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STUDIES IN THE THYMELAEACEAE, V. 2′-HYDROXYFLAVONE FROM *DAPHNOPSIS SELLOWIANA*: ISOLATION AND SYNTHESIS[1]

GÁBOR BLASKÓ,[2] LI XUN, and GEOFFREY A. CORDELL

Program for Collaborative Research in the Pharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612

ABSTRACT.—From the leaves of *Daphnopsis sellowiana* (Thymelaeaceae), 2′-hydroxyflavone [**1**], a rare natural product, has been isolated and characterized through its spectroscopic properties. Confirmation of the structure was achieved through total synthesis, which also afforded adequate material for complete ^{13}C-nmr analysis.

As part of our continuing studies of plants for new anticancer agents with some emphasis on the Thymelaeaceae (1-4), we have examined the cytotoxicity of several species of the genus *Daphnopsis*. Several members of this genus have been reported to have useful medicinal and practical properties, but there has been relatively little phytochemical work conducted. Thus, *Daphnopsis brasiliensis* Mart. et Zucc. has been reported to be a drastic purgative and useful in the treatment of psoriasis (5). Medicinal uses (5) have also been reported for *Daphnopsis schwartzii* Meisn., which, in the West Indies, is used as a diuretic, sialagogue, and stimulant (6). *Daphnopsis* species have been used as purgatives in South America (7), and *D. brasiliensis* is used for the manufacture of paper in Brazil (8).

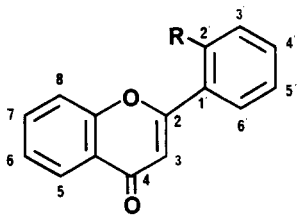
Daphnopsis racemosa Griseb., whose fibrous bark has been used for rope (9,10), is the only species to have been investigated heretofore phytochemically to yield a series of tigliane, daphnane, and 1α-alkyldaphnane esters (11,12). We report here our initial results of work on *Daphnopsis sellowiana* Taub. obtained from Brazil. Extracts of the plant displayed very good cytotoxic activity in the P-388 test system (13), and the principles responsible for this activity are presently under investigation. We report here on the isolation of a rare flavonoid from this plant and describe our attempts at its synthesis for the purposes of structure confirmation and ^{13}C-nmr assignment.

2′-Hydroxyflavone [**1**] was obtained as colorless needles crystallizing from EtOH. The ir spectrum indicated the presence of hydroxyl (ν max 3434 cm^{-1}), unsaturated carbonyl (ν max 1639 cm^{-1}), and *ortho* disubstituted aromatic (ν max 740 cm^{-1}) groups. From the mass spectrum, which showed a M^+ at *m/z* 238 analyzing from $C_{15}H_{10}O_3$, it appeared that the isolate was a simple flavone derivative, and the important fragment ion at *m/z* 121 indicated that the substituent group was located in ring B of the nucleus. The uv spectrum was shifted on the addition of NaOMe to afford a broad maximum at 406 nm, but no change was observed on the addition of NaOAc, NaOAc/H_3BO_3, $AlCl_3$, or $AlCl_3$/HCl to the uv spectrum. Consequently, hydroxyl group substitution at C-3, C-5, C-7, and C-4′ could be excluded.

The location of the hydroxyl group at C-2′ was readily apparent from the ^{1}H-nmr spectrum. Nine aromatic protons were observed in the region 6.98-8.18 ppm, including a singlet proton at 7.42 ppm for H-3. The remaining aromatic protons were examined through 2D-homonuclear correlation spectroscopy. As a result, the eight protons were identified as being part of two four-spin systems, and assignment could be made assuming that H-5 would be the most downfield proton. The hydroxyl group should therefore be located at C-2′. This compound, 2′-hydroxyflavone [**1**] was report-

[1]For the previous paper in the series, see Schun *et al.* (1).

[2]On leave from the Central Research Institute for Chemistry of the Hungarian Academy of Sciences, Budapest, Hungary.



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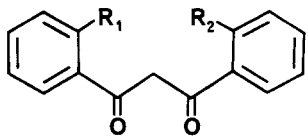
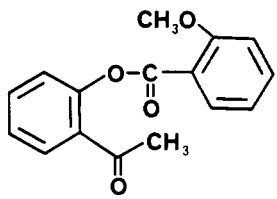


2 R_1=OMe, R_2=OMe
4 R_1=OH, R_2=OMe
6 R_1=OMe, R_2=H



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edly synthesized in 1912 (14) and subsequently isolated from the "flour" of *Primula florindae* F.K. Ward (15). At that time, structure determination was made through comparison with synthetic material, prepared by the published method, and ms. No ^{1}H-nmr spectral data were reported.

In order to confirm the structure of our isolate and to provide adequate material for unambiguous ^{1}H- and ^{13}C-nmr analysis, the earlier synthesis was repeated. Condensation of 2-methoxyacetophenone with 2-methoxy methyl benzoate using sodium, dispersed sodium, or NaH failed to produce the 1,3-diketone **2** (16).

In considering the Robinson approach (18), it was felt that the anhydride of 2-methoxybenzoic acid would form only with great difficulty. Consequently, we opted for the stepwise approach of an internal Claisen reaction to produce the desired intermediate 1,3-diketone. Thus, acylation of 2-hydroxyacetophenone with 2-methoxybenzoyl chloride in refluxing toluene in the presence of K_2CO_3 afforded **3** in 55% yield after chromatography. No partial internal Claisen reaction was observed (19). A substantially higher yield (92%) of crystallizable **3** resulted when the same reaction was conducted in pyridine/CH_2Cl_2 (20).

Two methods were then attempted for the internal Claisen rearrangement. With NaH in anhydrous toluene at 90° the desired 1,3-diketone **4** was produced in 50% yield, whereas with KOH in pyridine at 50° the yield of directly crystallizable **4** was 60%. The product displayed an intense color reaction with $FeCl_3$ and could be precipitated with $Cu(OAc)_2$ as its Cu^{2+} salt.

Because both 2′-methoxy- and 2′-hydroxyflavones (**5** and **1**, respectively) were desired synthetic targets, each was produced directly from **4**. Cyclization with ethanolic H_2SO_4 afforded **5** in 68% yield, whereas treatment of **4** with refluxing hydriodic acid gave **1** in 57% yield. The synthetic product was identical (mp, mmp, tlc, ir, uv, ^{1}H nmr, ^{13}C nmr, and ms) with the natural isolate.

We then chose to repeat the original Kostanecki-Tambor approach (17) for flavone synthesis involving the direct condensation of methyl 2-methoxybenzoate and acetophenone to afford **6**, which with refluxing HI afforded the basic flavone skeleton **7**.

With adequate material now available, attention focused on the ^{13}C-nmr spectroscopic properties. The ^{13}C-nmr spectrum of flavone [**7**] was initially determined by

Shoolery *et al.* (21), and using this as model, Wenkert and Gottlieb (22) derived assignments for a series of simple hydroxylated and methoxylated flavones. No ^{1}H- or ^{13}C-nmr data have been previously determined for 2′-hydroxyflavone [**1**], and ^{1}H-nmr assignments of flavone [**7**] have not been previously reported.

The most downfield signal in the ^{1}H-nmr spectrum of flavone [**7**] is the doublet of doublets (J=2.3, 8.7 Hz) at δ 8.23 corresponding to H-5. The homonuclear COSY spectrum indicated that this proton is coupled with signals at δ 7.70 and 7.42, which themselves are coupled to the doublet of doublets at δ 7.56, which must be H-8. Assignment of H-6 and H-7 was made on the basis of the respective *ortho* couplings with H-5 and H-8. The two-proton multiplets at δ 7.93 and δ 7.54 were assigned to H-2′,6′ and H-3′,5′, respectively, leaving the signal at δ 7.52 for H-4′.

The eight CH carbons of **7** observed from a DEPT experiment were assigned unambiguously on the basis of a ^{1}H-^{13}C-heteronuclear correlation experiment, and the five quaternary carbons were attributed on the basis of chemical shift theory. These assignments reaffirm those suggested previously by Wenkert and Gottlieb (22).

The ^{1}H-nmr spectra of **1** and **5** were assigned on the basis of homonuclear 2D correlation spectroscopy experiments and the protonated carbons could then be assigned through a ^{1}H-^{13}C heteronuclear correlation experiment. More detailed experimentation was, however, required to assign unambiguously the quaternary carbons of **1** and **5**. The experiments required to assign those carbon atoms in **5** will be described. From the APT spectrum it was clear that the five quaternary carbons (C-1′, C-2, C-2′, C-4a, and C-8a) resonated at δ 112.6, 123.7, 156.4, 157.9, and 160.7. Using the selective INEPT experiment (23), the three-bond couplings of the isolated protons with the aromatic carbons were determined using delay values calculated for Δ_1 and Δ_2, corresponding to J=8 Hz.

Irradiation of δ 7.67 (H-7) led to the enhancement of C-5 (δ 125.5) and C-8 (δ 118.0), which had been assigned previously, and also the quaternary carbon at δ 156.7, which can be assigned to C-8a. Similarly, irradiation of H-4′ (δ 7.47) enhanced the quaternary carbon at δ 157.9, which must be C-2′, and irradiation of H-6′ (δ 7.90) enhanced the quaternary carbons at δ 157.9 (C-2′) and δ 160.7, which must be C-2, and δ 112.5, which could be assigned to C-1′. Through elimination, the signal at δ 123.7 was assigned to C-4a. Assignments for the protonated and quaternary carbons in synthetic **1** were made in an exactly analogous manner. These data are summarized in Tables 1 and 2.

TABLE 1. ^{1}H-nmr Spectral Data for Flavone [**7**], 2′-Hydroxyflavone [**1**], and 2′-Methoxyflavone [**5**].[a]

Proton	Compound				
	Flavone [**7**]	2′-Hydroxyflavone [**1**]			2′-Methoxyflavone [**5**]
	$CDCl_3$	$CDCl_3$	$CDCl_3$+CD_3OD	DMSO-d_6	$CDCl_3$
3	6.83	7.42	7.45	7.19	7.15
5	8.23(2.3,8.7)	8.16(1.7,8.1)	8.19(0.9,7.6)	8.07(1.8,8.8)	8.23(1.4,7.8)
6	7.42(3.0,7.0,8.7)	7.48(2.1,6.5,6.5)	7.47(1.8,6.9,8.1)	7.51(1.7,7.4,8.5)	7.47(2.2,7.1,8.8)
7	7.70(1.2,6.5,9.0)	7.79(2.2,7.8,7.9)	7.78(1.2,6.9,8.3)	7.84(1.6,6.8,8.4)	7.67(1.4,6.7,8.1)
8	7.56(1.0,9.1)	7.67(2.1,6.9)	7.65(1.3,8.3)	7.59(7.4)	7.51(1.2,8.9)
2′	7.93	—	—	—	—
3′	7.54	6.88(1.7,7.8)	7.00(1.0,8.3)	7.10(8.3)	7.03(1.2,8.3)
4′	7.53	7.37(2.1,7.8,7.9)	7.38(1.1,6.1,7.9)	7.43(1.6,7.6,8.9)	7.39(1.8,6.6,8.6)
5′	7.54	7.01(2.5,5.2,8.6)	7.02(1.8,7.8,8.6)	7.04(1.0,7.8,8.6)	7.09(1.9,8.8)
6′	7.93	7.96(1.6,8.3)	7.96(1.4,7.6)	7.95(1.0,7.7)	7.90(1.2,7.8)
-OCH_3	—	—	—	—	3.93

[a]Obtained at 360 MHz, δ_{TMS}=0 ppm.

TABLE 2. ^{13}C-nmr Spectral Data for Flavone [**7**], 2′-Hydroxyflavone [**1**], and 2′-Methoxyflavone [**5**].[a]

Carbon	Compound		
	Flavone [**7**]	2′-Hydroxyflavone [**1**][b]	2′-Methoxyflavone [**5**]
2	163.3	160.7	160.7
3	107.5	111.0	112.6
4	178.1	177.2	178.8
4a	123.9	123.1	123.7
5	125.6	124.6	125.5
6	125.2	125.2	124.8
7	133.8	134.0	133.5
8	118.1	118.4	118.0
8a	156.2	155.8	156.4
1′	131.7	117.7	112.5
2′	126.3	156.6	157.9
3′	129.0	117.0	111.6
4′	131.6	132.5	132.3
5′	129.0	119.4	120.6
6′	126.3	128.5	129.2
OCH_3	—	—	55.6

[a]Obtained at 90.8 MHz in $CDCl_3$, $\delta_{TMS}=0$ ppm.
[b]Obtained in DMSO-d_6.

EXPERIMENTAL

GENERAL EXPERIMENTAL METHODS.—Melting points were determined using a Kofler hot-stage microscope and are uncorrected. Uv spectra were recorded on a Beckman DU-7 spectrophotometer and ir spectra on a Nicolet model MX-1 FT-IR interferometer. Nmr spectra were recorded on a Nicolet NB 360 instrument or a Varian XL-300 instrument. Mass spectra were recorded on a Varian MAT 112S instrument operating at 70 eV.

PLANT MATERIAL.—The leaves of *D. sellowiana* were collected in Brazil in August 1975. They were identified by personnel at the Economic Botany Laboratory, BARC-East, Beltsville, MD. A herbarium sample representative of the collection is deposited in the herbarium of the National Arboretum, Washington, DC.

EXTRACTION AND ISOLATION.—Air-dried leaves of *D. sellowiana* (6.8 kg) were soaked in petroleum ether at room temperature for 48 h and the marc extracted with EtOAc for 4 days. The marc was finally extracted with MeOH for 4 days, and the combined MeOH extracts evaporated in vacuo to afford a residue (131.2 g) that was partitioned between $CHCl_3$ (4×1 liter) and H_2O (1 liter). The $CHCl_3$ extracts were dried (Na_2SO_4), filtered, and evaporated to give a residue (33.6 g), a portion (30 g) of which was subjected to column chromatography on Si gel 60 eluting with $CHCl_3$-MeOH (9:1) to afford five fractions. Fraction 3 (3.05 g) on further chromatography afforded daphnoretin (28 mg, 0.00046%) identical (mp, mmp, uv, ir, ^{1}H nmr, ms) with material obtained previously in these laboratories (4) and 2′-hydroxyflavone [**1**] (13 mg, 0.0002%) as colorless needles; mp 249° [lit. (15) 250-251°]; ir ν max (KBr) 3434, 3068, 1639, 1631, 1621, 1614, 1607, 1565, 1479, 1463, 1450, 1384, 1326, 1295, 1249, 1114, 878, 756, 742 cm^{-1}; uv λ max (MeOH) (log ϵ) 245.5 (4.22), 289 sh (4.14), 306.5 (4.16), 332 nm (4.10); (MeOH+NaOMe) 252 sh (4.18), 300 (4.12), 310 (4.09), 406 nm (4.02); ^{1}H nmr see Table 1; ms *m/z* (rel. int.) 238 (M^+, 100%), 221 (18), 210 (17), 186 (4), 181 (8), 165 (2), 132 (4), 121 (71), 120 (41), 118 (38), 105 (19), 92 (27), 77 (3), 76 (9), 63 (16), 39 (11), 28 (24).

Fraction 4 yielded bicoumol (10 mg, 0.00016%) on crystallization, identified by comparison of its physical and spectral properties (mp, mmp, uv, ir, ^{1}H nmr, ms) with those reported previously (24).

1-(2-METHOXYPHENYL)-3-PHENYLPROPANE-1,3-DIONE [**6**].—To a mixture of methyl 3-methoxybenzoate (16.6 g, 0.1 mol) and acetophenone (12.0 g, 0.1 mol) was added granulated sodium (2.3 g, 0.1 mol) in small portions. The reaction mixture was externally cooled to prevent a rapid temperature increase on dissolution of the sodium and was then allowed to stand overnight at room temperature. Cold H_2O (100 ml) was carefully added to the solidified mixture to decompose the unreacted sodium, and

this was followed by Et_2O (100 ml). The resulting two-phase system was neutralized with HOAc, and after separation of the ethereal phase, the aqueous layer was further extracted with Et_2O (2×30 ml). Treatment of the combined organic layers with 10% NaOH (30 ml) yielded a white, microcrystalline precipitate (12.2 g, 48%) identified as the enol form of the desired product **6**. Acidification of the aqueous phase with concentrated HCl, followed by extraction with Et_2O (2×15 ml) afforded an additional amount of **6** (3.8 g, 15%) which was crystallized from Et_2O, mp 82-83°; uv λ max (MeOH) (log ε) 248 (3.85), 356 (4.26); ^1H nmr (360 MHz, $CDCl_3$) δ 3.39 (3H, s, $-OCH_3$), 6.98 (1H, dd), 7.05 (1H, ddd), 7.14 (1H, s, H-2), 7.43-7.52 (4H, m), 7.92-7.97 (3H, m); ^{13}C nmr (90.8 MHz, $CDCl_3$) δ 55.7 (OCH_3), 98.4 (C-2), 111.6 (C-3), 120.7 (C-5), 124.7 (C-1′), 127.1 (C-2″ and C-6″), 128.5 (C-3″ and C-5″), 130.2 (C-4″), 132.1 (C-6), 133.1 (C-4), 135.8 (C-1″), 158.4 (C-2′), 184.1 and 185.7 (C-1 and C-3); ms *m/z* (rel. int.) 254 (M^+, 13), 236 (13), 224 (17), 223 (100), 207 (2), 177 (3), 135 (85), 120 (8), 105 (51), 92 (12), 89 (4), 82 (1).

SYNTHESIS OF FLAVONE [**7**].—1-(2-Methoxyphenyl)-3-phenylpropane-1,3-dione [**6**] (2.0 g, 8 mmol) was refluxed in 57% HI (8 ml) for 4 h. The reaction mixture was cooled to room temperature and the solid material filtered and triturated with hot petroleum ether (bp 60-70°) (3×25 ml). The combined organic solutions were evaporated in vacuo until initiation of crystallization. The product [**7**] (480 mg, 27%) was collected by filtration, washed with cold petroleum ether and dried, mp 96-97° [lit. (17) mp 97°]; uv λ max (MeOH) (log ε) 250 (4.05), 296 (4.22); no change on addition of $NaOCH_3$ or $AlCl_3$; ^1H nmr see Table 1; ^{13}C nmr see Table 2; ms *m/z* (rel. int.) 222 (M^+, 100), 221 (24), 194 (18), 165 (5), 129 (2), 120 (58), 97 (13), 92 (24), 82 (7).

2-(2-METHOXY-BENZYLOXY)-ACETOPHENONE [**3**].—Hydroxyacetophenone (6.8 g, 0.05 mol) and 2-methoxybenzoychloride (8.5 g, 0.05 mol) (25) were dissolved in anhydrous CH_2Cl_2 (25 ml). To this stirred reaction mixture, pyridine (5.75 ml) in anhydrous CH_2Cl_2 (12.5 ml) was added dropwise at 0°. The reaction mixture was kept overnight at room temperature, and the resulting pyridine hydrochloride removed by filtration. Following successive extraction with 5% HCl (2×40 ml), H_2O (40 ml), 5% aqueous NaOH (2×10 ml), and H_2O (40 ml), the organic layer was dried (anhydrous Na_2SO_4), filtered, and evaporated in vacuo. Recrystallization of the residue from Et_2O afforded **3** (14.42 g, 92%), mp 77-79°; ^1H nmr (360 MHz, $CDCl_3$) δ 2.54 (3H, s, $-CH_3$), 3.87 (3H, s, $-OCH_3$), 7.01 (1H, d), 7.04 (1H, ddd), 7.22 (1H, d), 7.30 (1H, ddd), 7.52 (2H, ddd), 7.81 (1H, dd), 8.1 (1H, dd); ms *m/z* (rel. int.) 270 (M^+, 3), 252 (1), 136 (3), 135 (100), 120 (7), 107 (4), 92 (4), 79 (10), 77 (68).

1-(2-HYDROXYPHENYL)-3-(2-METHOXYPHENYL)-PROPANE-1,3-DIONE [**4**].—Powdered KOH (1.6 g) was added to a solution of 2-(2-methoxybenzyloxy)-acetophenone [**3**] (5.32 g, 0.02 mol) in anhydrous pyridine (20 ml) and the reaction mixture stirred at 50-55° for 3 h. Treatment of the cold reaction mixture with 10% aqueous HOAc (50 ml) resulted in the separation of a brown oil that was dissolved in $CHCl_3$ (60 ml). The organic phase was successively extracted with 5% HCl (2×25 ml), H_2O (40 ml), and 10% aqueous NaOH (25 ml), and the $CHCl_3$ solution concentrated in vacuo. The major portion of the product [**4**] (2.40 g, 45%) crystallized, and additional quantities (1.44 g, 27%) could be obtained in oil form from the mother liquor and by reextraction of the aqueous MaOH layer with $CHCl_3$ after neutralization with HCl. The product displayed the following physical and spectroscopic properties, mp 244-245°; uv λ max (MeOH) (log ε) 251 (3.96), 315 (3.89), 372 nm (4.17); (MeOH+$NaOCH_3$) 250 (3.83), 362 nm (4.31); ^1H nmr (360 MHz, $CDCl_3$) δ 3.99 (3H, s), 6.92 (1H, ddd), 6.99 (1H, ddd), 7.03 (1H, d), 7.09 (1H, ddd), 7.26 (1H, s, H-2), 7.47 (1H, dd), 7.51 (1H, ddd), 7.74 (1H, dd), 7.98 (1H, dd); ms *m/z* (rel. int.) 270 (M^+, 6), 239 (5), 136 (12), 135 (100), 121 (30), 105 (4), 92 (19), 89 (4), 77 (32).

2′-METHOXYFLAVONE [**5**].—1-(2-Hydroxyphenyl)-3-(2-methoxyphenyl)-propane-1,3-dione [**4**] (1.9 g, 7 mmol) was refluxed in EtOH (40 ml) containing 10 drops of H_2SO_4 for 1 h. The reaction mixture was refrigerated overnight, and the product was filtered, washed with cold EtOH, and dried. 2′-Methoxyflavone [**5**] (1.18 g, 67%) was recrystallized from EtOH, mp 103-104°; uv λ max (MeOH) (log ε) 235 (4.17), 250 (4.15), 289 sh (4.10), 308 nm (4.18); no change on addition of $NaOCH_3$, $AlCl_3$; ^1H nmr see Table 1; ^{13}C nmr see Table 2; ms *m/z* (rel. int.) 252 (M^+, 88), 235 (5), 233 (11), 209 (4), 181 (9), 165 (4), 153 (3), 132 (48), 131 (48), 131 (64), 122 (12), 120 (100), 92 (33), 89 (23).

2′-HYDROXYFLAVONE [**1**].—1-(2-Hydroxyphenyl)-3-(2-methoxyphenyl)-propane-1,3-dione [**4**] (1.9 g, 7 mmol) was heated in 57% HI (8 ml) at 100° for 4 h. The precipitate that formed on cooling was removed by filtration and recrystallized from EtOH to afford 2′-hydroxyflavone [**1**] (900 mg, 54%), mp 248-249° [lit. (15) 250-251°]; uv λ max (MeOH (log ε) 247 (4.22), 292 (4.14), 308 (4.17), 331 nm (4.10); (MeOH+NaOMe) 251 sh (4.18), 301 (4.12), 310 (4.10), 406 nm (4.02); no change on addition of $AlCl_3$; ^1H nmr see table 1; ^{13}C nmr see Table 2; ms *m/z* (rel. int.) 238 (M^+, 100), 221 (19), 210 (23), 196 (4), 181 (14), 165 (3), 152 (10), 133 (2), 126 (2), 121 (92), 120 (57), 118 (46), 105 (19), 92 (57), 90 (27).

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