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4-ARYLCOUMARINS FROM *COUTAREA HEXANDRA**

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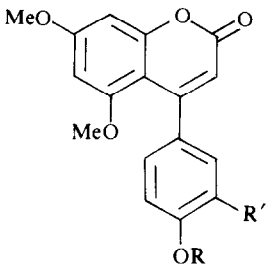
Key Word Index—*Coutarea hexandra*; Rubiaceae; neoflavonoids; 4-arylcoumarins.

Abstract—Four new 4-arylcoumarins have been isolated from *Coutarea hexandra* and their structures established as 5,7,4′-trimethoxy-4-phenylcoumarin, 4′-hydroxy-5,7-dimethoxy-4-phenylcoumarin, 3′-hydroxy-5,7-4′-trimethoxy-4-phenylcoumarin and 3′,4′-dihydroxy-5,7-dimethoxy-4-phenylcoumarin.

INTRODUCTION

Although coumarins have been extensively studied, only a few examples of natural coumarins with a substituted 4-phenyl ring are reported in the literature; from the Rubiaceae only exostemin [1] (**1** with an additional 8-hydroxyl) has been isolated so far. In the course of our research of pharmacologically active and insecticidal substances from Brazilian plants, we examined caulis of *Coutarea hexandra*. The plant, widespread in north-eastern Brazil and commonly known as 'quina-quina', is used in folk medicine as succedaneum of the true cinchona. An earlier examination [2] of the bark-extract of the plant had revealed the absence of alkaloids and the presence of an unidentified saponin.

Now, from a benzene extract of caulis of the plant, we have isolated four new 4-arylcoumarins, to which the structures **1**–**4**, were assigned on the basis of a combination of spectral data.



	R	R′
1	Me	H
2	H	H
3	Me	OH
4	H	OH
5	Me	OMe
6	H	OMe

RESULTS AND DISCUSSION

The four substances, $C_{18}H_{16}O_5$ (**1**), $C_{17}H_{14}O_5$ (**2**), $C_{18}H_{16}O_6$ (**3**) and $C_{17}H_{14}O_6$ (**4**) were inter-related by methylation: with diazomethane, **2** gave **1**, while **4** yielded a mixture of **3** and two other products, $C_{19}H_{18}O_6$ (**5**) and $C_{18}H_{18}O_6$ (**6**), not present in the extract.

All the compounds showed analogous UV [3] and IR spectra and a highly diagnostic resonance of the H-3 proton (*ca* δ 5.9) in the ^{1}H NMR spectra [4] which suggested a 4-phenylcoumarin skeleton. Mass spectral data supported the assignment; the fragmentation of **4** was coincident with that of the isomeric melanein (6,3′-dihydroxy-7,4′-dimethoxy-4-phenylcoumarin) [5], whereas those of the others are in agreement with the shift's rule (see Experimental). Common features in the ^{1}H NMR spectra are also two *meta*-coupled aromatic protons and at least two methoxy groups, one of which is noticeably shifted upfield (*ca* δ 3.40). The shielding effect was attributed to the 4-phenyl substituent [1] and, considering the sharp absorption at 1710 cm^{-1} [6], we assumed the compounds to be 5,7-dimethoxy-4-arylcoumarins. The ^{1}H NMR spectra (in $CDCl_3$ or CD_3COCD_3) were definitive in the cases of **1** and **2**—two doublets (2H each) *ortho*-coupled—for the substitution pattern of the 4-aryl group, but were not so for the other compounds, showing a complex set (3H) of peaks. Only when the solvent was substituted by C_5D_5N [7, 8] did a clear coupling pattern of the H-2′, H-5′ and H-6′ protons appear, which in particular allowed the distinction between the two isomers **3** and **6**. The acetyl derivatives, **2a** (R = COMe), **3a** (R′ = OCOMe), **4a** (R = COMe, R′ = OCOMe) and **6a** (R = COMe) were also prepared.

The influences of C_5D_5N and of acetylation on the 4-aryl protons resonances are reported and compared in Table 1. A small quantity of vanillin was also isolated from the extract; it should be noted that the coumarin, **6**, with the same 4-phenyl ring substitution pattern is absent in the mixture.

EXPERIMENTAL

Plant material. Caulis of *Coutarea hexandra* (Jacq.) Schum. were collected in north-eastern Brazil (Pacatuba, Fortaleza) and identified by José Elias de Paula (Universidade Federal de Brasilia).

Extraction and fractionation. Extraction with hot C_6H_6 of

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Table 1. ^{1}H NMR of 4-aryl group substitution pattern of coumarins **3**, **4** and **6** and their acetyl derivatives; δ-values, J in Hz

Compound	Solvent	H-2′ *d*, J = 2	H-6′ *dd*, J = 2 and 9	H-5′ *d*, J = 9
3	$CDCl_3$	6.90–6.60 (3H, complex)		
3	C_5D_5N	7.21	6.84	7.03
3a	$CDCl_3$	6.90	7.07	6.87
4	CD_3COCD_3	6.98–6.68 (3H, complex)		
4	C_5D_5N	6.96	7.23	7.28
4a	CD_3COCD_3	7.40–7.05 (3H, complex)		
6	$CDCl_3$	7.04–6.64 (3H, complex)		
6	C_5D_5N	7.00	6.78	7.20
6a	$CDCl_3$	6.72	6.68	6.89

ground material (6.5 kg) gave a residue of 29.5 g (4.5%), a portion of which (9.5 g) was passed through a column of Si gel with $CHCl_3$–MeOH mixtures. Extended CC and crystallization gave the pure 4-arylcoumarins in the reported amounts.

General. Mps were uncorr. Elemental analyses were in agreement with molecular formulae. ^{1}H NMR was at 60 MHz. MS were recorded by direct inlet at 70 eV.

5,7,4′-Trimethoxy-4-phenylcoumarin (**1**, 100 *mg*). $C_{18}H_{16}O_5$, mp 151–152° (EtOH); UV λ_{max}^{MeOH} nm (log ε): 250 (4.07), 325 (4.29); ^{1}H NMR ($CDCl_3$): δ7.20 (2H, *d*, J = 8.5 Hz, H-2′, H-6′), 6.87 (2H, *d*, J = 8.5 Hz, H-3′, H-5′), 6.50 (1H, *d*, J = 2.5 Hz, H-8), 6.22 (1H, *d*, J = 2.5 Hz, H-6), 5.96 (1H, *s*, H-3), 3.83 (6H, *s*, OMe-7, OMe-4′), 3.46 (3H, *s*, OMe-5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1610, 1595, 1510, 1158, 1111, 1052, 952, 872, 860, 830; MS *m/z* (rel. int.): 312 [M]$^+$ (80), 284 [M − CO]$^+$ (100), 269 [M − MeCO]$^+$ (37), 241 [M − 43 − CO]$^+$ (2).

4′-Hydroxy-5,7-dimethoxy-4-phenylcoumarin (**2**, 30 *mg*). $C_{17}H_{14}O_5$ mp 214–215° (MeOH); UV λ_{max}^{MeOH} nm (log ε): 256 (4.04), 324 (4.22); UV λ_{max}^{NaOMe} nm: 256, 368; ^{1}H NMR (CD_3COCD_3): δ8.50 (1H, *s*, exchangeable D_2O, OH-4′), 7.14 (2H, *d*, J = 8.5 Hz, H-2′, H-6′), 6.82 (2H, *d*, J = 8.5 Hz, H-3′, H-5′), 6.51 (1H, *d*, J = 2.5 Hz, H-8), 6.37 (1H, *d*, J = 2.5 Hz, H-6), 5.80 (1H, *s*, H-3), 3.91 (3H, *s*, OMe-7), 3.53 (3H, *s*, OMe-5); $\Delta\delta$ = $\delta C_5D_5N - \delta CD_3COCD_3$ = H-2′ + H-6′ (+0.19), H-3′ + H-5′ (+0.32), H-8 (+0.11), H-6 (+0.01), H-3 (+0.38) OMe-7 (−0.16), OMe-5 (−0.23); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1708, 1612, 1598, 1512, 1159, 1112, 1054, 952, 870, 860, 832; MS *m/z* (rel. int.): 298 [M]$^+$ (100), 270 [M − CO]$^+$ (82), 255 [M − MeCO]$^+$ (29), 227 [M − 43 − CO]$^+$ (15). Acetyl derivative (**2a**): $C_{19}H_{16}O_6$, mp 161–162° (Et_2O); ^{1}H NMR: δ 7.26 (2H, *d*, J = 8.5 Hz, H-2′, H-6′), 7.04 (2H, *d*, J = 8.5 Hz, H-3′, H-5′), 6.46 (1H, *d*, J = 2.5 Hz, H-8), 6.29 (1H, *d*, J = 2.5 Hz, H-6), 5.83 (1H, *s*, H-3), 3.86 (3H, *s*, OMe-7), 3.44 (3H, *s*, OMe-5), 2.26 (3H, *s*, COMe); Me derivative: methylation of **2** with CH_2N_2 gave **1**.

3′-Hydroxy-5,7,4′-trimethoxy-4-phenylcoumarin (**3**, 300 *mg*). $C_{18}H_{16}O_6$, mp 153–154° (EtOH); UV λ_{max}^{MeOH} nm (log ε): 252 (4.13), 329 (4.32); UV λ_{max}^{NaOMe} nm: 250, 288 sh, 329, 400 sh; ^{1}H NMR (4-aryl proton resonances are reported in Table 1) ($CDCl_3$): δ 5.92 (1H, *s*, H-3), 5.87 (1H, *s*, exchangeable D_2O, OH-3′), 3.86 and 3.78 (3H and 3H, *s* and *s*, OMe-7, OMe-4′), 3.43 (3H, *s*, OMe-5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3525, 1710, 1615, 1597, 1510, 1158, 1111, 1052, 945, 909, 859, 828; MS *m/z* (rel. int.): 328 [M]$^+$ (100), 300 [M − CO]$^+$ (51), 285 [M − MeCO]$^+$ (31), 257 [M − 43 − CO]$^+$ (17). Acetyl derivative (**3a**): $C_{20}H_{18}O_7$, mp 197–198° (Et_2O); ^{1}H NMR (4-aryl proton resonances are reported in Table 1) ($CDCl_3$: δ 6.42 (1H, *d*, J = 2.5 Hz, H-8), 6.14 (1H, *d*, J = 2.5 Hz, H-6), 5.92 (1H, *s*, H-3), 3.83 and 3.80 (3H and 3H, *s* and *s*, OMe-7, OMe-4′), 3.46 (3H, *s*, OMe-5), 2.27 (3H, *s*, COMe). Me derivative: methylation of **3** in MeOH with CH_2N_2 gave 5,7,3′,4′-tetramethoxy-4-phenylcoumarin (**5**): $C_{19}H_{18}O_6$, mp 169–170° ($CHCl_3$–MeOH); UV λ_{max}^{MeOH} nm (log ε): 248 (4.13), 328 (4.26); ^{1}H NMR ($CDCl_3$): δ 6.93–6.73 (3H, complex, H-2′, H-5′, H-6′), 6.51 (1H, *d*, J = 2.5 Hz, H-8), 6.25 (1H, *d*, J = 2.5 Hz, H-6), 6.00 (1H, *s*, H-3), 3.91 and 3.85 (3H and 6H, *s* and *s*, OMe-7, OMe-3′, OMe-4′), 3.48 (3H, *s*, OMe-5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1708, 1610, 1595, 1510, 1158, 1111, 1052, 944, 902, 855, 826; MS *m/z* (rel. int.): 342 [M]$^+$ (100), 314 [M − CO]$^+$ (40), 299 [M − MeCO]$^+$ (9), 271 [M − 43 − CO]$^+$ (2).

3′-4′-Dihydroxy-5,7-dimethoxy-4-phenylcoumarin (**4**, 350 *mg*). $C_{17}H_{14}O_6$, mp 211–212° (MeOH), UV λ_{max}^{MeOH} nm: 253, 285sh, 326, 438; ^{1}H NMR (4-aryl proton resonances are reported in Table 1) (CD_3COCD_3): δ 6.53 (1H, *d*, J = 2.5 Hz, H-8), 6.38 (1H, *d*, J = 2.5 Hz, H-6), 5.85 (1H, *s*, H-3), 3.92 (3H, *s*, OMe-7), 3.55 (3H, *s*, OMe-5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3540, 3260, 1707, 1611, 1595, 1513, 1158, 1111, 1052, 945, 910, 872, 858, 828; MS *m/z* (rel. int.): 314 [M]$^+$ (100), 286 [M − CO]$^+$ (98), 271 [M − MeCO]$^+$ (20), 243 [M − 43 − CO]$^+$ (4). Acetyl derivative (**4a**): $C_{19}H_{16}O_7$, mp 155–156° (Et_2O); ^{1}H NMR (4-aryl proton resonances are reported in Table 1) (CD_3COCD_3): δ 6.60 (1H, *d*, J = 2.5 Hz, H-8), 6.40 (1H, *d*, J = 2.5 Hz, H-6), 5.97 (1H, *s*, H-3), 3.93 (3H, *s*, OMe-7), 3.54 (3H, *s*, OMe-5), 2.30 and 2.27 (3H and 3H, *s* and *s*, 2 × COMe). Me derivatives: methylation of **4** in $CHCl_3$–Me_2CO with CH_2N_2 and work-up after 2 hr afforded a mixture of **3**, **5** and **6** in equal amounts. The products were separated on Si gel with hexane–EtOAc (3:1); 4′-hydroxy-5,7,3′-trimethoxy-4-phenylcoumarin (**6**): $C_{18}H_{16}O_6$, mp 173–174° (Et_2O); UV λ_{max}^{MeOH} nm (log ε): 251 (4.07), 329 (4.19); λ_{max}^{NaOMe} nm: 250, 331, 395; ^{1}H NMR (4-aryl proton resonances are reported in Table 1) ($CDCl_3$): δ 6.52 (1H, *d*, J = 2.5 Hz, H-8), 6.26 (1H, *d*, J = 2.5 Hz, H-6), 6.02 (1H, *s*, H-3), 3.88 and 3.86 (3H and 3H, *s* and *s*, OMe-7, OMe-7′), 3.36 (3H, *s*, OMe-5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3524, 1709, 1611, 1595, 1510, 1158, 1111, 1052, 943, 903, 855, 825; MS *m/z* (rel. int.): 328 [M]$^+$ (100), 300 [M − CO]$^+$ (66), 285 [M − MeCO]$^+$ (9) 257 [M − 43 − CO]$^+$ (3). Acetyl derivative (**6a**): $C_{20}H_{18}O_7$, mp 169–170° (Et_2O); ^{1}H NMR (4-aryl proton resonances are reported in Table 1) ($CDCl_3$): δ 6.52 (1H, *d*, J = 2.5 Hz, H-8), 6.22 (1H, *d*, J = 2.5 Hz, H-6), 6.05 (1H, *s*, H-3), 3.88 and 3.81 (3H and 3H, *s* and *s* OMe-7, OMe-3′), 3.48 (3H, *s*, OMe-5), 2.35 (3H, *s*, COMe).

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