Synthesis of New Naturally Occurring 4-Phenyl-2*H*-1-benzopyran-2-ones

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Synopsis. 5,7-Dimethoxy-4-(4-hydroxyphenyl)-2*H*-1-benzopyran-2-one and 5,7-dimethoxy-4-(4-methoxyphenyl)-2*H*-1-benzopyran-2-one, two new neoflavonoids occurring in *Courtarea hexandra* have been synthesized via Pechmann condensation. Attempts made to synthesize another 4-arylcoumarin, 5-hydroxy-7-methoxy-4-(2,5-dihydroxyphenyl)-2*H*-1-benzopyran-2-one, constituent of the same plant, led to the formation of the hitherto unknown 2-ethoxy-6-hydroxy-4*H*-1-benzopyran-4-one.

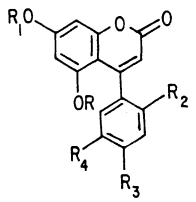
A few 4-phenylcoumarins having rare type of oxygenation pattern have recently been isolated[1,2] from the caulis of *Courtarea hexandra,* a folk medicinal plant used in Brazil as an antimalarial and antidiabetic agent. The structures to these compounds were assigned on the basis of their spectral data alone. In order to provide confirmation to the proposed structures of the natural products, we have attempted the syntheses of three of them (**1** and **2**,[1] and **3**[2]) and those of their dihydroxy analogues via Pechmann condensation of phloroglucinol and corresponding suitably substituted ethyl benzoylacetate.

Results and Discussion

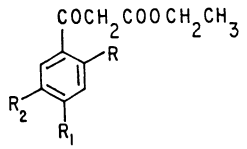
Ethyl 4-(benzyloxy)benzoylacetate (**4**) and ethyl 4-methoxybenzoylacetate (**6**) were prepared by treating 4-(benzyloxy)acetophenone[3] and 4-methoxyacetophenone,[4] respectively with diethyl carbonate in the presence of sodium hydride; **4** and **6** were fully characterized from their spectral data. Pechmann condensation of **4** with phloroglucine yielded 5,7-dihydroxy-4-(4-hydroxyphenyl)-2*H*-1-benzopyran-2-one (**5**), which on methylation with diazomethane yielded mainly the coumarin **1** along with a small amount of the coumarin **2**. The IR, UV, and ^{1}H NMR spectral data of **1** and **5** supported their structures. Similarly, the ester **6** on condensation with phloroglucine yielded the 4-phenylcoumarin **7**, which on methylation with dimethyl sulfate gave 5,7-dimethoxy-4-(4-methoxyphenyl)-2*H*-1-benzopyran-2-one (**2**); **2** and **7** were fully characterized from their spectral data. The mp behavior, and UV, IR, and ^{1}H NMR spectral data of our synthetic **1** and **2** were in agreement with those of the corresponding natural samples,[1] thus confirming the structures of the natural products occurring in *Courtarea hexandra.* However, a direct comparison of our synthetic samples with the natural samples could not be done because of the non-availability of the latter with us.

For the preparation of 5-hydroxy-7-methoxy-4-(2,5-dihydroxyphenyl)-2*H*-1-benzopyran-2-one (**3**),[2] ethyl 2,5-bis(benzyloxy)benzoylacetate (**8**), prepared by the reaction of 2,5-bis(benzyloxy)acetophenone[5] with diethyl carbonate in the presence of NaH was condensed with phloroglucine, as well as with mono-*O*-methylphloroglucine[6] under four different experimental conditions. The condensations in the presence of H_3PO_4, $POCl_3$, and concd H_2SO_4 led to the formation of only tarry materials, from which no crystalline substance could be isolated. Condensation in the presence of ethanolic HCl, in both the cases yielded the compound **9**, quite different from the required coumarin **3**; structure of **9** was established from a detailed study of its UV, IR, ^{1}H NMR, and mass spectra.

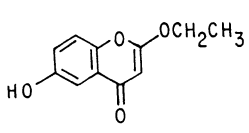
The UV absorption maxima of **9** at 202, 218, 258 (sh), 267, 280 (sh), and 326 nm suggested it to be a



(1) $R=R_1=CH_3$, $R_2=R_4=H$, $R_3=OH$
(2) $R=R_1=CH_3$, $R_2=R_4=H$, $R_3=OCH_3$
(3) $R=R_3=H$, $R_1=CH_3$, $R_2=R_4=OH$
(5) $R=R_1=R_2=R_4=H$, $R_3=OH$
(7) $R=R_1=R_2=R_4=H$, $R_3=OCH_3$



(4) $R=R_2=H$, $R_1=OCH_2C_6H_5$
(6) $R=R_2=H$, $R_1=OCH_3$
(8) $R=R_2=OCH_2C_6H_5$, $R_1=H$



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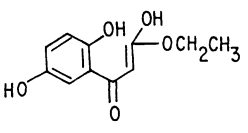

(10)

chromone; the IR spectra supported this and further indicated **9** to be an alkoxy- and hydroxy-substituted chromone as it exhibited strong absorptions at 3200, 1660, 1623, and 1280 cm^{-1}. A bathochromic shift of 38 nm in its λ_{max} in the presence of NaOMe and the presence of a D_2O exchangeable singlet (1H) at δ 9.80, a triplet (for 3H) at δ 1.40, and a quartet (for 2H) at δ 4.15 in its ^1H NMR spectrum confirmed **9** to be monohydroxy-monoethoxy-substituted. As there was no change in the λ_{max} of **9** on addition of NaOAc, the position of -OH group was indicated to be either C-6 or C-8; the location of -OH at C-6 was substantiated by the chemical shift values of the three protons in the aromatic ring in the ^1H NMR spectrum (a multiplet for 2H at δ 7.15 and an ortho-coupled doublet for 1H at δ 7.26). These data suggested **9** to be the hitherto unknown 2-ethoxy-6-hydroxy-4*H*-1-benzopyran-4-one; this structure was fully confirmed by its mass spectrum, which exhibited prominent peaks at *m/z* 207 $(M+1)^+$, 206 (M^+), 178 $(M-CO)^+$, 150 $(M-CO-C_2H_4)^+$, 137 (A_1+H), 136 $(A_1)^+$, 108 (A_1-CO) and 80 $(A_1-CO-CO)$. We believe that **9** is formed via the intermediate **10**, derived from the ester **8** under strongly acidic conditions of the experiment.

Experimental

All melting points were taken on a Nalge micro melting point apparatus and are uncorrected. Silica gel was used for all thin-layer and column chromatographic separations. UV spectra were recorded in methanol on a Perkin Elmer 554 spectrophotometer. IR spectra were recorded on Shimadzu model 535 spectrophotometer and ^1H NMR spectra on 90 MHz Perkin Elmer R-32 and 200 MHz Jeol JNM FX-200 FT NMR spectrometers using TMS as the internal standard. The mass spectra were recorded on a Varian Mat 311A instrument.

Ethyl 4-(Benzyloxy)benzoylacetate (4). To a vigorously stirred suspension of sodium hydride (4g) in dry ether (100 ml) containing diethyl carbonate (5.48 ml), a solution of 4-(benzyloxy)acetophenone[3] (5 g) in dry benzene (100 ml) was added dropwise during the course of 6 h. The mixture was then refluxed for 30 h, cooled, treated with ice and acidified with dilute hydrochloric acid; the organic layer that separated was washed with sodium hydrogen carbonate solution and dried. Residue obtained on removal of benzene and ether was macerated with petrol to remove unreacted diethyl carbonate; ethyl 4-(benzyloxy)benzoylacetate was obtained as an oil (**4**, 4 g); IR (Nujol) ν_{max}: 1735, 1660, 1260, 1105, 1030, and 830 cm^{-1}; UV λ_{max}: 210, 274 nm; ^1H NMR (90 MHz, $CDCl_3$): δ=1.25 (3H, t, *J*=7 Hz, $-COOCH_2C\underline{H}_3$), 3.90 (2H, s, $-COC\underline{H}_2COOC_2H_5$), 4.20 (2H, q, *J*=7 Hz, $-COOC\underline{H}_2CH_3$), 5.10 (2H, s, $-OC\underline{H}_2C_6H_5$), 7.00 (2H, d, *J*=8.5 Hz, H-3 and H-5), 7.35 (5H, s, $-OCH_2C_6\underline{H}_5$), and 7.85 (2H, d, *J*=8.5 Hz, H-2 and H-6). Found: C, 72.80; H, 6.40%; Calcd for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04%.

5,7-Dihydroxy-4-(4-hydroxyphenyl)-2*H*-1-benzopyran-2-one (5). A cooled suspension of ethey 4-(benzyloxy)benzoylacetate (**4**, 1.5 g) and phloroglucine (0.71 g) in absolute ethanol (50 ml) was saturated with dry HCl gas (5.5 h). The reaction mixture was left at 28 °C for 2 d, water was added and the solution was concentrated in vacuo and cooled, when a yellowish-orange solid precipitated. It was filtered and crystallized from methanol as yellow crystals (**5**, 500 mg), mp 293—294 °C; IR (KBr) ν_{max}: 3530, 3235, 1660, 1550, 1480, 1360, 1020, and 830 cm^{-1}; UV λ_{max} (log ε): 260 (3.95), 322 (3.98); +NaOMe: 272, 304, 368 nm; ^1H NMR (90 MHz, CD_3COCD_3): δ=5.70 (1H, s, H-3), 6.25 (1H, s, H-6), 6.30 (1H, s, H-8), 6.80 (2H, d, *J*=8.5 Hz, H-3′ and H-5′), 7.23 (2H, d, *J*=8.5 Hz, H-2′ and H-6′), 8.50 (1H, s, -OH), 8.60 (1H, s, -OH).

5,7-Dimethoxy-4-(4-hydroxyphenyl)-2*H*-1-benzopyran-2-one (1). To a solution of (**5**, 100 mg) in methanol (8 ml), a saturated solution of diazomethane in ether (7 ml) was added under stirring. After 45 min, the reaction mixture was evaporated in vacuo and the residue was column-chromatographed using benzene-ethyl acetate (4 : 1) as eluent to give **1** (40 mg); mp 214—216 °C (mp of the natural product[1] 214—215 °C); IR (KBr) ν_{max}: 3300, 1706, 1612, 1159, 1048, 962, and 835 cm^{-1}; UV λ_{max} (log ε): 254 (4.09), 322 (4.05); +NaOMe: 254, 328, 372 nm; ^1H NMR (200 MHz, CD_3COCD_3): δ=3.56 (3H, s, C-5-OMe), 3.96 (3H, s, C-7-OMe), 5.84 (1H, s, H-3), 6.40 (1H, d, *J*=2.5 Hz, H-6), 6.56 (1H, d, *J*=2.5 Hz, H-8), 6.92 (2H, d, *J*=8.5 Hz, H-3′ and H-5′), 7.16 (2H, d, *J*=8.5 Hz, H-2′ and H-6′), 8.56 (1H, s, C-4′-OH). Fuund: C, 68.20; H, 5.00%; Calcd for $C_{17}H_{14}O_5$: C, 68.46; H, 4.70%.

Ethyl 4-Methoxybenzoylacetate (6). To a vigorously stirred suspension of sodium hydride (5.8 g) in dry ether (100 ml), diethyl carbonate (15 ml) was added in one lot and to this mixture, a solution of 4-methoxyacetophenone (9 g)[4] in dry ether (100 ml) was added dropwise during 6 h. The mixture was then refluxed for 30 h, cooled, treated with ice and acidified with dil HCl. The organic layer was separated, washed with sodium hydrogencarbonate solution, dried, concentrated and treated with dry hexane when **6** was obtained as an oil (8 g); IR (Nujol) ν_{max}: 1730, 1670, 1600, 1360, 1250, 1160, 1100, 1020, and 830 cm^{-1}; UV λ_{max}: 216, 276 nm; ^1H NMR (90 MHz, $CDCl_3$): δ=1.25 (3H, t, *J*=7 Hz, $-COOCH_2C\underline{H}_3$), 3.80 (3H, s, $-OCH_3$), 3.90 (2H, s, $-OC\underline{H}_2-COOCH_2CH_3$), 4.20 (2H, q, *J*=7 Hz, $-COOC\underline{H}_2CH_3$), 6.85 (2H, d, *J*=8.5 Hz, H-3 and H-5), and 7.85 (2H, d, *J*=8.5 Hz, H-2 and H-6). Found: C, 65.10%; H, 5.90%; Calcd for $C_{12}H_{14}O_4$: C, 64.86%; H, 6.31%.

5,7-Dihydroxy-4-(4-methoxyphenyl)-2*H*-1-benzopyran-2-one (7). Through a cooled solution of **6** (4 g) and phloroglucine (2.25 g) in absolute ethanol (100 ml), a stream of dry HCl gas was passed for 6 h and the reaction mixture was left at 30 °C for 3 d. Water was added and the solution was concentrated in vacuo. The solid obtained was filtered, washed with water and crystallized from methanol as yellowish brown solid (2.5 g); mp 256—258 °C; IR (Nujol) ν_{max}: 3300, 3190, 1688, 1620, 1595, 1510, 1170, 820, and 700 cm^{-1}; UV λ_{max} (log ε): 260 (4.07), 315 (4.05); +NaOMe: 262, 315, 380 nm; ^1H NMR (90 MHz, DMSO-d_6): δ=3.82 (3H, s, C-4′-OCH_3), 5.76 (1H, s, H-3), 6.28 (1H, d, *J*=2.5 Hz, H-6), 6.35 (1H, d, *J*=2.5 Hz, H-8), 6.93 (2H, d, *J*=8.5 Hz, H-3′ and H-5′), 7.32 (2H, d, *J*=8.5 Hz, H-2′ and H-6′), and 9.7 (1H, s, -OH). Found: C, 68.00; H, 4.60%; Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.23%.

5,7-Dimethoxy-4-(4-methoxyphenyl)-2*H*-1-benzopyran-2-one (2). A solution of **7** (0.5 g) in acetone (50 ml) was refluxed with potassium carbonate (1 g) and dimethyl sulfate (0.23 ml) for 3 h. Potassium salts were filtered off and washed with hot acetone. The combined filtrate and washings were concentrated and treated with ice. The solid obtained was filtered, washed with water and dried. It crystallized from methanol as yellowish-brown crystals **2** (0.4 g), mp 151—152 °C (mp of the natural product[1] 151—152 °C); IR (Nujol) ν_{max}: 1710, 1620, 1595, 1158, 1100, 1050, 940, 860, and 830 cm^{-1}; UV λ_{max} (log ε): 255 (4.04), 315 (4.00); ^1H NMR (90 MHz, $CDCl_3$): δ=3.50 (3H, s, C-5-OCH_3), 3.86 (6H, s, C-7 and C-4′-OCH_3), 5.96 (1H, s, H-3), 6.22 (1H, d, *J*=2.5 Hz, H-6), 6.50 (1H, d, *J*=2.5 Hz, H-8), 6.87 (2H, d, *J*=8.5 Hz, H-3′ and H-5′), and 7.20 (2H, d, *J*=8.5 Hz, H-2′ and H-6′).

Ethyl 2,5-Bis(benzyloxy)benzoylacetate (8). To a vigorously stirred suspension of NaH (10 g) in dry ether (100 ml) containing diethyl carbonate (6.2 ml), a solution of 2,5-bis(benzyloxy)acetophenone[5] (10 g) in dry benzene (100 ml)

was added dropwise during the course of 6 h. The mixture was refluxed for 36 h. Usual work-up gave the ester **8** as an oil (8 g); IR (KBr) ν_{max}: 2910, 2850, 1730, 1660, 1600, 1460, 1380, 1200, 1020, 810, and 740 cm^{-1}; UV λ_{max}: 210, 286, 334 nm; ^1H NMR (90 MHz, $CDCl_3$): δ=1.23 (t, J=7H, 3H, $-COOCH_2C\underline{H}_3$), 4.00 (s, 2H, $-COC\underline{H}_2COOCH_2CH_3$), 4.10 (q, J=7 Hz, 2H, $-COOC\underline{H}_2CH_3$), 5.03 (s, 2H, $-OC\underline{H}_2C_6H_5$), 5.11 (s, 2H, $-OC\underline{H}_2C_6H_5$), 7.05 (m, 2H, H-3, and H-4), 7.42 (m, 10H, 2×$-OCH_2C_6\underline{H}_5$), and 7.50 (d, 1H, J=2.5 Hz, H-6). Found: C, 73.90; H, 6.20%; Calcd for $C_{25}H_{24}O_5$: C, 74.26; H, 5.94%.

2-Ethoxy-6-hydroxy-4*H*-1-benzopyran-4-one (9). Through a cooled suspension of the ester **8** (2 g) and phloroglucine (0.75 g) in absolute ethanol (100 ml), a stream of dry HCl gas was passed for 6 h. The reaction mixture was left at 30 °C for 4 d. After usual work up, only one solid compound could be isolated which crystallized from methanol as yellow crystals **9** (100 mg), mp 228—230 °C; IR (Nujol) ν_{max}: 3200, 1660, 1623, 1615, 1560, 1500, 1460, 1410, 1380, 1280, 1230, 1190, 1082, 970, 830, 807, and 710 cm^{-1}; UV λ_{max} (log ε): 202 (4.25), 218 (4.29), 258 (sh) (3.85), 267 (3.89), 280 (sh) (3.76), 326 (3.57); +$AlCl_3$: 202, 218, 258 (sh), 267, 280 (sh), 326; +NaOAc: 205, 210, 258 (sh), 267, 280 (sh), 326; +NaOAc/Boric Acid: 210, 258 (sh), 267, 280 (sh), 326; +NaOMe: 202, 237, 274, 288, 364 nm; ^1H NMR (200 MHz, DMSO-d_6): δ=1.40 (t, J=7 Hz, 3H, $-OCH_2C\underline{H}_3$), 4.15 (q, J=7 Hz, 2H, $-OC\underline{H}_2CH_3$), 5.80 (s, 1H, H-3), 7.15 (m, 2H, H-5 and H-7), 7.26 (d, J=8 Hz, 1H, H-8), and 9.80 (s, 1H, -OH); EIMS m/z (%): 207 (9), 206 (M^+) (64), 178 $(M-CO)^+$ (10.5), 150 $(M-CO-C_2H_2)^+$ (5), 149 $(M-CO-C_2H_2-H)^+$ (3.5), 137 $(A_1+H)^+$ (12.8), 136 $(A_1)^+$ (100), 134 $(178-CH_2{=}CHOH)^+$ (10.5), 121 (149—CO) (3.5), 108 $(A_1-CO)^+$ (12.8), 80 (A_1—CO—CO) (7). Found: C, 64.00; H, 4.50%; Calcd for $C_{11}H_{10}O_4$; C, 64.08; H, 4.85%.

The condensation of the ester **8** with monomethyl ether of phloroglucine[6] by the procedure given above yielded only **9**.

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