Old and New Alkaloids from *Zanthoxylum arborescens*†

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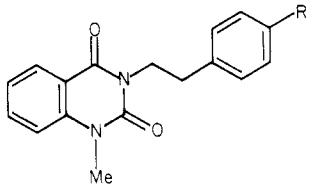
The new alkaloids (2*S*,5*S*)-2,5-dibenzyl-1,4-dimethylpiperazine, 8-hydroxy-4,7-dimethoxyfuranoquinoline, and 8-isopentenyloxy-4,7-dimethoxyfuranoquinoline were isolated from *Zanthoxylum arborescens* (Rutaceae). The β-D-glucopyranoside of hordenine (previously known only as a synthetic) was also found. The known alkaloids skimmianine, tembetarine, hordenine, *N*,*N*-dimethyltryptamine, *N*-methyltryptamine, 1-methyl-3-(2′-phenylethyl)-1*H*,3*H*-quinazoline-2,4-dione and 1-methyl-3-[2′-(4″-methoxyphenyl)ethyl]-1*H*,3*H*-quinazoline-2,4-dione also were isolated. Structure proof of the two new furanoquinoline alkaloids necessitated a revision in the previously suggested structure for perfamine, a cyclohexadienone alkaloid from *Haplophyllum perforatum*.

Dreyer investigated[1] the alkaloid content of seed husks from the Mexican wild citrus relative *Zanthoxylum arborescens* and found two novel quinazolone alkaloids, **1** and **2**. We have studied the alkaloid content of leaves,

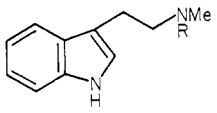


1, R = OMe
2, R = H

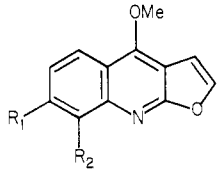
bark, and wood from the same species and have discovered the same two quinazolones as well as other alkaloids, both new and previously known.

Results

Leaves. The major alkaloid of the leaves was found to be the potent hallucinogen *N*,*N*-dimethyltryptamine (**3**).



3, R = Me
4, R = H



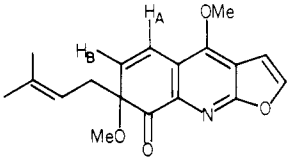
5, $R_1 = R_2$ = OMe
6, R_1 = OMe; R_2 = 
7, R_1 =  ; R_2 = OMe
8, R_1 = OMe; R_2 = OH
9, R_1 = OH; R_2 = OMe
17, $R_1 = R_2$ = H
18, R_1 = H; R_2 = OMe

This is its first recorded occurrence in the genus *Zanthoxylum*.[2] An accompanying alkaloid was *N*-methyltryptamine (**4**). The leaves contained relatively large amounts of the quinazolones **1** and **2** and the very common skimmianine (**5**). Three new alkaloids were also discovered, and the structure eludication of each is described in the following.

A relatively nonpolar alkaloid, **6**, had a UV spectrum with an acid shift which was typical of a furoquinoline. There were two methoxy groups as evidenced by the ^{1}H NMR (4.01 and 4.42 ppm) and ^{13}C NMR (56.89 and 58.85 ppm) spectra. The presence of an isopentenyl ether function was indicated by methyl singlets at 1.67 and 1.73 ppm in the ^{1}H NMR spectrum, a two-proton doublet at 4.84 ppm, and an *m*/*e* 245 mass spectrum fragment (M^+ − 68). These data along with the molecular formula from a high-resolution mass spectrum ($C_{18}H_{19}NO_4$) indicated that the unknown was either the new substance **6** [8-(2-isopentenyloxy)-4,7-dimethoxyfuro[2,3-*b*]quinoline] or its isomer **7**. The latter is a known compound,[3] and a standard sample[4] proved to be nonidentical with our unknown. Final proof of structure **6** was based upon correlation with a second furanoquinoline.

The UV spectrum of the second unknown, as measured in neutral, acidic, and basic solutions, identified it as a phenolic furanoquinoline. Two methoxy groups were present (^{1}H NMR δ 4.06, 4.40; ^{13}C NMR δ 57.03, 59.02). The high-resolution mass spectrum established the molecular formula as $C_{13}H_{11}NO_4$, and the total data indicated that the unknown must be **8** (8-hydroxy-4,7-dimethoxyfuranoquinoline) or its isomer **9** (haplopine). This was reinforced by methylation of the unknown to yield skimmianine (**5**). We had recently[5] identified haplopine from *Zanthoxylum microcarpum*, but it was not identical with the unknown, which, therefore, must have structure **8**. Alkaloid **8** was isoprenylated to yield an alkaloid identical with the first unknown furanoquinoline, which has, therefore, been assigned structure **6**.

A compound with structure **8** was reported[6] to have been formed by an acidic fragmentation rearrangement of the cyclohexadienone alkaloid perfamine, isolated[6] from *Haplophyllum perforatum*. Because of this, perfamine was assigned structure **19**. We obtained a sample of the



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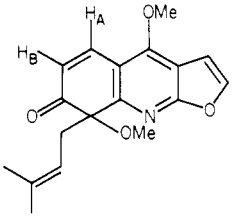

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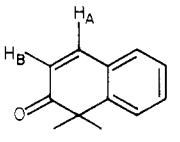

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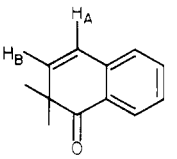

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† Paper 7 in the series "Constituents of *Zanthoxylum*". For paper 6 see: R. T. Boulware and F. R. Stermitz, *J. Nat. Prod.*, **44**, 200 (1981).

(1) D. L. Dreyer and R. C. Brenner, *Phytochemistry*, **19**, 935 (1980).
(2) I. Mester, *Fitoterapia*, **44**, 123 (1973); **48**, 268 (1977).
(3) D. L. Dreyer, *Phytochemistry*, **8**, 1013 (1969).
(4) We are indebted to D. L. Dreyer for the standard sample.
(5) R. T. Boulware and F. R. Stermitz, *J. Nat. Prod.*, **44**, 200 (1981).
(6) D. M. Razakova, I. A. Bessonova, and S. Yu. Yunusov, *Khim. Prir. Soed.*, 791 (1976), 738 (1979).

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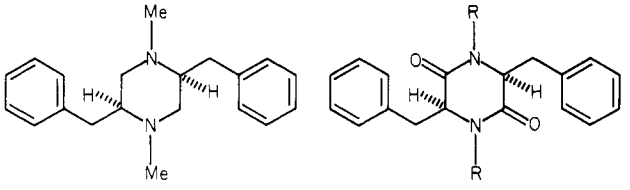
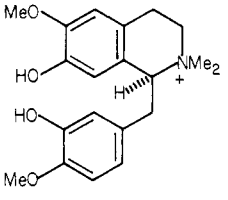
purported compound 8[7] and found it to be identical with haplopine (9) by ^{1}H NMR, UV, and TLC in three different solvent systems, but different from our isolate. If the rearrangement product of perfamine is indeed haplopine and not 8, then the structure of perfamine must be reassigned as **20**. This received confirmation from examination of the reported[6] ^{1}H NMR spectrum of perfamine. Protons H_A and H_B occur at 8.0 and 6.2 ppm, as expected for **20** and not **19**. Good models are available in the ^{1}H NMR spectra[8] of **21** and **22**. In the former, H_A is a multiplet at 7.1–7.5 ppm while H_B is a doublet at 6.05. In **22**, H_A and H_B are reported[8] as an AB quartet (Δ_{AB} 17 Hz) centered at 6.25 ppm.

Relatively large quantities of a further unknown alkaloid were also found in the leaves. This optically active substance yielded an electron impact mass spectrum with only two major peaks: *m/e* 203 ($C_{13}H_{19}N_2$ by high resolution) and *m/e* 70 (C_4H_8N by high resolution). The chemical ionization mass spectrum (preferably with NH_3) showed that 203 was not the molecular ion, but rather *m/e* 295, a peak not observed in the electron impact mode. This indicated a molecular formula of $C_{20}H_{26}N_2$ for the unknown. The ^{1}H NMR spectrum indicated 13 rather than 26 protons, while the ^{13}C NMR spectrum showed 8 resonances. Two resonances were probably the result of two identical carbons each, which would mean that we were seeing half the required number of carbons. These data indicated a high degree of symmetry or magnetic equivalence among the various carbons and hydrogens. The NMR spectra were best interpreted as the result of a monosubstituted benzene, an N-CH_3 group, and three additional carbons making up a $C_6H_5CH_2CH(NCH_3)CH_2$ array. If two of these units were joined, the result would be structure **10** or the corresponding trans isomer. The trans isomer has a center of symmetry and would not exhibit optical rotation, while the cis-isomer **10** would be optically active, as was the unknown alkaloid. The correctness of structure **10** for the unknown was established by total synthesis. The synthetic compound showed slightly greater purity (mp 123–124.5 °C and $[\alpha]_D$ +118° as opposed to mp 116–120 °C and $[\alpha]_D$ +96° for the isolated alkaloid). ^{1}H and ^{13}C NMR, IR, and mass spectra and TLC behavior of the synthetic and isolated alkaloids were essentially identical.[9]



10

11, R = H
12, R = Me



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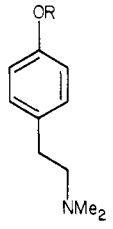
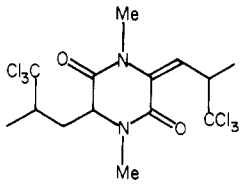


14, R = H
15, R = β-D-glucopyranosyl



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Bark. The bark was found to contain relatively small amounts of **1** and **6** and a very high concentration of the known (+)-tembetarine, **13**.

Wood. Hordenine (**14**) and **13** were present as were larger amounts of a very polar alkaloid whose NMR spectra, mp, and optical rotation indicated it to probably be the β-D-glucopyranoside (**15**) of hordenine. This substance has not been reported as a natural product as far as we could find, but had been prepared synthetically be Wieniawski.[10] We synthesized **15** from hordenine and acetobromoglucose according to Wieniawski's procedure. The synthetic and natural substances were essentially identical by mp, optical rotation, TLC, and ^{13}C and ^{1}H NMR spectra.

Discussion

The most novel of the findings reported here is undoubtedly the discovery of **10**. As far as we are aware, this is the first report of such a piperazine in nature. It is presumed to be biosynthetically related to L-phenylalanine diketopiperazine (**11**) by an N-methylation and reduction. Some diketopiperazines are known as microbial products, and some have also been found in lichens and sponges.[11a] A simple N-methylated diketopiperazine derivative, **16**, (presumably derived from leucine) has been reported[11b] from the sponge *Dysidea herbacea* or its blue-algal symbiont, for example.

Alkaloids **10** and **13–15** are all products of a biosynthetic pathway starting from phenylalanine or tyrosine. The very large quantity of **13** (the quaternary methyl derivative of reticuline) that was found, without the presence of any other benzylisoquinoline-derived alkaloids, indicates that quaternization of reticuline has effectively removed it from the mainstream of biosynthetic reactions.

The other alkaloids are all tryptophan or anthranilate derived. Skimmianine (**5**) is probably the most common alkaloid of the Rutaceae and occurs in over 50% of the species that have been investigated.[2] The second most common is probably dictamnine (**17**), which has been shown to be the precursor of skimmianine. Because γ-fagarine (**18**) is also a common furanoquinoline and was shown[12] to be the precursor of skimmianine in *Ruta graveolens* cell suspensions, the most likely scheme for the biosynthesis of skimmianine has been **17** → **18** → **9** → **5**. Our finding of the new alkaloid **8** in *Z. arborescens* along with skimmianine indicates that an alternate pathway to the latter is likely in this plant.

Although indole alkaloids are common in the Rutaceae, only 1 of 245 species studied through 1977[2] contained *N,N*-dimethyltryptamine. It was found[13] to be the major

(7) We appreciate the kindness of I. A. Bessonova, who supplied us with a sample of the perfamine rearrangement product.
(8) L. H. Klemm, C. E. Klopfenstein, and J. Shabtai, *J. Org. Chem.*, **35**, 1069 (1970); L. H. Klemm, J. Shabtai, and D. R. Taylor, *ibid.*, **33**, 1480 (1968).
(9) The characterization and synthesis of **10** has been reported in preliminary form by J. Grina and F. R. Stermitz, *Tetrahedron Lett.*, 5257 (1981).
(10) W. Wieniawski, *Acta Polon. Pharm.*, **19**, 285 (1962).
(11) R. Kazaluskas, P. T. Murphy, and R. J. Wells, *Tetrahedron Lett.*, 4945 (1978).
(12) D. Boulanger, B. K. Bailey, and W. Steck, *Phytochemistry*, **12**, 2399 (1973).
(13) C. Kan-Fan, B. C. Das, P. Boiteau, and P. Potier, *Phytochemistry*, **9**, 1283 (1970).

Table I. Alkaloid Content (Percent of Dry Weight Plant)

compd	bark	wood	leaves	compd	bark	wood	leaves
1	0.007		0.01	8			0.03
2			0.04	10			0.006
3			0.09	13	0.15	0.01	
4			0.002	14		0.02	
5			0.01	15		0.03	
6	0.007		0.05				

alkaloid component of leaves from the Madagascar tree *Vepris ampody* H. Perr. The 5-methoxy derivative is, however, widespread.

Experimental Section

General Methods. ^1H NMR spectra were recorded on Varian EM-360, Varian T-60, JEOL FX-100, and Nicolet NT-360 instruments and ^{13}C NMR spectra were obtained on a JEOL FX-100 spectrometer at 25.05 MHz. Chemical shifts are reported as parts per million downfield from Me_4Si. IR spectra were obtained on a Beckman IR 4240 or a Beckman Acculab 3 spectrophotometer as thin films on salt plates, KBr pellets, or as $CHCl_3$ solutions. UV spectra were recorded on a Varian Techtron Model 635 UV–vis spectrophotometer. Electron impact (EIMS), methane chemical ionization (CIMS-CH_4), and ammonia chemical ionization (CIMS-NH_3) mass spectra were measured on a VG MM-16 spectrometer with a Systems Industries interface and a Digital PDP8-A computer. High-resolution electron impact (HREIMS) mass spectra were obtained on an AEI MS-902 spectrometer with the same interface and computer or from the NSF Regional Center at the University of Nebraska. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Melting points were obtained on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Thin-layer (TLC) and preparatory layer chromatography (PLC) was accomplished on 0.25- and 2-mm precoated plates of silica gel 60 F-254 (Merck) or on 0.25- and 1.5-mm precoated plates of aluminum oxide F-254 type T (Merck). Visualization was with ultraviolet light, iodine, iodoplatinic acid, and/or phosphomolybdic acid. Flash chromatography refers to a low-pressure system described by Still.[14] Medium-pressure liquid chromatography (MPLC) was performed on a system similar to that described by Meyers.[15] Sephadex LH-20-100 (Sigma) was used for gel chromatography.

Tetrahydrofuran was distilled from sodium/benzophenone immediately before use. All reactions were performed under an argon atmosphere.

Extraction Procedures. *Zanthoxylum arborescens* Rose (Rutaceae) was collected in Western Mexico in 1978 (Colorado State University Herbarium voucher specimens 59 066–59 068). The bark, wood, and leaves were separated, dried, and powdered.

A 230-g sample of bark was extracted in a Soxhlet apparatus with 3 L of hexane and then with 3 L of MeOH. The hexane extract was evaporated in vacuo to yield 3.2 g of residue. This residue was subjected to flash chromatography (EtOAc/hexane 1:1). The alkaloid-containing fractions were combined and purified by MPLC (EtOAc/hexane 1:5). Fraction 4 afforded 17 mg of a yellow solid, **1**, and fraction 6 contained 19 mg of a yellow solid, **6**. The MeOH extract of the bark was evaporated in vacuo to yield 25 g of residue. Half of this residue was triturated twice with 25 mL of 1 M hydrochloric acid. The acidic solution was washed twice with 30 mL of $CHCl_3$. The aqueous solution was then made basic to pH 9.5 (NH_4OH), and 2 g KI was added. (Addition of KI allowed direct isolation of the iodide salts of quaternary alkaloids.) The basic aqueous solution was extracted three times with 50 mL of $CHCl_3$ and four times with 50 mL of 1-butanol. The 1-butanol was evaporated in vacuo to yield 2.2 g of crude alkaloid. Trituration of this residue with acetone afforded 350 mg of a tan solid, **13**.

A 265-g sample of wood was extracted in a Soxhlet apparatus with 3 L of hexane and then with 3 L of MeOH. The hexane extract contained 0.7 g of residue after evaporation in vacuo and showed no alkaloids by TLC (iodoplatinic acid visualization). The MeOH extract of the wood was evaporated in vacuo to yield 10 g of residue. Half of this residue was triturated twice with 25 mL of 1 M hydrochloric acid. The acidic aqueous solution was washed twice with 50 mL of $CHCl_3$. The aqueous solution was then made basic to pH 9.5 (NH_4OH), and 1 g KI was added. This basic aqueous solution was extracted three times with 50 mL of $CHCl_3$ and twice with 50 mL of 1-butanol. The $CHCl_3$ extract was evaporated in vacuo to yield 0.2 g of crude alkaloid that crystallized in $CDCl_3$ to yield a solid, **14**. The 1-butanol extract was evaporated in vacuo to yield 1.3 g of a crude alkaloid mixture. This mixture was applied to a Sephadex LH-20-100 column and eluted ($CHCl_3$/MeOH 1:1). Fractions 14–26 were combined and purified by flash chromatography (MeOH/H_2O/NH_4OH 15:3:1) to afford 39 mg of a yellow solid, **15**. Fractions 30–36 were combined and subjected to MPLC (MeOH followed by MeOH/H_2O/NH_4OH 15:3:1). Fraction 5 contained 15 mg of a solid, **13**.

A 1.2-kg sample of leaves was extracted in a Soxhlet extraction apparatus with 5 L of hexane and then with 5 L of MeOH. The hexane extract was evaporated in vacuo. Viscous residue (43 g) resulted, which was triturated with EtOAc and then with MeOH. The MeOH-soluble material (4.6 g) was subjected to flash chromatography (EtOAc/hexane 1:1) for preliminary purification. Fractions 3–5 were combined and evaporated in vacuo. Upon addition of a hexane/EtOAc (4:1) mixture, 220 mg of a white crystalline solid, **6**, was obtained by filtration. The filtrate was purified by flash chromatography (EtOAc/hexane 1:4) to yield 310 mg of a yellow solid, **2**, and 60 mg of a tan solid, **1**. Fractions 6–13 of the first chromatography were purified by flash chromatography (EtOAc/hexane 1:4) to yield 10 mg of a yellow solid, **5**. The MeOH extract of the leaves was evaporated in vacuo, dissolved in 1000 mL of 1 M sulfuric acid, and washed with 1600 mL of $CHCl_3$. The acidic aqueous solution was then made basic to pH 9 (NH_4OH) and extracted with 1 L of $CHCl_3$. The $CHCl_3$ extract was evaporated to yield 2.23 g of a crude alkaloid mixture. The crude alkaloid mixture (1 g) was flash chromatographed (EtOAc, followed by EtOAc/EtOH/NH_4OH 35:5:1). Fraction 2 afforded 40 mg of a light brown solid, **8**. Fractions 4 and 5 were again flash chromatographed (EtOAc) to yield 20 mg of a tan solid, **10**. Fractions 10 and 11 (300 mg) were partially purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH 85:5:1) to yield a brown oil, part of which was further purified by alumina PLC ($CHCl_3$/MeOH 50:1) to afford a white solid, **3**. Another 1-g portion of the crude alkaloid mixture was flash chromatographed (EtOAc/MeOH/NH_4OH 40:5:1). Fractions 32–45 were combined and purified by silica gel PLC (CH_2Cl_2/MeOH/NH_4OH 85:15:1) to yield 6 mg of a tan gum, **4**.

Table I gives an estimate of the alkaloid content (percent of dry weight plant) based upon isolated material along with NMR and TLC analyses of crude or unseparated fractions.

Alkaloid Identifications. 1-Methyl-3-[2′-(4″-methoxyphenyl)ethyl]-1*H*,3*H*-quinazoline-2,4-dione (1): mp 134–135 °C (lit.[1] mp 133–134 °C). Identical with standard sample[4] by ^1H NMR, ^{13}C NMR, UV, IR, EIMS, and TLC.

8-(2-Isopentenyloxy)-4,7-dimethoxyfuro[2,3-*b*]quinoline (6): mp 120.5–121.5 °C (hexane/EtOAc); silica gel TLC R_f 0.49 (EtOAc/hexane 1:1); UV λ_{max}^{EtOH} (nm) 334, 322, 250 (H^+ 345, 322, 250); ^1H NMR ($CDCl_3$, 360 MHz) δ 1.67 (s, 3 H), 1.73 (s, 3 H), 4.01 (s, 3 H), 4.42 (s, 3H), 4.84 (d, J = 7 Hz, 2 H), 5.73 (t, J = 7 Hz, 1 H), 7.02 (d, J = 3 Hz, 1 H), 7.19 (d, J = 9 Hz, 1 H), 7.56 (d, J = 3 Hz, 1 H), 7.99 (d, J = 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.98, 25.75, 56.89, 58.85, 70.35, 101.77, 104.39, 112.10, 114.73, 117.71, 121.09, 137.15, 140.83, 141.76, 142.69, 152.33, 156.82, 163.89; IR ($CHCl_3$, cm^{-1}) 2940, 2870, 1635, 1620, 1587, 1510, 1490, 1400, 1370, 1273, 1110, 1095, 1055, 995; EIMS (*m/e*, %) 313 (4), 245

(14) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
(15) A. I. Meyers, J. Slade, R. K. Smith, E. D. Mihelich, F. M. Hershenson, and C. D. Liang, *J. Org. Chem.*, **44**, 2247 (1979).

Table II

compd	R_f values: 15:3:1 MeOH/H_2O/NH_4OH	5:4:1 PhMe/EtOAc/HCOOH	6:2:2:1 hexane/EtOAc/$CHCl_3$/MeOH
8	0.80	0.40	0.31
haplopine[5]	0.95	0.34	0.22
perfamine product[6,7]	0.96	0.35	0.21

(100), 230 (31), 227 (75), 216 (23), 202 (25); CIMS-CH_4 (*m/e*, %) 314 (8), 274 (12), 247 (16), 246 (100), 245 (34); HREIMS (*m/e*) calcd for $C_{18}H_{19}NO_4$ 313.1313, found 313.1300. A standard sample of **7** was available,[4] and this was *not* identical with **6**.

(+)-Tembetarine (13): Identical with a previously isolated[16] sample by ^1H NMR, ^{13}C NMR, IR, UV, optical rotation, and TLC.

Hordenine (14): Identical with a previously isolated[16] sample by ^1H NMR, UV, and TLC.

(−)-4-[2-(Dimethylamino)ethyl]phenyl β-D-glucopyranoside (15): mp 164–166 °C (lit.[10] mp 169–170.5 °C); $[\alpha]^{25}_D$ −49.8 (*c* 0.51, MeOH) (lit.[10] $[\alpha]^{20}_D$ −50 (*c*, 0.2, H_2O)); UV λ_{max}^{EtOH} (nm) 280, 274, 228; ^1H NMR (CD_3OD, 360 MHz) δ 2.44 (s, 6 H), 2.65–2.74 (m, 2 H), 2.76–2.84 (m, 2 H), 3.37–3.45 (m, 4 H), 3.69 (dd, *J* = 5 Hz, *J* = 11 Hz, 1 H), 3.87 (d, *J* = 11 Hz, 1 H), 7.05 (d, *J* = 7 Hz, 2 H), 7.18 (d, *J* = 7 Hz, 2 H), anomeric proton coincident with HOD resonance at 4.85 (br s); CIMS-CH_4 (*m/e*, %) 328 (22), 167 (15), 166 (100), 164 (21), 127 (13), 121 (29); silica gel TLC R_f 0.51 ($MeOH/H_2O/NH_4OH$ 15:3:1); ^{13}C NMR (CH_3OD) δ 32.36, 44.15, 61.09, 61.73, 70.54, 74.05, 77.14, 101.55, 117.08, 129.57, 133.25, 156.61. Identical with a synthetic sample by ^1H NMR, ^{13}C NMR, UV, IR, CIMS-CH_4, and TLC.

1-Methyl-3-(2′-phenylethyl)-1*H*,3*H*-quinazoline-2,4-dione (2): mp 96–99 °C (lit.[1] mp 100–102 °C); identical with a standard sample[4] by ^1H NMR and TLC.

Skimmianine (5): Identical with a previously isolated[16] sample by ^1H NMR, UV, and TLC.

8-Hydroxy-4,7-dimethoxyfuranoquinoline (8): mp 129–130 °C (hexane/EtOAc); UV λ_{max}^{EtOH} (nm) 340, 325, 310 (sh), 250 (OH^- 375, 340, 323, 268, 217) (H^+ 360, 325, 312, 257, 233, 210); ^1H NMR ($CDCl_3$, 60 MHz) δ 4.06 (s, 3 H), 4.40 (s, 3 H), 6.95 (d, *J* = 3 Hz, 1 H), 7.15 (d, *J* = 10 Hz, 1 H), 7.48 (d, *J* = 3 Hz, 1 H), 7.65 (d, *J* = 10 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 57.03 (q), 59.02 (q), 102.16 (s), 104.91 (d), 112.56 (d), 112.85 (d), 113.72 (s), 136.32 (s), 138.13 (s), 142.45 (d), 144.20 (s), 157.38 (s), 164.12 (s); IR (thin film, cm^{-1}) 3400, 2925, 1620, 1500, 1355, 1265, 1085, 750, 715; EIMS (*m/e*, %) 245 (100), 244 (20), 230 (43), 227 (68), 216 (22), 202 (54), 140 (27), 44 (23), 43 (52); HREIMS (*m/e*) calcd for $C_{13}H_{11}NO_4$ 245.0677, found 245.0682.

In Table II TLC comparisons are made between **8**, haplopine,[5] and the perfamine rearrangement product.[6,7]

(+)-(2*S*,5*S*)-2,5-Dibenzyl-1,4-dimethylpiperazine (10): mp 116–120 °C (EtOAc); $[\alpha]^{23}_D$ +96 (*c* 0.11, EtOH); silica gel TLC R_f 0.32 (EtOAc); UV λ_{max}^{EtOH} (nm) 253, 222; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.29 (dd, *J* = 3 Hz, *J* = 13 Hz, 1 H), 2.38 (s, 3 H), 2.53 (dd, *J* = 6 Hz, *J* = 13 Hz, 1 H), 2.65 (m, 1 H), 2.79 (dd, *J* = 8 Hz, *J* = 11 Hz, 1 H), 3.00 (dd, *J* = 3 Hz, *J* = 11 Hz, 1 H), 7.18–7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 33.09 (t), 42.67 (q), 55.28 (t), 62.64 (d), 125.81 (d), 128.20 (d), 129.20 (d), 139.76 (s); EIMS (*m/e*, %) 203 (100), 160 (6), 117 (6), 111 (10), 91 (14), 83 (10), 78 (7), 71 (8), 70 (78), 57 (10), 43 (10), 42 (21), 41 (6), 40 (13); HREIMS (*m/e*) calcd for $C_{13}H_{19}N_2$ 203.1548, found 203.1589, calcd for C_4H_8N 70.0657, found 70.0679; CIMS-NH_3 (*m/e*, %) 295 (100); IR (thin film, cm^{-1}) 2940, 2785, 1490, 1450, 1157, 735, 695.

***N*,*N*-Dimethyltryptamine (3)**: mp 39–44 °C (lit.[17] mp 44.6–46.8 °C); silica gel TLC R_f 0.59 (methanol/water/ammonium hydroxide 15:3:1); UV λ_{max}^{EtOH} (nm) 293, 284, 279, 275 (sh), 226; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.48 (s, 6 H), 2.83 (t, *J* = 8 Hz, 2 H), 3.07 (t, *J* = 8 Hz, 2 H), 5.2 (br s, 1 H), 7.05 (d, *J* = 2 Hz, 1 H), 7.12 (t, *J* = 7 Hz, 1 H), 7.20 (t, *J* = 7 Hz, 1 H), 7.37 (d, *J* = 7 Hz, 1 H), 7.61 (d, *J* = 7 Hz, 1 H), 8.2 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.40, 45.12, 60.07, 111.04, 113.26, 118.34, 118.63, 121.37, 121.61, 127.10, 136.09; IR (thin film, cm^{-1}) 3400, 3225, 2920, 1455, 740; EIMS (*m/e*, %) 188 (3), 144 (1), 143 (1), 130 (2), 77 (2), 71 (1), 69 (1), 59 (3), 58 (100).

***N*-Methyltryptamine (4)**: silica gel TLC R_f 0.38 ($MeOH/H_2O/NH_4OH$ 15:3:1); UV λ_{max}^{EtOH} (nm) 292, 284, 275, 229; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.25 (br s, 1 H), 2.45 (s, 3 H), 2.93–2.97 (m, 4 H), 7.04–7.75 (m, 5 H), 8.01 (br s, 1 H); EIMS (*m/e*, %) 176 (5), 174 (4), 134 (11), 132 (10), 131 (75), 130 (50), 103 (8), 91 (6), 85 (17), 82 (26), 77 (10), 58 (9), 51 (5), 44 (100), 43 (29), 42 (8). **4** was identical with a standard sample (Aldrich Chemical Co.) by ^1H NMR and TLC.

Synthetic Procedures. Methylation of 8. A 10-mg sample of **8** was methylated according to the procedure of Johnstone and Rose[18] using powdered KOH and MeI in Me_2SO. The resulting product was identical with a standard sample of skimmianine (**5**).

Isopentenylation of 8. A 7.9-mg sample of **8** was alkylated by the method of Johnstone and Rose[18] using prenyl bromide (gift from J. Godschalx and J. K. Stille, Colorado State University) and powdered KOH in Me_2SO. The product was purified by silica gel PLC (EtOAc/hexane 1:1) to yield 3 mg of a tan solid identical with the natural product 8-(2-isopentenyloxy)-4,7-dimethoxyfuro[2,3-*b*]quinoline (**6**) by TLC **6** and ^1H NMR.

(−)-4-[2-(Dimethylamino)ethyl]phenyl β-D-glucopyranoside (15): **15** was prepared from hordenine and tetraacetyl-α-D-glucopyranosyl bromide according to the method of Wieniawski.[10]

***cyclo*(L-Phe)$_2$ (11).** The L-phenylalanine cyclic dipeptide **11** was prepared in 70% yield from *t*-BOC-L-phenylalanine and L-phenylalanine methyl ester hydrochloride (US Biochemical Corp.) according to the procedure of Nitecki;[19] mp 302–304 °C (lit.[19] mp 308–310 °C).

***cyclo*(*N*-Me-L-Phe)$_2$ (12).** The *N*-methyl-L-phenylalanine cyclic dipeptide **12** was prepared in 77% yield as described by Radding and Goodman[20] from *cyclo*(L-Phe)$_2$ with NaOH and MeI in DMF; mp 147–150 °C (lit.[20] mp 150–151 °C); ^1H NMR ($CDCl_3$, 60 MHz) δ 2.20 (m, 1 H), 2.75 (s, 3 H), 2.83 (m, 1 H), 4.03 (m, 1 H), 6.93–7.40 (m, 5 H).

(+)-(2*S*,5*S*)-2,5-Dibenzyl-1,4-dimethylpiperazine (10). *cyclo*(*N*-Me-L-Phe)$_2$ (0.26 mmol) was dissolved in 10 mL of THF, and 0.77 mmol of $LiAlH_4$ was added. The mixture was kept at reflux for 12 h and then poured into 30 mL of water. The aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ solutions were washed with water, 10% $NaHCO_3$ solution, and saturated NaCl solution. The $CHCl_3$ was evaporated in vacuo, and the residue was purified by silica gel PLC (EtOAc) and recrystallized from EtOAc to yield 0.162 mmol of the crystalline solid **10**: mp 123–124.5 °C; silica gel TLC R_f 0.32 (EtOAc); $[\alpha]^{23}_D$ +118 (*c* 0.054, EtOH); ^1H NMR ($CDCl_3$, 360 MHz) δ 2.25 (dd, *J* = 3 Hz, *J* = 11 Hz, 1 H), 2.36 (s, 3 H), 2.50 (dd, *J* = 10 Hz, *J* = 12 Hz, 1 H), 2.60 (m, 1 H), 2.76 (dd, *J* = 10 Hz, *J* = 13 Hz, 1 H), 2.98 (dd, *J* = 3 Hz, *J* = 13 Hz, 1 H), 7.18–7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 33.15, 42.73, 55.46, 62.75, 125.75, 128.15, 129.20, 139.88; IR (thin film, cm^{-1}) 2940, 2780, 1490, 1450, 1156, 732, 693; EIMS (*m/e*, %) 203 (100), 160 (6), 148 (4), 117 (4), 111 (7), 91 (11), 70 (80), 42 (15); CIMS-NH_3 (*m/e*, %) 295 (100). Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.63; H, 8.85; N, 9.52.

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