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SYNTHESIS OF ANTHOCYANIDINS—II

THE SYNTHESIS OF 3-DEOXYANTHOCYANIDINS FROM 5-HYDROXY-FLAVANONES

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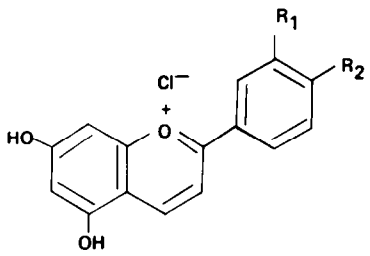
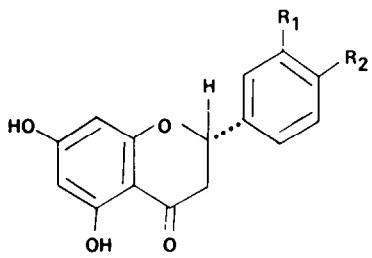
[Dedicated to Prof. ROBERT B. WOODWARD on the occasion of his 60th birthday]

Abstract—The 3-deoxyanthocyanidins apigeninidin chloride (**1**) and 4'-O-methylluteolinidin chloride (**3**) have been synthesized from the flavanones naringenin (**4**) and hesperetin (**6**), respectively. The overall process calls for: (a) borohydride reduction of the flavanone-5-acetate to the corresponding flavan; (b) benzoquinone oxidation of the flavan to the flavylium salt.

Apigeninidin (**1**) and luteolinidin (**2**) are the most common of the natural 3-deoxyanthocyanidins, a group of yellow flavylium pigments found primarily in mosses[1] and ferns,[2] the most primitive of land plants.

In the previous paper[9] we reported that the sodium borohydride reduction of methylated flavanones to flavan-4-ols, followed by chloranil oxidation, gave the corresponding 3-deoxyanthocyanidins in good yeilds. To





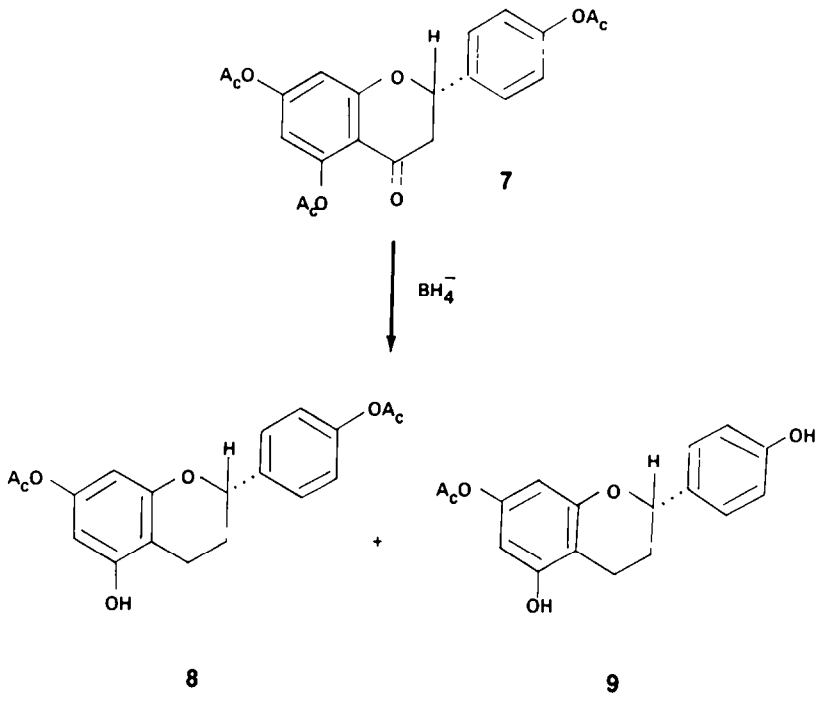
	R_1	R_2	
1	H	OH	**4**
2	OH	OH	**5**
3	OH	OCH_3	**6**

These pigments are the chemical ancestors of the red and purple anthocyanidins bearing oxygen at C_3, that are found widely spread in the more evolved angiosperms.[3] The emergence of a pathway for the hydroxylation at the C_3 position was a crucial step that occurred early in the biochemical evolution of plants.[4] This acquired ability for the synthesis of red to blue anthocyanidins played a role in the further evolution of land plants, by attending the emergence of more complex reproductive functions with increased dependence on flower color for pollination and seed dispersal.[5]

In the applied field, a more recent interest in these yellow pigments has been awakened by the work of Jurd,[6] who has shown the potential usefulness of 3-deoxyanthocyanidins as food colorants. Although apigeninidin chloride has been prepared before through total synthesis by Robinson,[7] we decided to examine an alternative route for either **1** or **3**, taking advantage of the availability of the flavanones naringenin (**4**) and hesperetin (**6**) as by-products of the citrus industry.[8]

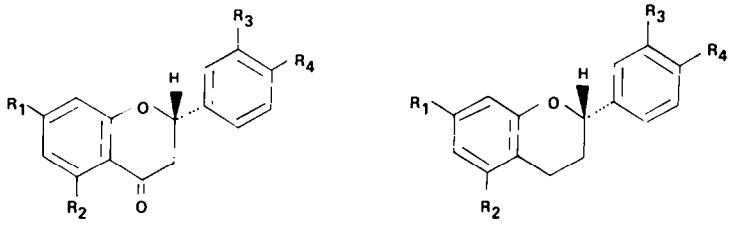
extend this reaction to the synthesis of the naturally-occurring phenolic anthocyanidins **1–3**, we have studied the reduction of the fully-acetylated flavanones, as our first attempts at reducing the phenols **4–6** gave complex mixtures containing much polymeric material. As a first case, naringenin triacetate (**7**) was reduced with $NaBH_4$ in THF–EtOH (1:1) at room temperature (Scheme 1). TLC examination of the crude reaction mixture showed four major products which were separated by column chromatography on SilicAR CC-7. Two of the products showed flavanoid ketonic absorption in the IR and were assumed to be partially hydrolyzed starting material. The other two products showed only ester carbonyl absorption and were obviously reduction products. Analysis of the MS, IR and NMR data (Experimental) showed the less polar product to be 4',7 - diacetoxy - 5 - hydroxyflavan (**8**) and the more polar to be 7 - acetoxy - 4,5 - dihydroxyflavan (**9**).

Although unexpected, the reduction of an *o*-acetoxy aromatic ketone to the hydrocarbon instead of the



Scheme 1.

Table 1. Reduction of 5-hydroxyflavanones to flavans using sodium borohydride



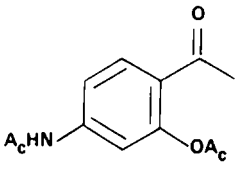
				Yield (%) [a]
7	$R_1 = R_2 = R_4 = OAc$, $R_3 = H$	**8**	$R_1 = R_4 = OAc$, $R_2 = OH$, $R_3 = H$	45
		9	$R_1 = OAc$, $R_2 = R_4 = OH$, $R_3 = H$	20
7		**12**	$R_1 = R_2 = R_4 = OAc$, $R_3 = H$	57[b]
7		**21**	$R_1 = R_2 = R_4 = OH$, $R_3 = H$	52[c]
13	$R_1 = R_3 = R_4 = OCH_3$, $R_2 = OH$		Resinous Material	0
14	$R_1 = R_3 = R_4 = OCH_3$, $R_2 = OAc$	**15**	$R_1 = R_3 = R_4 = OCH_3$, $R_2 = OH$	64
16	$R_1 = R_2 = R_3 = OAc$, $R_4 = OCH_3$	**17**	$R_1 = R_3 = OAc$, $R_2 = OH$, $R_4 = OCH_3$	40
16		**18**	$R_1 = R_2 = R_3 = OAc$, $R_4 = OCH_3$	44[b]
19	$R_1 = R_2 = R_3 = R_4 = OAc$	**20**	$R_1 = R_2 = R_3 = R_4 = OAc$	36[b]

[a] *Yields are of crystallized product. For details, see Experimental.*

[b] *The crude product was re-acetylated before flavan isolation.*

[c] *The crude product was deacetylated before flavan isolation*

alcohol had precedence. McLoughlin[10] had reported that $NaBH_4$ reduction of the ketone **10** at room temperature gives the *o*-alkyl phenol **11**, while Bell[11] found that *o*- and *p*-hydroxyacetophenones could be reduced to the corresponding alkyl phenols with $NaBH_4$ in aqueous NaOH at reflux.



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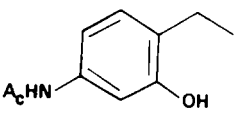

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In the flavanone series, the reduction occurred in all cases where a 5-OAc group was present in the molecule as shown in Table 1. Reduction stopped at the 4-alcohol stage in the case of 7-OAc flavanone, indicating that at room temperature, elimination does not occur in this series. For synthesizing flavans from 5-hydroxyflavanones on a large preparative scale, this reaction has advantages over other known procedures previously found effective, such as Clemmensen reduction[12] and Raney nickel desulfuration of 1,2-ethylenedithioketals.[13]

The oxidation of polyhydroxyflavans to 3-deoxyanthocyanidins with benzoquinones, as shown in Table 2, proceeded only with chloranil in an acetic acid-aqueous HCl mixture, and failed if HCl was ommitted. This catalytic effect of acid on chloranil dehydrogenations has been noted previously in the steroid field,[14] and it seems to function by protonation of the chloranil, thereby increasing its oxidation strength. As is evident from the data in Table 2, oxidation only occurs in those compounds containing a nonvicinal 4'- or 7-OH group. This would suggest that the first step involves formation of a quinone methide; compounds like **20** containing vicinal dihydroxy groups being oxidized to an *o*-quinone instead.[15]

The effect of varying the oxidation potential of the quinone is shown in Table 3. Only chloranil and bromanil gave satisfactory yields of apigeninidin from the oxidation of 4',5,7-triacetoxyflavan (**12**).

A plausible mechanism for the oxidation of **8** to **1** is shown in Scheme 2. Under the acidic reaction conditions the quinone methide first formed is then isomerized to a flav-2- or flav-3-ene, which is in turn oxidized to the 3-deoxyanthocyanidin.

Table 3. Relative effectiveness of halogenated benzoquinones for the oxidation of 4',5,7-triacetoxyflavan (**12**) to apigeninidin chloride (**1**)[a]

Benzoquinones (arranged by increasing electron acceptor potentials)	Apigeninidin Yield (%)[b]
p-Benzoquinone	no reaction
Tetrafluoro-p-benzoquinone	7
Tetrachloro-p-benzoquinone (chloranil)	30
Tetrabromo-p-benzoquinone (bromanil)	27
Tetrachloro-o-benzoquinone (o-chloranil)	6
Tetrabromo-o-benzoquinone (o-bromanil)	4
Dicyano-dichloro-p-benzoquinone (DDQ)	0[c]

[a] *Oxidations done with 10 mg 12 and 15 mg quinone, in 1 ml acetic acid, plus 0.1 ml 6 N HCl and 0.4 ml water, at 100° C for 1 hr.*

[b] *By UV analysis of purified product on polyclar using $\varepsilon_{476\ nm}$ = 38,000 (0.01 N HCl in MeOH) for pure apigeninidin.*

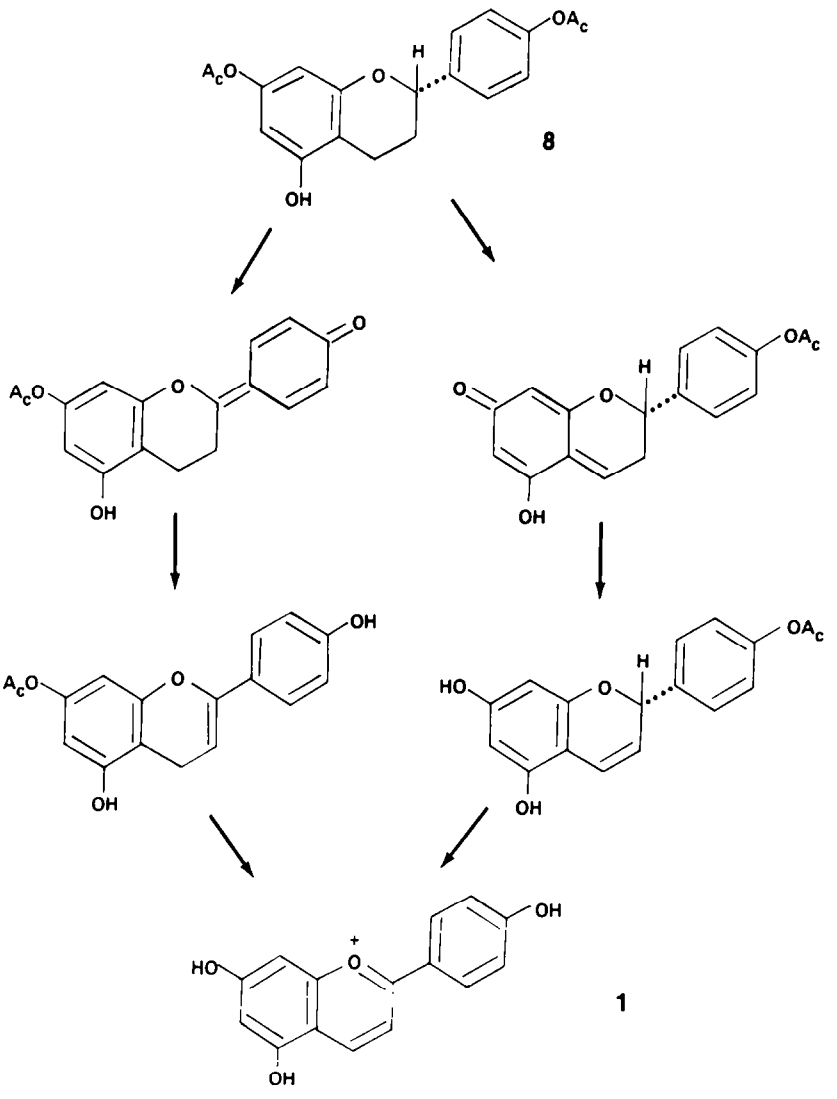
[c] *Reaction done at 25° C for 30 minutes, with formation of brown tars. No apigeninidin found on polyclar chromatography.*

Table 2. Quinone oxidation of polyhydroxyflavans

Flavan	3-Deoxyanthocyanidin Yield (%)[a] Benzoquinone	Chloranil
8	0	31
9	0	25
12	0	26
21	–	14
21	–	8[b]
15	–	trace[b]
17	0	16
18	0	20
20	0	0

[a] *Reaction conditions 10 mg flavan and 15 quinone, dissolved in 1 ml acetic acid, 0.4 ml water and 0.1 ml 6 N HCl, heated at 100° for one hour. Anthocyanidin yields are spectrophotometric [$\varepsilon_{476\ nm}$ = 38,000 (0.01 N HCl in MeOH)] after chromatography on acid-treated polyclar.*

[b] *HCl and H_2O omitted.*



Scheme 2.

EXPERIMENTAL

M.ps are uncorrected. Chemical shifts in ^{1}H NMR spectra are given in ppm downfield from TMS. Abbreviations: s, singlet; b.s., broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Chloranil (Eastman) was recrystallized from toluene before use. All other reagents were used as received from the supplier and were reagent grade. Microanalyses were performed by Galbraith Analytical Laboratories, Knoxville, Tenn.

4',5,7-Triacetoxyflavan (**12**). To a soln of 5.0 g of **7** in a mixture of 125 ml THF and 125 ml EtOH was added 500 mg $NaBH_4$. After stirring at room temp. for 30 min, an additional 500 mg $NaBH_4$ was added and stirring continued for a total of 1 hr. The soln was then poured into 750 ml of cold 0.5% HOAc and extracted with 3 × 250 ml $CHCl_3$. Drying (Na_2SO_4) and evaporating the $CHCl_3$ gave a light yellow oil. The oil was dissolved in 25 ml Ac_2O and 30 ml pyridine and allowed to stand at room temp. overnight. It was then poured into 200 ml ice water and extracted with 150 ml $CHCl_3$. The $CHCl_3$ layer was washed with 200 ml ice water, 200 ml cold 3% HCl and 200 ml cold 0.5% $NaHCO_3$. Drying and evaporating the $CHCl_3$ again gave a pale yellow oil. This oil was chromatographed on a 2.5 × 40 cm silicAR CC-7 column using 50% $CHCl_3$-hexane as eluant. The early fractions were combined and crystallized from MeOH to give 2.77 g (two crops, 57%) of *4',5,7-triacetoxyflavan* (**12**), m.p. 102–3°. IR (KBr)μ: 5.65, 7.27, 8.22, 8.89, 9.24, 9.40, 9.79. NMR ($CDCl_3$): 2H m at 1.7–2.1 (C_3H), 3H s at 2.20 (OAc), 6H s at 2.24 (OAc), 2H m at 2.5–2.7 (C_4H), 1H q at 4.96 (C_2H), 2H q at 6.50 (C_6H and C_8H), 4H q at 7.20 (C_2H, C_3H, C_5H and C_6H). MS *m/e* (rel. intensity): 384 (18), 342 (18), 300 (19), 258 (25), 120 (38), 69 (21) and 43 (100). Calc. for $C_{21}H_{20}O_7$: C, 65.63; H, 5.20. Found: C, 65.78; H, 5.09%).

Sodium borohydride reduction of triacetylnaringenin (**7**). 1 g of **7** was reduced with $NaBH_4$ in 50% EtOH–THF as described above. The crude product (reacetylation omitted) was chromatographed on silicAR CC-7 using 1,2 and 4% MeOH in $CHCl_3$ as eluant. The fractions were monitored by TLC analysis and combined to give four products. NMR and IR showed the first and third (in order of elution) to be flavans and the second and fourth to be flavanones. Crystallization of the first product from MeOH gave 376 mg (44%) of *4',7 - diacetoxy - 5 - hydroxyflavan* (**8**) m.p. 155.5–7°. IR ($CHCl_3$)μ: 5.68, 6.21, 7.26, 8.09, 8.88, 9.22 and 9.80. MS *m/e* (rel. intensity): 342 (62), 300 (77), 258 (100), 139 (60), 120 (95) and 43 (42). NMR (DMSO-d_6): 2H m at 2.0 (C_3H), 3H s at 2.16 (OAc), 3H s at 2.21 (OAc), 2H m at 2.58 (C_4H), 1H d at 4.97 (C_2H), 2H q at 6.06 (C_6H and C_8H), 4H q at 7.20 (C_2H, C_3H, C_5H and C_6H), 1H b.s. at 9.56 (OH). (Calc. for $C_{19}H_{18}O_6$: C, 66.67; H, 5.26. Found: C, 66.94; H, 5.38%). Crystallization of the third component from ethyl acetate–hexane gave 149 mg (20%) of *4',7 - dihydroxy - 7 - acetoxyflavan* (**9**) m.p. 186–8°. IR (KBr)μ: 3.00, 5.83, 6.21, 7.88,

8.38, 8.88, 9.26 and 9.68. MS *m/e* (rel. intensity): 300 (41), 258 (58), 139 (100), 120 (97), 71 (43), 55 (68) and 43 (82). NMR (DMSO-d_6): 2H m at 2.06 (C_3H), 3H s at 2.16 (OAc), 2H m at 2.6 (C_4H), 1H q at 4.82 (C_2H), 2H m at 6.05 (C_6H and C_8H), 4H q at 6.88 (C_2H, C_3H, C_5H and C_6H), 2H b.s. at 9.24 (OH). (Calc. for $C_{17}H_{16}O_5$: C, 68.00; H = 5.33. Found: C. 67.87; H, 5.24%).

3',4',7-*Trimethoxy-5-hydroxyflavan* (**15**). To a soln of 900 mg of **14**[16,17] in a mixture of 25 ml THF and 25 ml EtOH was added 100 gm $NaBH_4$. After stirring for 30 min at room temp., an additional 100 mg $NaBH_4$ was added and stirring continued for a total of 1 hr. The soln was then poured into 200 ml of cold 0.5 N HOAc and extracted with 3 × 100 ml $CHCl_3$. Drying and evaporating the $CHCl_3$ gave an oil. The oil was purified by passing through a short (10 × 2.5 cm) silicAR column using 30% EtOAc–hexane as eluant, then crystallized from MeOH at −20° to give 495 mg (64%) of 3',4',7 - *trimethoxy* - 5 - *hydroxyflavan* (**15**), m.p. 163.5–165°. IR (KBr)μ: 6.16, 6.28, 6.61, 7.90, 8.72, 9.25, 9.74. MS *m/e* (rel. intensity): 316 (26), 164 (100), 71 (37), 69 (30), 57 (64), 55 (36) and 43 (62). NMR ($CDCl_3$): 2H m at 2.12 (C_2H), 2H m at 2.68 (C_4H), 3H s at 3.68 (OCH_3), 6H s at 3.86 (OCH_3), 1H q at 4.88 (C_2H), 2H q at 6.02 (C_6H and C_8H), 3H m at 6.89 (C_2H, C_5H, C_6H). (Calc. for $C_{18}H_{20}O_5$: C, 68.35; H, 6.33. Found: C, 68.37; H, 6.39%).

3',4',5,7-*Tetraacetoxyflavan* (**20**). 1 g of **19**[18] was reduced with $NaBH_4$ and the crude product acetylated as described above for **7**. Chromatography of the resulting oil on a 40 × 2.5 cm SilicAR CC-7 column using 60% $CHCl_3$–hexane as eluant separated the mixture into two components. Crystallization of the material of higher R_f from MeOH afforded 345 mg (36%) of 3',4',5,7-*tetraacetoxyflavan* (**20**), m.p. 143–4°. IR (KBr)μ: 5.63, 7.27, 8.22, 8.88, 9.25 and 9.80. MS *m/e* (rel. intensity): 442 (29), 400 (52), 358 (100), 316 (85), 274 (46), 139 (48), 136 (62) and 43 (84). NMR ($CDCl_3$): ~2H b.m. at 2.1 (C_3H), 12H s at 2.30 (OAc), 2H q at 6.58 (C_6H and C_8H), 3H m at 7.3 (C_2H, C_5H, C_6H). (Calc. for $C_{23}H_{22}O_9$: C, 62.44; H, 4.98. Found: C, 62.44; H, 5.01%).

4' - *Methoxy* - 3',7 - *diacetoxy* - 5 - *hydroxyflavan* (**17**). 2 g of **16** was reduced with $NaBH_4$ in 50% EtOH–THF as above. The crude product was chromatographed on silicAR CC-7 using $CHCl_3$ as eluant. The fractions containing the material of highest R_f were combined and recrystallized from MeOH to give 702 mg (2 crops, 40%) of **17**, m.p. 158–60°. IR ($CHCl_3$)μ: 5.67, 6.22, 7.27, 7.85, 8.20, 8.88 and 9.25. MS *m/e* (rel. intensity): 372 (7), 330 (10), 288 (6.2), 150 (40), 135 (7), 45 (10) and 43 (100). NMR (DMSO-d_6): 2H m at 2.0 (C_3H), 3H s at 2.16 (OAc), 3H s at 2.20 (OAc), 2H m at 2.5 (C_4H), 3H s at 3.74 (OCH_3), 1H b.d. at 4.92 (C_2H), 2H q at 6.06 (C_6H and C_8H), 3H m at 7.10 (C_2H, C_5HM C_6H), 1H m at 9.62 (OH). (Calc. for $C_{20}H_{20}O_7$: C, 64.52; H, 5.38. Found: C, 64.83; H, 5.48%).

4'-*Methocy*-3',5,7-*triacetoxyflavan* (**18**). 5 g of **16** was reduced with $NaBH_4$ in 50% EtOH–THF and the crude product reacctylated as described above for **7**. The resulting oil was chromatographed on a 40 × 2.5 cm silicAR CC-7 column using hexane–$CHCl_3$ (1:1) as eluant. The fractions containing the component of higher R_f were combined and allowed to stand in 20 ml MeOH at 5° overnight. Filtration gave 2.12 g. (44%) of 4' - *methoxy* - 3',5,7 - *triacetoxyflavan* (**18**), m.p. 106–7°. IR (KBr)μ: 5.63, 7.27, 7.82, 8.26, 8.86, 9.41 and 9.77. MS *m/e* (rel. intensity): 414 (45), 372 (100), 330 (49), 288 (40), 287 (39), 150 (85) and 43 (49). NMR ($CDCl_3$): ~2H m at 2.0–2.4 (C_3H), 2H m at 2.6–3.0 (C_4H), 3H s at 2.32 (OAc), 3H s at 2.36 (OAc), 3H s at 2.38 (OAc), 3H s at 4.00 (OCH_3), 1H q at 5.10 (C_2H), 2H q at 6.85 (C_6H and C_8H). 3H m at 7.2–7.6 (C_2H, C_5H, C_6H). (Calc. for $C_{22}H_{22}O_8$: C, 63.77; H, 5.31. Found: C, 63.70; H, 5.15%).

4',5,7-*Trihydroxyflavan* (**21**). Naringenin triacetate **7** (2.0 g) was reduced with $NaBH_4$ as above. The crude product was then added to 60 ml EtOH and 40 ml H_2O containing 400 mg imidazole.[19] The resulting mixture was heated at reflux under N_2 for 18 hr, then neutralized with 6 N HCl and concentrated to 40 ml *in vacuo*. Extraction with 4 × 50 ml ether, drying the Et_2O layers over Na_2SO_4 and evaporating to dryness gave an oil. This oil was chromatographed on a 40 × 2.5 cm column of silicAR using 5% MeOH–$CHCl_3$ as eluant. The early fractions gave crude naringenin, while the later fractions (combined after TLC analysis) afforded 680 mg (52%) of 4',5,7-*trihydroxyflavan* (**21**), m.p. 211–3° (EtOH–H_2O, carcoal). IR (KBr)μ: 2.93, 6.15, 6.56, 8.01, 8.72, 9.36 and 9.71. MS *m/e* (rel. intensity): 258 (100), 139 (80), 133 (23), 120 (100), 91 (23), 69 (22) and 55 (21). NMR (DMSO-d_6): 2H m at 1.86 (C_3H), 2H m at 2.40 (C_4H), 1H b.d. at 4.70 (C_2H), 2H q at 5.72 (C_6H and C_8H), 4H q at 6.90 (C_2H, C_3H, C_5H, C_6H), 3H m at 8.98 (OH). (Calc. for $C_{15}H_{14}O_4$: C, 69.77; h, 5.43. Found: C, 69.50; H, 5.32%).

Apigeninidin chloride (**1**). A mixture of 500 mg of **12**, 750 mg chloranil, 25 ml HOAc, 5 ml H_2O and 1.5 ml 6 N HCl was heated with sitrring at 100° for 1 hr. After cooling in ice the soln was diluted to 250 ml with 0.01 N HCl in MeOH and passed through a 4.5 × 10 cm column of acid-treated[20] polyclar AT. The column was washed with a second 250 ml of 0.01 N HCl in MeOH and the combined eluants concentrated on a rotary evaporator (< 40°) to 25 ml. This solution was then freeze-dried and the residue washed with 2 × 10 ml EtOAc to give 144 mg (36%) of **1** as a red orange solid. A sample recrystallized from EtOH–4 N NCl was identical by TLC (cellulose) and IR (KBr) comparison with an authentic sample prepared by Robinson's procedure.[7] $UV_{(0.01\ N\ HCl\ in\ MeOH)}$ λ_{max} nm (log ϵ): 240 (3.98), 277 (4.24), 324 (3.66) and 475 (4.51).

4'-*Methylluteolinidin chloride* (**3**). A mixture of 500 mg of **18**, 700 mg chloranil, 25 ml HOAc, 5 ml H_2O and 1.5 ml 6 N HCl was heated at 100° for 1 hr with stirring. The soln was then cooled in ice and diluted with 200 ml 0.01 N NCl in MeOH. This soln was filtered through a pad of 15 g acid-treated polyclar. The pad was washed with an additional 200 ml 0.01 NHCl in MeOH and the combined filtrates concentrated on a rotary evaporator to approximately 25 ml. Freeze-drying the remaining soln gave a thick oil which solidified after trituration with 2 × 10 ml EtOAc and 15 ml 4 N HCl to give 92 mg (22%) of 4'-*methylluteolinidin chloride*. A sample was further purified by chromatography on a 10 × 2.5 cm polyclar column using 0.01 N HCl in MeOH as eluant. $UV_{(0.01\ N\ HCl\ in\ MeOH)}$ λ_{max} nm (log ϵ): 240 (4.11), 279 (4.26), 320 (3.58) and 488 (4.51). IR (KBr)μ: 8.06 (8.05), 7.82 (7.86), 7.41 (7.43), 6.57, 6.42 (6.44), 6.06 (6.07) and 2.91 (2.89). Values in parenthesis are the strongest peaks found in the IR spectrum of apigeninidin chloride.

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REFERENCES

[1]E. Nilsson and G. Bendz, *Flavonoids in Bryophytes*. In *Chemistry in Botanical Classification* (Edited by G. Bendz and J. Santesson). The Nobel Foundation, Uppsala (1974).
[2]J. B. Harborne, *Phytochemistry* **5**, 589 (1966).
[3]C. F. Timberlake and P. Bridle, *The Anthocyanins*. In *The Flavonoids* (Edited by J. B. Harborne, T. J. Mabry and H. Mabry), Part 1. Academic Press, New York (1975).
[4]T. Swain, *Evolution of Flavonoid Compounds*. In *The Flavonoids* (Edited by J. B. Harborne, T. J. Mabry and H. Mabry), Part 2. Academic Press, New York (1975).
[5]J. B. Harborne, *Functions of Flavonoids in Plants*. In *Chemistry and Biochemistry of Plant Pigments* (Edited by T. W. Goodwin), Vol. 1. Academic Press, London (1976).
[6]L. Jurd, *Food Technology* **18**, 157 (1964).
[7]G. M. Robinson, R. Robinson and A. R. Todd, *J. Chem. Soc.* 809 (1934).
[8]J. F. Kefford and B. V. Chandler, *The Chemical Constituents of Citrus Fruits*. Academic Press, New York (1970).
[9]J. G. Sweeny and G. A. Iacobucci, Part I, *Tetrahedron*, **33**, 2923 (1977).
[10]B. J. McLoughlin, *Chem. Comm.* 540 (1969).
[11]K. H. Bell, *Aust. J. Chem.* **22**, 601 (1969).
[12]A. Robertson, V. Venkateswarlu and W. B. Walley, *J. Chem. Soc.* 3137 (1954).
[13]E. J. Keogh, E. M. Philbin, S. Ushioda and T. S. Wheeler, *Ibid.* 3162 (1963).

[14]C. Djerassi (Editor), *Steroid Reactions*, p. 230. Holden-Day, San Francisco (1963) and Refs. therein.
[15]H. Loth and H. Diedrich, *Tetrahedron Letters* 715 (1968).
[16]J. Shinoda and S. Sato, *J. Pharm. Soc. Japan* **49**, 64 (1929).
[17]L. Waring, *Ibid.* **60**, 420 (1940).
[18]V. K. Jain, *U.S. Pat.* 3,803,117 (9 April 1974).
[19]J. H. Looker, M. J. Holm, J. L. Minor and S. A. Kagal, *J. Heterocyclic Chem.* **1**, 253 (1964).
[20]R. E. Wrolstad and B. J. Struthers, *J. Chromat.* **55**, 405 (1971).