON_2$ + H 511.4628.

Membranacin (9): oil; $[\alpha]_D$ + 27.3 (*c* 1.1 mg/mL) MeOH; UV (MeOH) λ_{max} (log ϵ) 207 (4.12); CD (MeOH) $\Delta\epsilon$ (nm) -2.49×10^4 (238); NMR and MS data.[18]

GC−MS Analysis of the Mixture 1−8. GC−MS analysis of the mixture was performed using the conditions indicated in general. The retention time/percentage composition (uncorrected) of the components of the mixture are: **1**, 36.8/ 8%; **2**, 38.4/ 3%; **3**, 40.8/ 2%; **4**, 42.7/ 22%; **5**, 43.4/ 3%; **6**, 44.5/ 58%; **7**, 45.7/ 3% and **8**, 47.4/ 1%. EIMS *m/z* of each component 143 (100), 129 (ca. 18).

Acid Hydrolysis. Either 5 mg of the mixture of *N*-acyltryptamines or 3 mg of compound **6** were treated with 0.5 mL of H_2SO_4 8 M. The reaction mixture was refluxed during 30 min. The fatty acids were extracted with $CHCl_3$. In each case, the resulting organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo to yield 2.5 mg and 1 mg of a solid residue, respectively. The resulting residues were methylated with an ethereal solution of CH_2N_2 and analyzed by GC−MS.

GC−MS Analysis of Lignoceric Acid Methyl Ester. GC−MS analysis of lignoceric acid methyl ester was performed using the conditions indicated in general. The retention time was 15.1 min; EIMS *m/z* 382 (M^+, 78), 351 (M-31, 9), 87 (91), 74 (100). Identification of the methyl ester was made by comparison of their mass spectrum with that of Public/NIST library.

GC−MS Analysis of the Fatty Acids Methyl Esters from Compounds 1−8. GC−MS analysis of the fatty acid methyl esters obtained from acid hydrolysis of the mixture **1**−**8** was performed using the conditions indicated in general experimental procedures. Identifications of the methyl esters were made by comparison of their mass spectra with those of Public/NIST library. Data for individual methyl esters. The retention time (min)/ percentage composition (uncorrected)/ EIMS *m/z* of the methyl esters are: palmitic 8/ 7.8%/ 270 (M^+, 62), 239 (M-31, 30), 87 (84), 74 (100); stearic 9.9/ 3.2%/ 298 (M^+, 47), 267 (M-31, 14), 87 (80), 74 (100); arachidic 11.7/ 1.6%/ 326 (M^+, 44), 295 (M-31, 10), 87 (84), 74 (100); behenic 13.4/ 21.7%/270 (M^+, 62), 239 (M-31, 30), 87 (84), 74 (100); tricosanoic 14.2/ 2.9%/ 368 (M^+, 57), 337 (M-31, 8), 87 (87), 74 (100); lignoceric 15.0/ 58.9%/ 382 (M^+, 73), 351 (M-31, 11), 87 (89), 74 (100); pentacosanoic 15.7/ 2.6%/ 396 (M^+, 62), 365 (M-31, 7), 87 (91), 74 (100); cerotic 16.5/ 1%/ 410 (M^+, 100), 379 (M-31, 9), 87 (67), 74 (71).

Preparation of per-(*S*)- and per-(*R*)-MTPA Ester Derivatives. To a solution of **9** (1.5 mg in 0.5 mL of $CDCl_3$ in a NMR tube) was sequentially added pyridine-d_5 (100 μL), 4-(dimethylamino)-pyridine (0.5 mg), and (*R*)-(−)-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (25 mg). The mixture was heated at 50 °C for 4 h under a N_2 atmosphere to give the *S*-Mosher ester **9s**: ^1H NMR (500 MHz) δ 1.66 (H-14), 4.09 (H-16), 1.85 (H-17a), 1.70 (H-17b), 1.79 (H-18a), 1.65 (H-18b), 3.64 (H-19), 3.68 (H-20), 1.76 (H-21a), 1.75 (H-21b), 1.89 (H-22a), 1.78 (H-22b), 3.98 (H-23), 1.66 (H-25).

Treatment of **9** (1.5 mg) with (*S*)-(+)-methoxy-α-(trifluoromethyl)-phenylacetyl chloride as described above yielded the *R*-Mosher ester **9r**: ^1H NMR (500 MHz) δ 1.54 (H-14), 3.99 (H-16), 1.91 (H-17a), 1.79 (H-17b), 1.90 (H-18a), 1.74 (H-18b), 3.78 (H-19), 3.63 (H-20), 1.72 (H-21a), 1.66 (H-21b), 1.86 (H-22a), 1.70 (H-22b), 3.96 (H-23), 1.69 (H-25).

$\Delta\delta_H(S-R)$: + 0.12 (H-14), +0.10 (H-16), −0.06 (H-17a), −0.09 (H-17b), −0.12 (H-18a), −0.09 (H-18b), −0.14 (H-19), +0.05 (H-20), +0.04 (H-21a), +0.09 (H-21b), +0.03 (H-22a), +0.08 (H-22b), +0.02 (H-23) and −0.03 (H-25).

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