

Article

Synthesis of Neoflavonoids: 4-(4'-methoxyphenyl)- 3,4-dihydrocoumarins

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Os neoflavonóides 7-hidroxi-5-metil-4-(4'-metoxifenil)-3,4-diidrocoumarina (**1**), 5-hidroxi-7-metil-4-(4'-metoxifenil)-3,4-diidrocoumarina (**2**), 5-metil-7-O-cumaroil-4-(4'-metoxifenil)-3,4-diidrocoumarina (**3**), 5-hidroxi-4-(4'-metoxifenil)- α -pirano-(6'',5'':7,8)-3,4-diidrocoumarina (**7**) e 7-pentadecil-4-(4'-metoxifenil)-3,4-diidrocoumarina (**8**) foram sintetizados por condensação, catalisada pelo tricloreto de alumínio, entre o cloreto do ácido 4-metoxicinâmico com orcinol, 5,7-dihidroxicoumarina e cardanol hidrogenado. Os produtos das reações foram caracterizados com base nos dados espectrais de RMN ¹H e ¹³C, usando-se principalmente a técnica de espectroscopia nOe diferencial.

The neoflavonoids 7-hydroxy-5-methyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (**1**), 5-hydroxy-7-methyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (**2**), 5-methyl-7-O-cumaroyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (**3**), 5-hydroxy-4-(4'-methoxyphenyl)- α -pirano-(6'',5'':7,8)-3,4-dihydrocoumarin (**7**), and 7-pentadecyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (**8**) were synthesized via the AlCl₃-catalyzed condensation of 4-methoxycinnamic acid chloride with orcinol, 5,7-dihydroxycoumarin and hydrogenated cardanol. The compounds were characterized on the basis of their ¹H- and ¹³C-NMR spectroscopic properties, including nOe difference spectroscopy.

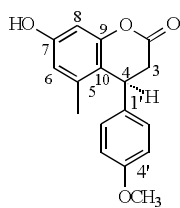
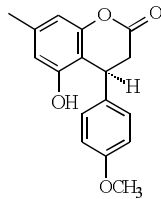
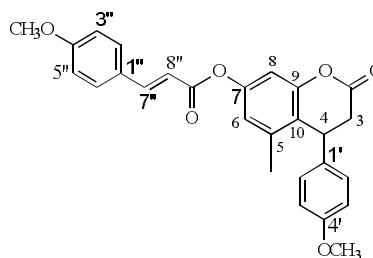
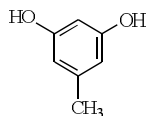
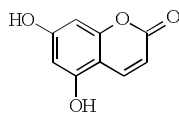
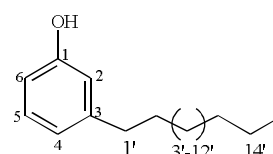
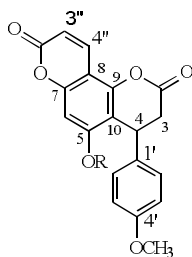
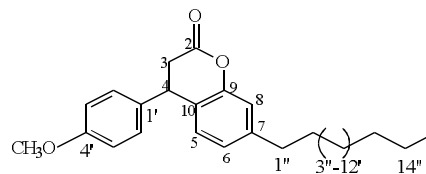
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Introduction

Neoflavonoids¹ include the important derivatives 3,4-dihydro-4-aryl-coumarins. Some of these display pharmacological properties, such as those of bactericide², molluscicide³, and insecticide⁴. The 4-aryl-3,4-dihydro coumarins have mainly been prepared by two methods: Pechmann condensation of an acetophenone and benzoylacetic acid (ArCOCH₂COOH)^{3,5}, and β -addition of a phenolic compound to a cinnamic acid⁶.

The condensation of cinnamic acids with phenols to yield 4-phenyl- and 4-aryl-dihydrocoumarins is well known, and has been reported by Simpson and Stephen⁶, who pointed out that good yields are generally obtained when the reaction between cinnamic acid and phenols is carried out by boiling with concentrated hydrochloric acid. Krajnak *et al.*⁷ found that 72% vv sulfuric acid at 160 °C was very effective for condensing cinnamic acid with p-cresol and p-methoxy-phenol. The condensation of phenols with cinnamic acid in the presence of polyphosphoric

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**1****2****3**Orcinol **4**5,7-dihydroxycoumarin **5**Hydrogenated cardanol **6**
7 R=H
7a R=Me
7b R=Ac
**8**

acid led to the formation of chalcones and flavanones, and with 4-methoxycinnamic acid the products were 4-(4-methoxyphenyl)-3,4-dihydrocoumarins and 7-methoxycoumarin which was formed through an intramolecular conversion of 4-methoxycinnamic acid⁸.

This paper reports the synthesis of new 4-(4-methoxyphenyl)-3,4-dihydrocoumarins via the condensation of 4-methoxycinnamic acid with natural and synthetic phenols in the presence of aluminium trichloride.

Results and Discussion

Some 4-(4-methoxyphenyl)-3,4-dihydrocoumarins were synthesized by β -addition of different phenols with 4-methoxycinnamic acid under milder conditions than those earlier reported. Aluminium trichloride was added to the phenol dissolved in carbon disulfide, followed by the addition of 4-methoxycinnamic acid chloride at room temperature. 4-methoxycinnamic acid was prepared by the reaction of anisaldehyde and malonic acid in the presence of pyridine⁹. The corresponding 4-methoxycinnamic acid chloride was obtained using oxalyl chloride dissolved in to-

luene¹⁰. The following phenols were used: orcinol (**4**), 5,7-dihydroxycoumarin (**5**), and hydrogenated cardanol (**6**, 3-pentadecylphenol).

The condensation of orcinol (**4**) with 4-methoxycinnamic acid produced a mixture of two constitutional isomeric neoflavonoids: 7-hydroxy-5-methyl-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (**1**) and 5-hydroxy-7-methyl-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (**2**), which were chromatographically separated. A third compound was identified as 7-O-(4'-methoxycinnamoyl)-5-methyl-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (**3**). Table 1 summarizes ¹H and ¹³C-NMR spectral data of the three compounds (**1-3**). The difference in the chemical shifts of the carbon atoms of the methyl group at C-5 of (**1**) (δ_c 18.75) and at C-7 of **2** (δ_c 21.27) revealed the upfield shift produced by the γ -effect ($\Delta\delta_c = 18.75$ (**1**) - 21.27 (**2**) = -2.52 ppm) of carbon C-4 in (**1**). An analogous γ -effect ($\Delta\delta_c = 18.86$ (**3**) - 21.27 (**2**) = -2.41 ppm) was observed in the methyl carbon at C-5 of (**3**) (Table 1). The minor chemical shift of the carbon C-4 (δ_c 34.21) in (**2**), when compared to the corresponding values of **1** (δ_c 36.64) and

(3) (δ_c 37.12), was used to confirm this deduction, since these results are in accordance with the major γ -effect of a hydroxy function in comparison with a methyl group¹¹ (Table 1). Additional confirmation was obtained by homonuclear nOe difference spectra ($^1H^1H$ -nOe)^{11,12}, since only the irradiation of the H-4 signal caused an enhancement effect (nOe = 8%) in the methyl group signal (δ_H 2.07, s, Me-5) for compound (1).

5,7-Dihydroxycoumarin (5) was prepared by the reaction of phloroglucinol and ethyl propiolate ($HC\equiv CCOOCH_2CH_3$) in the presence of zinc chloride¹³.

Ethyl propiolate was synthesized using propiolic acid and dry ethanol in the presence of sulfuric acid¹⁴. The reaction of the coumarin 5 with 4-methoxycinnamic acid chloride led to the formation of compound 7. The comparison of the NMR spectral analysis of 7 with the corresponding spectroscopic data of its methylated (7a) and acetylated (7b) derivatives (Table 2) allowed the definition of its chemical structure as 5-hydroxy-4-(4'-methoxyphenyl)- α -pirano-(6'',5'':7,8)-3,4-dihydrocoumarin. The presence of the hydroxyl group at C-5 of 7 was deduced by downfield shifts observed for the signals of H-6 [$\Delta\delta_H$ = 6.97 (7b) -

Table 1. 1H (200 MHz) and ^{13}C (50 MHz) NMR spectral data for compounds 1, 2 and 3 [$CDCl_3$ as solvent, TMS as internal standard, chemical shifts in δ (ppm), and coupling constants (J) in Hertz]*.

	1		2		3	
	δ_c	δ_H	δ_c	δ_H		
2	168.91	-	167.82	-	166.98	
3	38.01	3.02 (dd, J = 15.1;5.4) 2.99 (dd, J = 15.1;2.8)	37.23	2.97 (d, J=4.6)	37.64	3.1-2.9 (m)
4	36.64	4.27 (dd, J = 5.4;2.8)	34.21	4.49 (t, J=4.6)	37.12	4.33 (dd, J = 2.2 and 6.3)
5	137.98	-	152.72	-	137.91	-
6	113.94	6.52 (d, J = 2.2)	110.17	6.40 (br s)	119.62	6.43 (s)
7	155.93	-	139.67	-	150.35	-
8	102.04	6.59 (d, J = 2.2)	112.40	6.55 (br s)	108.75	6.51 (s)
9	152.41	-	152.55	-	152.33	-
10	115.08	-	109.60	-	120.94	-
1'	132.40	-	132.78	-	131.68	-
2', 6'	127.85	6.93 (d, J = 8.7)	127.88	7.04 (d, J = 8.7)	127.95	6.96 (d, J = 8.3)
3', 5'	114.37	6.77 (d, J = 8.7)	114.43	6.78 (d, J = 8.7)	114.39	6.79 (d, J = 8.3)
4'	158.60	-	158.80	-	158.81	-
Me-5	18.75	2.07(s)	-	-	18.86	2.17 (s)
Me-7	-	-	21.27	2.28 (s)	-	-
MeO-4'	55.18	3.71(s)	55.25	3.73 (s)	55.17	3.73 (s)
HO-7	-	6.87(s)	-	-	-	-
HO-5	-	-	-	5.16(s)	-	-
1''	-	-	-	-	126.65	-
2'', 6''	-	-	-	-	130.07	7.52 (d, J = 8.6)
3'', 5''	-	-	-	-	114.39	6.92 (d, J = 8.6)
4''	-	-	-	-	161.78	-
7''	-	-	-	-	146.73	7.81 (d, =15.9)
8''	-	-	-	-	114.04	6.47 (d, =15.9)
9''	-	-	-	-	165.45	-
MeO-4''	-	-	-	-	55.35	3.83 (s)

*Multiplicity of the carbon-13 signals was deduced by comparison with the PND- and DEPT - ^{13}C -NMR spectra.

Table 2. ^{13}C (50 MHz) NMR spectral data for compounds **7** and derivatives **7a** and **7b** [DMSO* and CDCl_3 as solvent, TMS as internal standard, chemical shifts in δ (ppm), and coupling constants (J) in Hertz]*.

C	7*		7a		7b	
	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}
2	166.96	-	165.97	-	166.84	-
3	36.96	3.31 (m) 2.90 (br dd, J = 14.3)	36.76	3.02 (m)	35.68	3.06 (d, J = 5.0)
4	32.82	4.66 (br dd, J = 5.4)	33.95	4.90 (m)	34.32	4.41 (t, J = 5.0)
5	155.13	-	155.55	-	153.03	-
6	98.85	6.56 (s)	95.25	6.62 (s)	106.47	6.97 (s)
7	151.95	-	148.08	-	147.30	-
8	104.08	-	102.95	-	106.14	-
9	154.58	-	158.90	-	158.15	-
10	105.60	-	110.28	-	113.11	-
1'	132.92	-	132.19	-	130.25	-
2', 6'	127.90	7.00 (d, J = 8.6)	127.66	6.98 (d, J = 8.8)	126.53	6.93 (d, J = 8.8)
3', 5'	114.45	6.85 (d, J = 8.6)	114.40	6.79 (d, J = 8.8)	113.64	6.44 (d, J = 9.8)
4'	158.45	-	159.34	-	158.68	-
2''	159.95	-	160.57	-	164.04	-
3''	112.02	6.25 (d, J = 9.7)	113.08	6.29 (d, J = 9.7)	115.12	6.44 (d, J = 9.8)
4''	139.44	8.08 (d, J = 9.7)	137.45	8.04 (d, J = 9.7)	135.72	8.09 (d, J = 9.8)
MeO-4'	55.18	3.68 (s)	55.23	3.75 (s)	54.24	3.74 (s)
MeO-5	-	-	56.42	3.85 (s)	-	-
MeCO	-	-	-	-	19.66	2.17 (s)

6.62 (**7a**) = 0.35 ppm], C-6 [$\Delta\delta_{\text{C}}$ = 106.47 (**7b**) - 95.25 (**7a**) = 11.22 ppm], C-10 [$\Delta\delta_{\text{C}}$ = 113.11 (**7b**) - 110.28 (**7a**) = 2.83 ppm] and C-8 [$\Delta\delta_{\text{C}}$ = 106.14 (**7b**) - 102.95 (**7a**) = 3.19 ppm] in the comparative analysis of the ^1H and ^{13}C NMR of the derivatives **7a** and **7b** in combination with the homonuclear $^1\text{H}\{^1\text{H}\}$ -nOe difference spectra performed with specific resonance of the methoxyl group at C-5 (δ_{H} 3.85) of **7a**, which induced a signal enhancement of H-6 (δ_{H} 6.62, nOe = 11%).

Cardanol is a mixture of 3-pentadecylphenols, differing in number and position of double bonds in the side chain¹⁵. This mixture is obtained from the cashew nut shell liquid (CNSL) of *Anacardium occidentale*. CNSL is a by-product of the cashew nut processing industries. A similar condensation of hydrogenated cardanol (**6**) with 4-methoxycinnamic acid chloride afforded 7-pentadecyl-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (**8**), which was characterized by the ^1H and ^{13}C NMR spectra described in Table 3. The compound 7-hydroxy-5-methyl-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (**1**) displayed *in vitro* activity against *Tripanosoma*

cruzi, and the corresponding cinnamic ester (**3**) did not show any activity against this microorganism¹⁶.

Experimental

General experimental procedures - Melting points were measured on a Kofler Hotstage and are uncorrected. ^1H - and ^{13}C -NMR spectra were recorded on a Bruker WH-200 Mhz.

Synthesis of neoflavonoids 7-hydroxy-5-methyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (1) and 5-Hydroxy-7-methyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (2)

A mixture of orcinol (533 mg, 4.3 mmol), aluminium trichloride (667 mg, 5.0 mmol) and 4-methoxycinnamic acid chloride (786 mg, 4.0 mmol) in carbon disulfide (15 mL) was stirred for three days at room temperature. The product was purified by silica gel column chromatography. The fraction eluted with hexane:chloroform (20:80) afforded an amorphous solid (**2**, 15 mg, 0.67 %. m.p.: 148.8-149.7 °C; for NMR spectral data see Table 1). The

Table 3. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectral data of cardanol (**6**) and the acetyl derivative (**8**) [CDCl_3 as solvent, TMS as internal standard, chemical shifts in δ (ppm), and coupling constants (J) in Hertz]*.

8			Hydrogenated cardanol 6		
C	δ_c	δ_H , J(Hz)	C	δ_c	δ_H , J(Hz)
2	167.99		1	155.19	-
3	37.32	-	2	115.39	6.70 (s)
4	39.60		3	144.41	-
5	127.89	4.24 (dd, J = 3.5,5.3)	4	121.03	6.78 (d, J = 7.5)
6	124.64	6.92-6.81 (m)	5	129.37	7.19 (t, J = 7.5)
7	144.10	-	6	112.56	6.48 (d, J = 7.5)
8	116.71	6.92-6.81 (m)	-	-	-
9	151.49	-	-	-	-
10	123.20	-	-	-	-
1'	132.47	-	-	-	-
2', 6'	128.56	7.06 (d, J = 8.6)	-	-	-
3', 5'	114.37	6.94 (d, J = 8.6)	-	-	-
4'	158.87	-	-	-	-
OMe	55.22	3.78 (s)	-	-	-
1"	35.43	2.58 (t, J = 8.0)	1	35.83	2.57 (t, J = 8.0)
2"	31.88	1.58 (m)	2	31.30	1.58 (m)
3"-12"	29.33-29.64	1.24 (br s)	3- 12	29.54	1.24 (br s)
13"	31.88	1.24 (br s)	13	31.94	1.24 (br s)
14"	22.65	1.24 (br s)	14	22.70	1.24 (br s)
15	14.09	0.86 (t, J = 6.4)	15	14.11	0.93(t, J=6.7)

*Type of carbon atoms deduced by comparison with PND and DEPT- ^{13}C -NMR. Homonuclear $^1\text{H}\times^1\text{H}$ -COSY 2D NMR. Chemical shifts and coupling constants (J) of the hydrogen atoms were obtained from the ^1H -NMR spectrum.

fraction eluted with chloroform:ethyl acetate 90:10 furnished a colorless solid (**1**, 416 mg, 18.17 %, m.p.: 135.4-136.4 °C; for NMR spectral data see Table 1).

5-Methyl-7-O-coumaroyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (**3**)

A solution of orcinol (711 mg, 5.73 mmol), aluminium trichloride (667 mg, 5.0 mmol), and 4-methoxycinnamic acid chloride (786 mg, 4.0 mmol) in carbon disulfide (15 mL) was stirred for one hour at room temperature. Ice was added to the reaction mixture, and the precipitate formed was filtered and purified by silica gel column chromatography. A colorless solid was obtained. (**3**, 73 mg, 2.87 %, m.p.: 121.1-126.4 °C: for NMR spectral data see Table 1)

Synthesis of 5-hydroxy-4-(4'-methoxyphenyl)- α -pirano-(6'',5'':7,8)-3,4-dihydrocoumarin (**7**).

A mixture of 5,7-dihydroxycoumarin (**5**, 400 mg, 5.0 mmol) and aluminium trichloride (1823 mg, 13.7 mmol) was added to freshly prepared 4-methoxycinnamic

acid chloride dissolved in nitrobenzene (30 mL). The reaction was stirred for three days at room temperature, then the reaction vessel was placed in an ice bath for one day. Ice was added to the reaction mixture, and a precipitate formed that was purified by silica gel column chromatography. The fraction eluted with chloroform:ethyl acetate (90:10) yielded a light yellow powder **7** (33 mg, 1.93 %, m.p.: 244.8-248.5 °C; for spectral data see Table 2).

Methylation of **7**

A solution of CH_2N_2 in diethyl ether was added to a solution of **7** (4.9 mg, 0.014 mmol) in diethyl ether, and the mixture was kept overnight. The residue obtained was chromatographed on silica gel. Upon concentration, the fraction eluted with chloroform-ethyl acetate (95:05), gave a colorless solid (**7a**, 4.9 mg, 95.8 %, m.p.: 228.4-229.6 °C).

Acetylation of **7**

The compound **7** (18 mg, 0.053 mmol) was acetylated (Ac_2O -py 4:1) at room temperature. The mixture was puri-

fied by silica gel column chromatography. The fraction eluted with chloroform furnished **7b** (8.5 mg, 42.50 %, m.p.: 180.1-181.5 °C).

Isolation of Cashew nut shell liquid (CNSL) components

Technical CNSL was furnished by Companhia Industrial Óleos Nordeste (CIONE) situated in Fortaleza-Ceará, Brazil.

Cashew nut shell liquid was distilled under vacuum after heating for 2 h at 130-200 °C (to complete decarboxilation and dehydration¹⁷), giving a pale yellow oil that darkens after a few days. This oil was submitted to column chromatography. Cardanol was obtained when the eluent was pure hexane and cardol.

3-Pentadecylphenol (**6**)

Cardanol (4 g) was dissolved in 10 mL of absolute ethanol, and 10% palladium on carbon (0.4 g) was added. The mixture was hydrogenated under pressure for three days and a solid material was obtained (4 g, 98 %, m.p.: 50-53 °C; for NMR spectral data see Table 3.)

7-Pentadecyl-4-(4'-methoxyphenyl)-3,4-dihydrocoumarin (**8**)

3-Pentadecylphenol (860 mg, 2.82 mmol) and aluminium trichloride (667 mg, 4.35 mmol) were added to freshly prepared 4-methoxycinnamic acid chloride [4-methoxycinnamic acid (726 mg, 4.07 mmol) and oxalyl chloride (2.23 g, 1.5 mL, 17.56 mmol) in carbon disulfide (10 mL)] and dissolved in nitrobenzene (15 mL). The reaction mixture was stirred for three days in an ice bath. After the usual work-up, a solid material was obtained and purified by silica gel column chromatography. The fraction eluted with hexane:chloroform 60:40 furnished a colorless solid **8** (111 mg, 8.47 % yield, m.p.: 86.7-87.1 °C; for spectral data see Table 3).

The compound 7-hydroxy-5-methyl-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (**1**) and the corresponding cinnamic ester (**3**) were tested against *Tripanosoma cruzi* at the Instituto de Ciências Biológicas de Minas Gerais, Brazil.

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