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Synthesis of Piperamides and New Analogues from Natural Safrole

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SYNTHESIS OF PIPERAMIDES AND NEW ANALOGUES FROM NATURAL SAFROLE.[a)]

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ABSTRACT: Species of the *Piper* genus are amply known for their biological activities. This paper describes a new synthetic route for the preparation of piperamides and analogues, using as an efficient precursor, the Brazilian natural product safrole (1). The amides (6a-c) were obtained in 25-32% overall yield.

The species of the *Piper* genus are widely used in folk medicine and among relevant biological activities reported for this genus can be emphasized the antitumor properties of some species[1]. In a previous work, we described the isolation of amides obtained from *Piper tuberculatum* Jacq. (Piperaceae) and their

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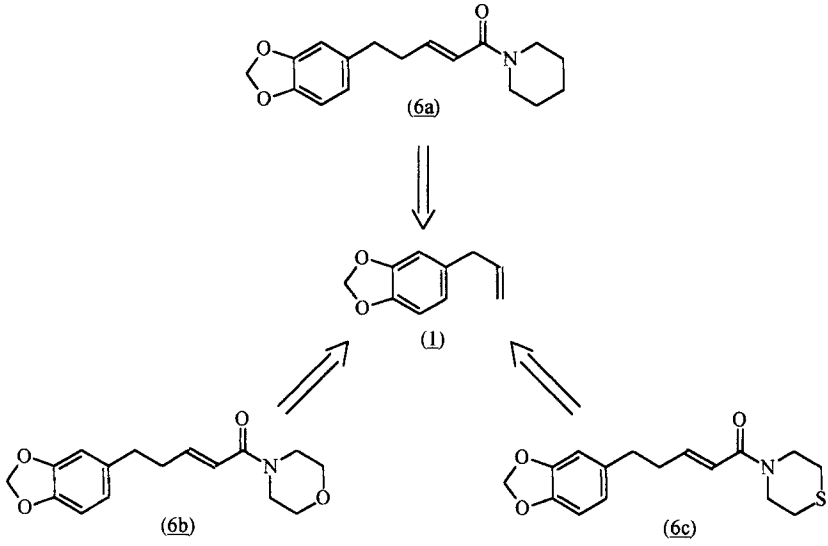
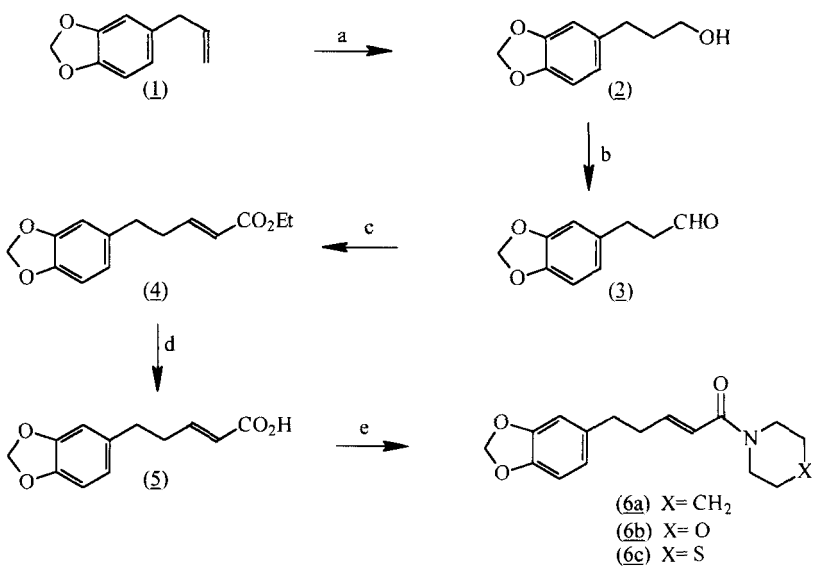
[a)] This paper represents the contribution # 31 from LASSBio.

hypotensive activity[2,3]. The synthesis and transformations of amides of *Piper* species have been described recently by other research groups[4,5]. As part of an ongoing research program about synthesis and biological evaluation of natural products, we report herein the synthesis of *N*-(4'-dihydro)-piperoylpiperidine (6a) and two analogues (6b-c), using safrole (1) as starting material (Scheme 1), a Brazilian natural product isolated from *Ocotea pretiosa*.



SCHEME 1

The synthesis of the amides (6a-c) was carried out using a common general protocol (Scheme 2). The safrole (1) was submitted to regioselective hydroboration-oxidation sequence, by treatment with diborane[6] followed oxidative cleavage of trialkylborane intermediate, furnishing the primary alcohol (2) in 79%

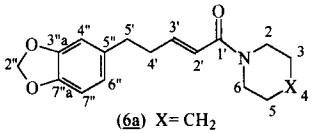


a) 1- 1 *M* BF_3.THF, rt, 1 h, 2- 30% H_2O_2, aqueous NaOH, reflux, 12 h (79%); b) PCC, CH_2Cl_2, rt, 1 h (70%); c) triethylphosphonoacetate, KH, DME, -78 °C, 1 h (78%); d)1 *N* aqueous LiOH, THF, rt, 4 h (94%); e) 1- $SOCl_2$, reflux, 1 h, 2- respective amine, CH_2Cl_2, rt, 30 min. (68-88%).

SCHEME 2

yield. Treatment of the primary alcohol (2) with pyridinium chlorochromate[7], in methylene chloride furnished, as the only product, in 70% yield, the corresponding aldehyde (3). The compound (4) was prepared from (3) by using the Horner-Wadsworth-Emmons modification of the Wittig reaction[8], with potassium salt of triethylphosphonoacetate in DME at -78 °C. The olefination product (4) was isolated in 78% yield as an only diastereomer with (*E*)-configuration at double bond level, which showed, in the ^{1}H NMR spectrum, a characteristic ABX pattern

TABLE 1: ^{1}H Nuclear magnetic resonance data at 200 MHz of the compounds (6a-c)[a].



(6a) X= CH_2
(6b) X= O
(6c) X= S

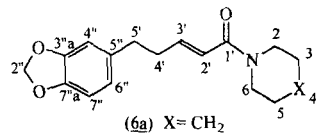
	δ (ppm) of compound		
H	**6a**	**6b**	**6c**
2	3.42 (2H, br s)	3.45 (2H, br s)	3.75 (br s)
3	1.45-1.70 (2H, m)	3.65 (2H, br s)	3.89 (br s)
4	1.45-1.70 (2H, m)	-	-
5	1.45-1.70 (2H, m)	3.65 (2H, br s)	3.89 (br s)
6	3.60 (2H, br s)	3.45 (2H, br s)	3.75 (br s)
		Common Chemical Shifts	
2'		6.20 (1H, dt, J = 15.1; 1.4 Hz)	
3'		6.80 (1H, dt, J = 15.1; 6.8 Hz)	
4'		2.50 (2H, dq, J = 7.9; 1.3 Hz)	
5'		2.70 (2H, t, J = 7.9 Hz)	
2''		5.91 (2H, s)	
4''		6.70 (1H, d, J = 1.3 Hz)	
6''		6.60 (1H, dd, J = 7.8; 1.7 Hz)	
7''		6.70 (1H, d, J = 7.8 Hz)	

[a] *ca.* 15 mg of the compound (6a-c) in 0.7 mL of $CDCl_3$.

centered at δ 5.82 and 6.97 (J =15.6 and 1.6 Hz). Next, the mild hydrolysis of the α,β-unsaturated ester (4) by treatment with an aqueous 1 *N* LiOH solution in THF[9] furnished the acid (5), as a solid (m.p. 102-104 °C), in 94% yield.

Finally, the synthesis of the desired amides was completed by treatment of (5) with thionyl chloride[10], and subsequent addition of the respective amine in dry CH_2Cl_2 , furnishing amides (6a-c) in 68%, 88% and 80%, respectively. The target compounds (6a-c) were full spectroscopically characterized by ^{1}H and ^{13}C NMR, as illustrated in the Tables 1 and 2.

TABLE 2: ^{13}C Nuclear magnetic resonance shifts at 50 MHz of the compounds (6a-c)[a].



(6a) X= CH_2
(6b) X= O
(6c) X= S

	δ (ppm) of compound		
C	**6a**	**6b**	**6c**
2	42.7	42.0	44.4
3	26.3	66.6	27.3
4	24.3	-	-
5	26.3	66.6	28.0
6	46.7	46.0	48.4
1'	165.2	165.4	165.6
2'	121.1	121.0	121.0
3'	143.7	145.2	145.0
4'	34.2	34.3	34.1
5'	34.2	34.1	34.1
2''	100.5	100.6	100.5
3''a	147.2	147.4	147.4
4''	107.8	108.0	108.0
5''	134.6	134.6	134.4
6''	120.9	120.3	120.8
7''	108.5	108.6	108.6
7''a	145.4	145.6	145.6

[a] *ca.* 30 mg of the compound (6a-c) in 0.7 mL of $CDCl_3$.

In conclusion, the synthetic methodology employed in this work, using safrole (1) as the starting material, represents an useful route to access the desired piperamide (6a) and two new analogues (6b-c). These compounds have been submitted to bioassays and preliminary results indicated important hypotensive effects, using both *in vivo* and *in vitro* methodologies[11].

Experimental Section.

^{1}H and ^{13}C NMR spectra were determined in deuterochloroform containing *ca.* 1% tetramethylsilane as an internal standard with a Brucker AC 200 spectrometer at 200 MHz and 50 MHz, respectively. Mass spectra (MS) were obtained by an electron impact (70 eV) with a GC/VG Micromass 12 spectrometer. The infrared (IR) spectra were obtained with a Philips PYE UNICAM SP3-100 spectrophotometer, using neat films on NaCl plates.

The progress of all reactions was monitored by tlc which was performed on 2.0 X 6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck). For column chromatography Merck silica gel (70-230 mesh) was used. Solvents used in the reactions were generally redistilled prior use. The usual "work-up" means that the organic extracts prior to concentration, under reduced pressure (80 mmHg), were dried over anhydrous sodium sulfate and filtered.

Procedure for the obtaining of the safrole (1).

The Sassafraz oil, obtained from a Brazilian plant (*Ocotea pretiosa*), was distilled under reduced pressure yielding safrole (1) as a pale yellow oil, in 89% yield.

3-(3',4'-methylenedioxyphenyl)-propan-1-ol (2)[6].

A solution of safrole (1) (5 g; 31 mmol) in 20 mL of dry THF maintained at 0 °C was treated with 55 mL (*ca.* 1 mmol) of a 1 *M* solution of B_2H_6 in dry THF.

The resulting mixture was stirred at 0 °C for 2 h. Then, methanol was added dropwise until no further gas was evolved, and 15 mL of 10% aqueous NaOH solution (1 mmol) and 15 mL of 30% aqueous H_2O_2 solution were added at 0 °C. The suspension formed was maintained at 60 °C for 12 h. After cooling, the reaction mixture was partitioned between diethyl ether (30 mL) and water (15 mL), followed by separation of the organic phase. The aqueous layer was further extracted with diethyl ether (3 X 15 mL) and the organic extracts were combined, treated with 15 mL of 10% aqueous HCl solution, dried and evaporated to give 3.9 g (69%) of the primary alcohol derivative (2) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82 (quintet, J = 11 Hz, 2H, Ar-CH_2-$C\underline{H}_2$-CH_2OH), 2.31 (br s, 1H, OH), 2.62 (t, J = 11 Hz, 2H, Ar-$C\underline{H}_2$-CH_2-CH_2OH), 3.62 (t, J = 11 Hz, 2H, Ar-CH_2-CH_2-$C\underline{H}_2OH$), 5.9 (s, 2H, $OC\underline{H}_2O$), 6.65 (m, 3H, Ar-$\underline{H}$); MS *m/z* (%): M^+ 180 (42), 149 (100), 121 (16).

3-(3',4'-methylenedioxyphenyl)-propan-1-al (3)[7].

To a suspension of 0.97 g (4.5 mmol) of pyridinium chlorochromate in 60 mL of dry CH_2Cl_2, was added a solution of the alcohol (2) (0.5 g; 3 mmol) in 10 mL of CH_2Cl_2 maintaining the reaction mixture under magnetic stirring. After 1 h, 30 mL of diethyl ether was added and the supernatant decanted from the black gum. The insoluble residue was washed throughly 3 times with 50 mL portions of anhydrous CH_2Cl_2 whereupon it became a black granulous solid. The combined organic solution was passed through a florisil column eluted with a mixture of *n*-hexane:ethyl acetate (95:5 to 80:20) and submitted at usual work-up to give 0.37 g

(70%) of the aldehyde (3) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.75 (t, *J* = 8 Hz, 2H, $ArCH_2C\underline{H_2}CHO$), 2.85 (t, *J* = 8 Hz, 2H, $ArC\underline{H_2}CH_2CHO$), 5.9 (s, 2H, $OC\underline{H_2}O$), 6.7 (m, 3H, Ar-H), 9.8 (s, 1H, CHO); MS *m/z* (%): M^+ 178 (49), 150 (12), 135 (100), 77 (19).

Ethyl (*E*)-3-(3',4'-methylenedioxyphenyl)-2-penten-1-oate (4)[8].

To a mixture of potassium triethylphosphonoacetate in DME [prepared from 0.132 g of potassium hydride (30% dispersion in mineral oil, 1.1 mmol) and 0.21 mL (1.04 mmol) of triethylphosphonoacetate in 5 mL of dry DME stirred under nitrogen at room temperature for 1 h] at -78 °C was added 0.15 g (0.8 mmol) of aldehyde (3) in 5 mL of dry DME. After stirring for 1 h at -78 °C and 1 h at 25-30 °C the temperature of reaction mixture was cooled to 0 °C and added dropwise *ca.* 1 mL of acetic acid. The solvent was evaporated and the resulting residue was diluted with water (20 mL) and extracted with methylene chloride (3 X 30 mL). The organic extracts were dried, evaporated and the resulting brownish oil was chromatographed on silica gel with a mixture of *n*-hexane:ethyl acetate (98:2 to 90:10) to furnish 0.154 g (78%) of α,β-unsaturated ester (4), as a brownish oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 6.8 Hz, 3H, $C\underline{H_3}$), 2.43 (q, *J* = 8 Hz, 2H, H-4), 2.64 (t, *J* = 8 Hz, 2H, H-5), 4.18 (q, *J* = 6.8 Hz, 2H, $ROC\underline{H_2}CH_3$), 5.82 (dt, *J* = 15.6 Hz; 1.6 Hz, 1H, H-2'), 5.91 (s, $OC\underline{H_2}O$), 6.59 (dd, *J* = 8.7; 1.7 Hz, 1H, H-6'), 6.66 (d, *J* = 1.7 Hz, 1H, H-4'), 6.72 (d, *J* = 8.7 Hz, 1H, H-7'), 6.97 (dt, *J* = 15.6; 1.6 Hz, 1H, H-3'); MS *m/z* (%): M^+ 248 (10), 203 (4), 148 (2), 135 (100).

3-(3',4'-methylenedioxyphenyl)-2-penten-1-oic acid (5)[9].

To a solution of 0.13 g (0.52 mmol) of the α,β-unsaturated ester (4) in 20 mL of THF were added 10 mL of 1 *N* aqueous LiOH solution. The resulting mixture was stirred at room temperature for 4 h, then neutralized with 1 *N* aqueous HCl solution (*ca.* 4 mL) until pH 4 and extracted with diethyl ether (2 X 15 mL). The organic extracts were jointed and submitted to usual work-up to give 0.108 g (94%) of the respective acid derivative (5) as a light brownish solid, m.p. 102-104 °C; MS *m/z* (%): M^+ 220 (17), 135 (100), 77 (11).

General Procedure for the Preparation of the Amides (6a-c)[10].

A solution of 0.148 g (0.7 mmol) of the acid (5) in 5 mL (70 mmol) of freshly distilled thionyl chloride was vigorously stirred under reflux for 1 h. After this time, the solvent was carefully evaporated at reduced pressure and a solution of 2.8 mmol of the respective amine in 8 mL of dry methylene chloride was added. The reaction mixture was stirred for 2 h at room temperature, then poured in 30 mL of water and extracted with methylene chloride (3 x 30 mL). The organic layers were jointed and submitted to usual work-up to give the respective amide derivative (6a-c) as described bellow.

***N*-(4'-dihydro)-piperoylpiperidine (6a).**

This compound was prepared from acid (5), in 68% yield, as a yellow oil; IR (film): ν C-H 2960 and 2880, ν C=O 1640, ν C-O 1260 and 1050 cm^{-1}; MS *m/z* (%):M^+ 287 (13), 202 (4), 174 (6), 135 (100).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.12; H, 7.40; N, 4.91.

***N*-(4'-dihydro)-piperoylmorpholine (6b).**

This compound was prepared from acid (5), in 88% yield, as a yellow oil; IR (film): ν C-H 2940 and 2880, ν C=O 160, ν C-O 1255 and 1050; MS *m/z* (%):M$^+$ 289 (16), 202 (5), 174 (7), 135 (100).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.5; H, 6.67; N, 4.89.

***N*-(4'-dihydro)-piperoylthiomorpholine (6c).**

This compound was prepared from acid (5), in 80% yield, as a yellow oil; IR (film): ν C-H 2920 and 2790, ν C=O 1620, ν C-O 1255 and 1040; MS *m/z* (%):M$^+$ 305 (14), 202 (5), 135 (100), 115 (2), 103 (10).

Anal. Calcd. for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59. Found: C, 62.97; H, 6.31; N, 4.55.

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