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SYNTHESIS OF ANTHOCYANIDINS—III[1]

TOTAL SYNTHESIS OF APIGENINIDIN AND LUTEOLINIDIN CHLORIDES

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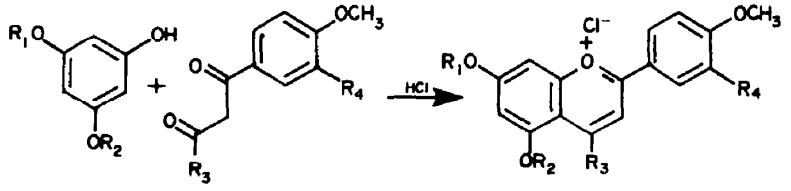
Abstract—The 3-deoxyanthocyanidins apigeninidin chloride (**6a**) and luteolinidin chloride (**6b**) have been synthesized in good yield through the oxidative (Pb^{4+}) decarboxylation of the corresponding 4-carboxyflav-2-enes **7a** and **7b**.

The anthocyanidins are a family of naturally occurring flavylium salts of general structure **6**. The ring A carries the oxygen substitution of phloroglucinol, a structural characteristic determined by their biosynthetic pathway.[2] The substitution pattern of ring B is more variable, R_2 and R_3 can be either H, OH or OMe. The nature of R_1 defines the chromatic character of these pigments: the 3-deoxyanthocyanidins (**6**; $R_1 = H$) are yellow (λ_{max} ~470–475 nm), while the anthocyanidins (**6**; $R_1 = OH$) are red (λ_{max} ~510–520 nm). In addition, the presence or lack of oxygen substitution at C3 profoundly affects the stability of the color in acidic aqueous media. Thus, apigeninidin (**6a**) remains unchanged in solution at pH 2.8 for a year, while cyanidin (**6c**) decolorizes in a few hours under similar conditions (25°, laboratory lights). This inherent greater stability of the yellow over the red anthocyanidins has led to their consideration as food colorants.[3]

The acid-catalyzed condensation of phloroglucinol (**1a**, Scheme 1) with benzoylacetone and benzoylpyruvic acid was shown by Bülow[4,5] to yield the respective 4-Me and 4-COOH flavylium salts in good yields. More recently,[6] these condensations were found to proceed equally well with the *p*-methoxybenzoyl analogs **2a** and **2b** (Scheme 1). The reaction between phloroglucinol and benzoylacetaldehyde, however, failed to yield the desired 4-unsubstituted flavylium salt.[7] This limitation of the Bülow's synthesis led Robinson[8] to develop, years later, the acid-catalyzed condensation of 2-O-benzoyl-phloroglucinaldehyde (**4**) with acetophenones **5** (Scheme 2), which allowed for the first time synthetic access to the anthocyanidins **6**, carrying hydrogen at C4.[9] Except for the unquestionable importance this synthesis had for the structural understanding of those natural products, it has been of limited value for their large scale preparation. The poor yields of **6** (10% or less) usually observed, resulting from the low reactivity of the hindered aldehyde **4**, contrast with the 80–90% generally obtained for Bülow's intermediates **3**.

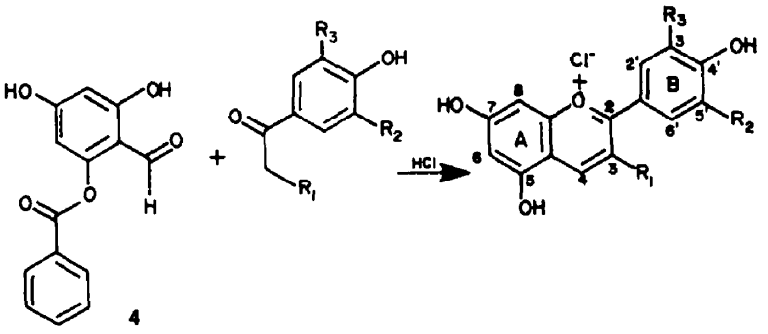
In this paper we describe a convenient synthesis of apigeninidin (**6a**) and luteolinidin (**6b**), based on the oxidative decarboxylation of the 4-carboxyflavenes **7**, prepared from the Bülow's intermediates **3c** and **3d** (Scheme 3). Thus, the condensation of phloroglucinol dimethylether (**1b**) with *p*-methoxybenzoyl pyruvic acid (**2b**) in HCl/HCOOH gave **3c** in 84% yield. As attempts to decarboxylate **3c** directly failed, it was reduced to the dihydro-derivative **7a** with sodium borohydride in MeOH, in quatitative yield.

With chloranil in AcOH, and also under air, **7a** dehydrogenates easily to give back the 4-carboxyflavylium **3c**. The oxidative decarboxylation of **7a** to **8a**, observed first by us during anodic oxidation experiments, was found to proceed best with lead tetraacetate in glacial AcOH, under N_2 at 50°. Under these conditions, **7a** decarboxylated smoothly to give **8a** in 80% yield. The reaction can be visualized (Scheme 3) as a concerted process in which the loss of CO_2 is facilitated by the electrophilicity of



1a: $R_1 = R_2 = H$ **2a**: $R_3 = CH_3$; $R_4 = H$ **3a**: $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
1b: $R_1 = R_2 = CH_3$ **2b**: $R_3 = COOH$; $R_4 = H$ **3b**: $R_1 = R_2 = R_4 = H$; $R_3 = COOH$
2c: $R_3 = COOH$; $R_4 = OCH_3$ **3c**: $R_1 = R_2 = CH_3$; $R_3 = COOH$; $R_4 = H$
3d: $R_1 = R_2 = CH_3$; $R_3 = COOH$; $R_4 = OCH_3$

Scheme 1.



5a: $R_1 = R_2 = R_3 = H$
5b: $R_1 = R_2 = H$; $R_3 = OH$
5c: $R_1 = R_3 = OH$; $R_2 = H$

6a: $R_1 = R_2 = R_3 = H$
6b: $R_1 = R_2 = H$; $R_3 = OH$
6c: $R_1 = R_3 = OH$; $R_2 = H$

Scheme 2.

Pb^{4+}, as well as the lowering of the bond energy C4-CO_2^+ induced by the stabilization of the carbonium ion in the resulting flavylium salt. This reaction finds an analogy in the generation of tropylium cations by the oxidative decarboxylation of cyclohepta-2,4,6-trienecarboxylic acid, under similar conditions.[10,11]

Compound **8a** was found identical to trimethylapigeninidin chloride by hplc, UV and IR comparison with an authentic sample,[12] prepared by chloranil oxidation of 4',5,7-trimethoxy-4-hydroxyflavan.

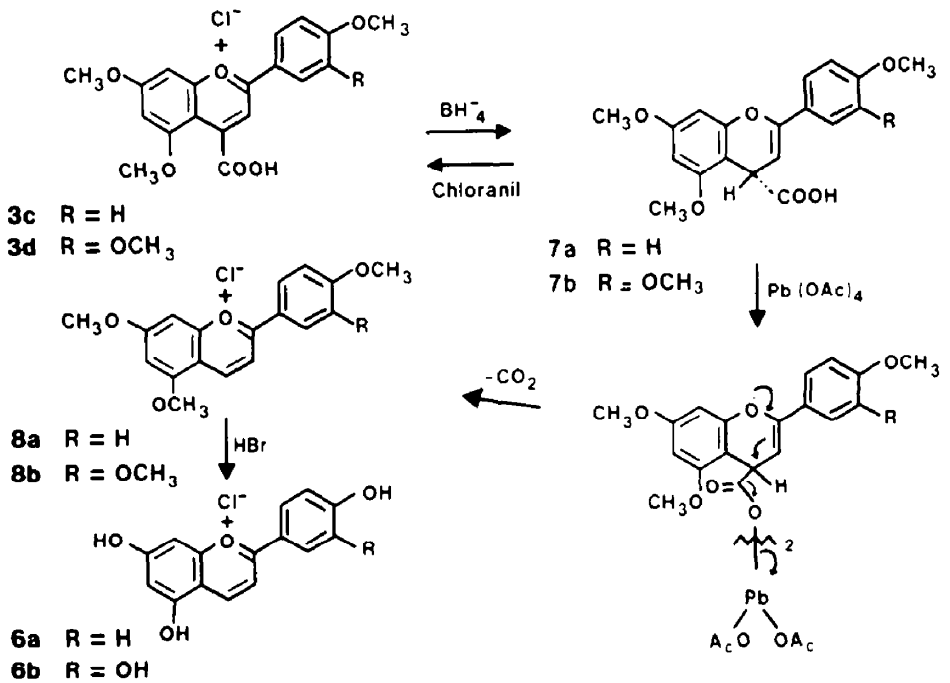
The demethylation of **8a**[13] was found to proceed best with 48% HBr, and the product **6a** was confirmed as apigeninidin by direct comparison with an authentic sample.[1]

The same synthesis was repeated starting with the 4-carboxyflavylium salt **3d**, to give the intermediates **7b** and **8b** in good yield. The flavylium salt **8b** was found identical to an authentic sample of tetramethyluteolinidin chloride,[12] by hplc, UV and IR comparisons. The demethylation of **8b** gave luteolinidin chloride (**6b**) in 78% yield, identical to an authentic sample prepared from eriodictyol by the procedure of Bate-Smith.[14]

EXPERIMENTAL

M.P. are uncorrected ^1H NMR spectra were recorded in DMSO-d_6. Chemical shifts are given in ppm downfield from TMS. Abbreviations: s, singlet; b.s., broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Microanalyses were performed by Galbraith Analytical Laboratories, Knoxville, Tennessee.

4',5,7-Trimethoxy-4-carboxyflavylium chloride (**3c**). A mixture of 1.0 g (6.5 mmoles) of **1b**, 1.3 g (5.9 mmoles) **2b**,[15] 25 ml 97% formic acid and 2.5 ml conc HCl was allowed to stand overnight



3c R = H
3d R = OCH_3
8a R = H
8b R = OCH_3
6a R = H
6b R = OH
7a R = H
7b R = OCH_3

Scheme 3.

at 5°. The soln was then added to 75 ml ether, and the resulting ppt was filtered to give 1.93 g (84%) of **3c**, orange-brown solid. Recrystallized from MeOH–Et_2O afforded 1.42 g (62%) of red crystals. UV (0.01 N HCl in MeOH) λ_{max} nm (log ϵ): 279 (4.32), 329 (3.81) and 476 (4.58). IR (KBr) cm^{-1}: 3450, 1730, 1640, 1600, 1580, 1560, 1515, 1460, 1370, 1335, 1310, 1280, 1245, 1180, 1040, 845. NMR: 2H d at 7.90 (C2' and C6'H), 1H s at 7.35 (C3H), 2H d at 6.95 (C3' and C5'H), 2H q at 5.95 (C6 and C8H), 3H s at 3.85 (OMe), 3H s at 3.65 (OMe), 3H s at 3.50 (OMe). Found: C, 58.03; H, 5.05; Cl, 9.06. Calc. for $C_{19}H_{17}O_6Cl \cdot H_2O$: C, 57.79; H, 4.82; Cl, 9.00%).

4',5,7-Trimethoxy-4-carboxyflav-2,3-ene (**7a**). To a soln of 2.0 g (5.1 mmoles) of **3c** in 200 ml MeOH was added 300 mg (7.9 mmoles) $NaBH_4$ in small portions. After stirring for 5 min at room temp, the soln had decolorized. It was then concentrated to 50 ml *in vacuo* and added to 800 ml of 0.5% aqueous AcOH. This mixture was extracted with 3 × 150 ml EtOAc, the combined extracts dried over Na_2SO_4 and evaporated to give **7a** as a pale tan solid, 1.7 g (97%). Recrystallized from MeOH at 5° afforded white crystals, m.p. 164–6°. The product developed a brown coloration on standing under air at room temp. UV (MeOH) λ_{max} nm (log ϵ): 206 (4.51), 222 sh. (4.34), 247 (4.29) and 270 sh (3.93). IR (KBr) cm^{-1}: 2920, 2820, 1710, 1670, 1620, 1610, 1590, 1510, 1500, 1295, 1250, 1215, 1200, 1165, 1145, 1105, 1050, 1040, 820. NMR: 2H d at 7.70 (C2' and C6'H), 2H d at 7.00 (C3' and C5'H), 1H d at 5.65 (C3H), 1H d at 4.30 (C4H), 9H b.s. at 3.80 (OMe). Ms *m/z* (rel. int.): 342 (24.5), 298 (28.6), 297 (100), 282 (13.7), 207 (30.7), 206 (66.1), 149 (13.0), 135 (56.0), 77 (16.2). (Found: C, 66.70; H, 5.49. Calc. for $C_{19}H_{18}O_6$: C, 66.67; H, 5.26%).

4',5,7-Trimethoxyflavylium chloride (**8a**). A mixture of 500 mg (1.46 mmoles) of **7a**, 750 mg (1.69 mmoles) of $Pb(OAc)_4$ and 15 ml AcOH (containing 2% Ac_2O) was heated at 50° for 2 hr under N_2. Upon cooling the solvent was removed *in vacuo* and a soln of 0.2 ml H_3PO_4 in 50 ml of 20% aqueous MeOH added. The resulting ppt of lead phosphate was removed by filtration, and the filtrate was passed through a Dowex 21-K (Cl^-) column previously equilibrated with the same solvent. The red–orange band was collected, concentrated *in vacuo*, and the concentrate was freeze-dried to give 385 mg (1.15 mmoles, 79%) of **8a**, orange solid. UV (0.01 N HCl in MeOH) λ_{max} nm (log ϵ): 474 (4.53), 324 (3.73), 278 (4.25) and 241 (3.88). IR (KBr) cm^{-1}: 3420, 1640, 1600, 1560, 1530, 1500, 1375, 1340, 1310, 1240, 1210, 1185, 1050. The product was identical by hplc (C_{18} μbondapak column; solvent: 30% MeOH–10% AcOH–60% H_2O), UV and IR comparison with an authentic sample of **8a**.[12] A portion of the product was converted to the $FeCl_4^-$ salt and recrystallized from AcOH, m.p. 188–9° (lit.[12] 186–7°).

Apigeninidin chloride (**6a**). A soln of 50 mg (0.15 mmoles) of **8a** and 200 mg phenol in 5 ml of 48% HBr was heated at reflux under argon for 16 hr. The resulting mixture was cooled in ice and filtered to give 43 mg of a brown–orange solid. This was dissolved in 5 ml MeOH and passed through a Dowex 21-K (Cl^-) equilibrated with 0.01 N HCl in MeOH. The MeOH eluant was evaporated and this residue dried to give 29 mg (0.10 mmoles, 66%) of **6a**, red–orange solid. UV (0.01 N HCl in MeOH) λ_{max} nm (log ϵ): 240 (3.93), 276 (4.27), 324 (3.65) and 476 (4.55). IR (KBr) cm^{-1}: 3400, 3040, 1635, 1530, 1505, 1330, 1230, 1175, 1145, 830. The product was identical by hplc (C_{18} μbondapak column; solvent: 20% MeOH–10% AcOH–70% H_2O), UV and IR comparison with an authentic sample of **6a** prepared from naringenin.[1]

3',4',5,7-Tetramethoxy-4-carboxyflavylium chloride (**3d**). A mixture of 3.0 g (19.5 mmoles) of **1b**, 4.0 g (15.9 mmoles) **2c**,[16] 27 ml 97% formic acid and 3 ml conc HCl was allowed to react overnight at 5°. Addition of 300 ml ether and filtration gave 6.22 g (14.7 mmoles, 92%) of **3d**, orange–brown solid. Recrystallization from MeOH–Et_2O afforded 4.87 g (72%), red crystals. UV (0.01 N HCl in MeOH) λ_{max} nm (log ϵ): 205 (4.50), 240 sh (4.17), 280 (4.32), 326 (3.74) and 495 (4.60). IR (KBr) cm^{-1}: 3430, 1735, 1640, 1575, 1510, 1460, 1390, 1370, 1325, 1290, 1245, 1215, 1155, 1045. NMR: 4H m at 6.9–7.6 (C2', C5', C6' and C3H), 2H q at 5.95 (C6 and C8H), 3H s at 3.80 (Me), 3H s at 3.75 (Me), 3H s at 3.65 (Me), 3H s at 3.45 (OMe). (Found: C, 58.04; H, 4.97; Cl, 8.38. Calc. for $C_{20}H_{19}O_7Cl \cdot \frac{1}{2}$ MeOH: C, 58.22; H, 4.97; Cl, 8.40).

3',4',5,7-Tetramethoxy-4-carboxyflav-2,3-ene (**7b**). To a soln of 1.0 g (2.37 mmoles) of **3d** in 60 ml MeOH was added 200 mg (5.30 mmoles) of $NaBH_4$, in four portions over 5 min. After an additional 10 min the soln was evaporated to dryness and a mixture of 100 ml EtOAc and 100 ml 0.02 M phosphate buffer pH 6 added. The aqueous layer was separated and extracted further with EtOAc (3 × 30 ml). The combined EtOAc layers were dried and evaporated to give a pale pink solid. Trituration with MeOH afforded 775 mg (2.08 mmoles, 88%) of **7b**, m.p. 173–5°. UV (MeOH) λ_{max} nm (log ϵ): 215 (4.64), 250 (4.24), 276 sh. (3.93) and 292 (3.91). IR (KBr) cm^{-1}: 3550, 3460, 1715, 1670, 1630, 1600, 1515, 1465, 1420, 1310, 1280, 1210, 1200, 1150, 1115, 1030, 800. NMR: 3H m at 6.9–7.5 (C2', 5' and C6'H), 2H b.d. at 6.35 (C6 and C8H), 1H d at 5.70 (C3H), 1H d at 4.30 (C4H), 12H b.s. at 3.80 (OCH_3). MS *m/z* (rel. int.): 372 (15.5), 328 (40.3), 327 (100), 311 (15.7), 207 (20.7), 206 (48.6), 165 (44.6), 164 (15.3), 138 (29.6), 73 (18.5), 70 (52.2), (61.1). (Found: C, 64.03; H, 5.70. Calc. for $C_{20}H_{20}O_7$: C, 64.52; H, 5.38).

3',4',5,7-Tetramethoxyflavylium chloride (**8b**). A soln of 500 mg (1.34 mmoles) of **7b** and 750 mg (1.69 mmoles) $Pb(OAc)_4$ in 15 ml AcOH (containing 2% Ac_2O), was stirred at 50° under N_2 for 2 hr. The solvent was then removed *in vacuo*, and the product was worked up as described above for **8a**. The eluate from the Dowex 21-K (Cl^-) was freeze-dried to give 474 mg (1.30 mmoles, 97%) of **8b**, red–brown solid. UV (0.01 N HCl in MeOH) λ_{max} nm (log ϵ): 240 (4.17), 278 (4.30), 320 (3.70) and 488 (4.61). IR (KBr) cm^{-1}: 3420, 1640, 1565, 1500, 1355, 1330, 1280, 1240, 1225, 1210, 1160, 1050. The product was identical by HPLC, UV and IR comparisons with an authentic sample of **8b**.[12] A portion was converted to the $FeCl_4^-$ salt and recrystallized from AcOH, m.p. 207–8° (lit.[17] 205–6°).

Luteolinidin chloride (**6b**). A soln of 400 mg (1.10 mmoles) of **8b** and 1.6 g (17.0 mmoles) phenol in 40 ml 48% HBr was heated at reflux for 16 hr, under a blanket of argon. The mixture was worked up as described before for **6a**, to give 263 mg (0.86 mmoles, 78%) of **6b**, orange–brown solid. UV (0.01 N HCl in MeOH) λ_{max} nm (log ϵ): 208 (4.50), 240 (4.16), 280 (4.28), 320 sh. (3.65) and 496 (4.59). IR (KBr) cm^{-1}: 3440, 3100, 1640, 1590, 1550, 1520, 1345, 1285, 1245, 1165. Comparison of the product with an authentic sample of **6b**[14] by hplc, IR and UV confirmed its identity.

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